

Risk management and risk assessment of novel plant foods: Concepts and principles

Ib Knudsen^a, Inge Søborg^b, Folmer Eriksen^a, Kirsten Pilegaard^a, Jan Pedersen^{a,*}

^a *Department of Toxicology and Risk Assessment, National Food Institute, Technical University of Denmark,
Mørkhøj Bygade 19, DK-2860 Søborg, Denmark*

^b *DHI, Centre for Environment and Toxicology, Artens Allé 5, DK-2979 Hørsholm, Denmark*

Received 22 March 2007; accepted 7 January 2008

Abstract

Worldwide 30 food plants deliver 95% of human daily intake of plant food calories and around 300 other plant species are delivering the last 5%. These some 300 food plants are likely to be considered traditional in Europe, while the nearly 7000 other plant species traditionally used in the human food supply in other parts of the world may be considered novel in Europe.

Novel food regulation is already in force in the European Community, Australia/New Zealand and in Canada where the novel plant foods need to go through a premarket assessment procedure. This paper propose criteria and definitions to be used in determining novelty of a plant food and also propose a safety assessment approach for novel plant food with no or limited documented history of safe consumption.

A 2-step management procedure is recommended for a smooth introduction of fruits and vegetables; first to establish the novelty and second to define and commit resources for the safety assessment. The procedure builds upon the use of a worldwide network of global, regional, local and ethnobotanical positive lists for food plants to guide the decision on novelty at the first step and to enable the safety assessment at the second step.

© 2008 Elsevier Ltd. All rights reserved.

Keywords: Novel foods; Traditional foods; Plant foods; Regional lists; History of safe use; Positive lists for food plants

1. Introduction

This paper deals with one segment of the novel foods, namely novel plant foods, with the main focus on novel foods derived from plants not known in the country or region. The paper does not deal with foods derived from genetically modified plants, but only foods derived from cultivated plants that may be developed through conventional breeding or plants from wild sources.

For nearly all plant foods it is very difficult to obtain scientific data, which document their history of safe consumption even though they may have been eaten for several hundreds of years. Nevertheless according to the regulation

of some countries there is a need to establish the safety of novel plant foods in order to accept their introduction on the market. While there already exist well established paradigms for safety assessment of isolated and extracted plant products like sugars, fats and defined chemical entities e.g. flavours, there are no commonly accepted international approaches to assess the safety of complex foods such as fruits, vegetables and other plant parts derived from novel sources.

The purpose of this paper is to propose a set of basic principles and concepts for safety assessment of plant foods, with a main focus on new fruits and vegetables with no history of safe consumption in a country or region and with the final aim to propose a procedure for the safety assessment based upon up-to-date scientific knowledge. This paper is based upon the work by a working group

* Corresponding author. Tel.: +45 7234 7610; fax: +45 7234 7699.
E-mail address: jp@food.dtu.dk (J. Pedersen).

under the Nordic Working Group on Food Toxicology and Risk Evaluation.

During the last two decades a lot of attention has been paid to the safety assessment of genetically modified organisms used as food. Several international reports have indicated that the safety assessment strategy recommended for genetically modified foods to a large extent also could be used for other kinds of novel foods. Another conclusion from many of these reports is that very little is known about the potential long-term health effects of any traditional food (e.g. [FAO/WHO, 2000](#)). Nonetheless, most traditional foods are treated as being safe because no widespread occurrence of acute severe adverse effects is reported after their consumption. Their safety has, however, rarely, if ever, been established. While it has been commonly accepted that for example food additives should be thoroughly tested for safety prior to use in the food production in order to secure that their level in the final food product would not constitute a human health risk, foods from new plant lines or new exotic fruits and vegetables have not been evaluated to the same extent for their potential adverse effects on human health although there are several examples of risks connected to such foods.

Considering fruits and vegetables with no history of safe use there is a need for identifying potential safety issues. It is also important to identify the type of information which would be useful for a safety assessment of such foods, and which type of analysis or tests, if any, that may be required before decision on marketing can be taken.

Today, Canada and Australia/New Zealand and the European Union (EU) have regulations for novel foods ([Health Canada, 1994, 1999](#); [FSANZ, 2004a,b](#); [EU, 1997](#)). The definition of novel foods varies between the regulations, but all require a pre-market safety assessment of such foods. However, the scientific guidelines for performing risk assessments of novel foods are generally poorly harmonised and in a continuing stage of development as more and more attention is paid to the safety of such foods and as more experience about safety testing methodology is obtained.

Closely connected to the safety issue is the formulation of the definition, which leads a food to be identified as novel. The prerequisite for commissioning a safety assessment to be done is the recognition of that food item to be novel within the actual regulatory framework. The definition of what constitutes a novel food is basically a management decision. This paper gives some suggestions for an approach that may be useful for making uniform management decisions, and at the same time explains the different roles of management and science in the process and underlines the need for keeping the two different sets of arguments apart.

The overall aim of this paper is thus to facilitate the introduction of novel plant foods on the market through a clear definition of the roles of risk management and risk assessment in the process by explaining what each part should do, thereby bringing the harmonisation process of safety assessments of exotic fruits and vegetables an important step further.

2. Historical experience

2.1. Food plants and food plant toxins

Nowadays the general advice on good eating habits from a nutritional view point is to eat a variety of foods, including fruits and vegetables each day to ensure the combined intake of the necessary amount of nutritionally important proteins, amino acids, fats and fatty acids, complex carbohydrates, fibres, vitamins and minerals and thereby also consumption of a variety of secondary plant metabolites such as plant phenols, isothiocyanates, indoles and carotenoids with and without acknowledged nutritional relevance. Many of these secondary metabolites are formed as part of the plants own defence against herbivores or plant diseases. Many of these plant constituents may have an upper safety level, and they may have health benefits to humans in lower levels. Intake of plant foods like cassava (*Manihot esculenta* Crantz) and grasspea (*Lathyrus sativus* L.) may give rise to acute and chronic intoxications in human. In spite of that, they are still used as food. The starch-filled roots of cassava have even a major role in today's food supply in many tropical regions. The roots contain cyanogenic glycosides, and raw or inadequately processed roots may cause acute symptoms or chronic neurological disorders ([Mlingi et al., 1992](#)). Excessive consumption of the seeds of the legume grasspea causes lathyrism, a neurodegenerative and irreversible spastic paraparesis ([Spencer et al., 1986](#); [Getahun et al., 2003](#)). The toxic substance is the neuroexcitatory amino acid β -*N*-oxalyl- α , β -diaminopropionic acid, ODAP ([Rao, 2001](#)). Since grasspea is highly drought- and flood-resistant, the seeds may still constitute a major part of the diet during famine crisis. Outbreaks of lathyrism epidemics have occurred within the last ten years in Afghanistan, Nepal and Ethiopia. Recently there has been a renewed interest in cultivating grasspea in Italy and Poland ([Getahun et al., 2005](#)), and the first variety of grasspea (Ceora) with low level of ODAP is just released in Australia ([Siddique and Hanbury, 2005](#)).

The above-mentioned examples show that plant foods still may give rise to safety concerns even in populations accustomed to their use. The examples also illustrate that proper use of plant foods both from a nutritional and safety point of view is the basic prerequisite for a stable and solid development and maintenance of the variety of human cultures and societies all over the world.

2.2. Novel food plants in a historical perspective

Since prehistoric times and over history new food items and new methods to prepare foods have gradually spread and enriched the human food supply. These introductions have generally been slowly implemented. Already our ancestors, the hunter-gatherers were forced to broaden their food resource base to encompass a wide array of food that was previously ignored in an attempt to overcome

food shortages. Data supporting this “broad-spectrum revolution” hypothesis has mainly been of faunal origin, but recent data from caves in the Levant confirms that the 25,000 years old plant material recovered were both broad in origin (142 taxa) and with a high amount of small-grained grasses compared to cereals (wild wheat and barley) (Weiss et al., 2004). In the following 15,000 years, the cereals gradually replaced these small-grained grasses. The proper shift from hunting and gathering to agriculture took place some 10,000 years ago in the Oriental region and broadened to the Europe, central Asia and India through the next millennia. Although the reasons for this “Neolithic revolution” are not fully understood, the resulting domesticated plants are still major food component in Europe such as wheat, barley and pea (Zohary and Hopf, 2000).

In historic times the single remarkable and epoch-making event, which produced a mass introduction of novel foods in Europe, was the exploration of the “new” world. A large part of the plant foods considered nowadays as an integrated part of the European diet was first introduced in Europe some 400–500 years ago, following this “Age of Exploration”. The food plants introduced during that period include potato, tomato, maize, groundnut and pepper fruit, which now are important staple foods and feeds. In the same period also cacao, vanilla, and allspice and a series of other spices, now highly appreciated as culinary delicacies, came along.

When the “Age of Exploration” began, the Solanaceae family was already reputed in Europe for its toxic and medicinal members. It is therefore understandable that there was some resistance to accept foods from this plant family such as potato, tomato and pepper fruits in Europe. They were all introduced in Europe shortly after 1500 AD but only pepper fruit (*Capsicum annuum* L.) was readily accepted as a food – as a substitute for black pepper (*Piper nigrum* L.). Tomato can illustrate the slow acceptance of Solanum-like fruits in Europe. It was first in the late 18th century that tomatoes were being grown and eaten in abundance in Italy and Spain. By 1800, when tomatoes had become the most common fruit in Spain, they were eaten in a small scale in France, while in Northern Europe they were still regarded with suspicion.

2.3. Before the EU regulation

Before the EU regulation on novel food came into place in 1997, a number of exotic food plants have been introduced on the European food market. These exotic foods have presumably been placed on the market based on the assumption that their safety could be assured by their use as food in other parts of the world. Well-known examples are squash, kiwi fruit, star fruit, cape gooseberry and durian fruit.

The occurrence of toxic glycoalkaloids i.e. α -solanine and α -chaconine in different *Solanaceae* plants such as potatoes has been investigated (Andersson, 1999). In a

1984 review of the literature, 12 separate reports of potato glycoalkaloid poisoning, involving more than 2000 cases with about 30 deaths, have been presented. Moreover, the review argues that most of the mild and even the more serious “solanine” poisonings go unrecorded and are diagnosed as “gastroenteritis” (Morris and Lee, 1984). The content of total glycoalkaloids varies considerably between the different potato varieties. Based upon a risk assessment of the content of total glycoalkaloids in potatoes, the Nordic Group on Food Toxicology and Risk Assessment suggested back in 1990 a *Maximum Tolerable Level* of total glycoalkaloids in potatoes on 200 mg/kg unpeeled potatoes with suggestion to reduce the level to 100 mg/kg for new varieties (Slanina, 1990).

The potato case illustrates the kind of acute human health problems the unconsidered introduction of novel plant foods may lead to. Another example is the potential of the kiwi fruit to provoke human allergenicity (Lucas et al., 2003, 2004; Bublin et al., 2004). No studies have been found investigating the influence of the novel plant foods on human long-term health effects such as cancer and cardiovascular disease in Europe.

2.4. After the EU regulation

Traditionally, foods have been considered safe because no reported evidence of adverse effects has accumulated over time, and/or because adequate experience has been acquired in the community with respect to proper food processing or preparation to address any identified hazards. The introduction of the Novel Food legislation in Europe (EC No. 258/97), with its definition of novel foods has created a need for the establishment of the safety of exotic fruits and vegetables novel in Europe. Since the 15 May 1997 these products have to be assessed for their safety, which have to be found acceptable, before the products are placed on the market. It has been suggested that a number of plant foods introduced in Europe over time and now being an integrated part of the European diet would never have been accepted and thereby reached the European market if they should have passed a pre-market approval like the one now being required according to the EU Novel Food regulation. The main difficulties experienced so far in relation to novel plant foods in EU relate to defining the borders of the area of regulation (“What is novel?”) and to the lack of regulatory and scientific consensus on the type of safety data needed to perform the safety assessment and complete the premarket approval for foods deemed to be novel.

3. Potential for new, novel plant foods to be introduced on the EU market

Nowadays the global food supply has become increasingly dependent on only a handful of crops. Three cereals meet more than 50% of the worldwide requirement for plant-derived proteins and calories: maize, wheat and rice.

Thirty plant species used today meet 95 % of the world's total food energy supply coming from intake of plant foods (FAO, 1996). The production figures from these 30 food plants are given in Table 1. Around 150 plant crops have a significant commercialisation on a global scale.

A number of other food plants are contributing to the last percentages of the daily plant food supply.

The EU AIR project NETTOX, 1995–1997, compiled and evaluated data on natural food plant toxicants in the European food supply in order to assess the human health risk of consuming plants with such toxicants, and to identify strategies to minimise such risks (NETTOX, 1998). For this purpose food experts from 15 European countries agreed on a comprehensive European list containing about 300 food plants including spices (and mushrooms) consumed in Europe in 1997. This NETTOX list has recently been revised, and edible plant parts have been added in an EU project EUROFIR (Pilegaard et al., 2007).

Ethnobotanical surveys performed by the *International Plant Genetic Resources Institute* (IPGRI) indicate that across the world 7000 plant species are cultivated or harvested from the nature to complement the food supply (Wilson, 1992; IPGRI, 2004). This corresponds to approximately 10% of the estimated number of edible species present in nature (Myers, 1983).

IPGRI hosts a list on their website with examples on neglected and under-utilised crop species (called NUS) in different parts of the world. This list comprises about 100 plants, some of which would likely be considered novel fruits or vegetables in the European Union (Annex 1).

Similarly, Hegarty et al. (2001) listed around 100 Australian bushfood plant species, which have been ingested by the aboriginals. For the great majority of the bushfoods examined, there are no reports on adverse effects following normal usage and intake despite enquiries in the communities where they are consumed. Although some of these plant foods may not be considered novel foods in an Australian/New Zealand context, they most likely would be considered novel in EU.

A compilation from 1999 of useful Peruvian plants has identified 782 edible plants species for that country alone (Brack Egg, 1999), and a global inventory of food crops listed several thousand edible species that are either cultivated or collected from the wild (Kunkel, 1984; Hermann, 2004). These few examples illustrate that there are many plants that have a history of (safe) use as food in the regions where they grow, but they would potentially be classified as novel foods if they were to be introduced onto the market in the European Community today.

In view of the on-going general climatic and demographic changes, the need for alternative crops to meet these conditions may only be encountered through the introduction and utilisation of novel food crops and varieties of novel food crops selected from this extant crop biodiversity. Therefore a number of non-traditional plant food crops may become introduced, not only in Europe, but also in the world market in the years to come, thereby underlining the need for introduction of generally agreed means and methods to assess the safety and the nutritional properties of the novel foods derived from such plants.

4. Assessment of novelty and safety of plant foods

Foods that are well known and traditional in one country or region may be unknown and thereby novel in another country or region. The knowledge and the traditions developed in each country or region on how to handle the individual plant food item are of great importance for the safe use of it. Some of these traditions actually assist in preventing development of acute or chronic diseases which may be linked to too high intakes of that food item or to the intake of un-prepared or wrongly prepared plant food.

The legislative approach taken to safeguard against such situations usually builds upon a distinction between the traditional foods and the so-called novel foods in that country or region. The European, the Australian/New Zealand and the Canadian Novel Food Regulations are good

Table 1
The world production figures of thirty major food crops taken from Faostat 2004 (megatons) (Janick, 1999)

Food group	Species	Production (megaton)	Food group	Species	Production (megaton)
Cereals	Maize	638	Vegetables	Tomato	113
	Rice	589		Watermelon	91
	Wheat	556		Cabbage	66
	Barley	142		Onion	57
	Sorghum	60		Bean	25
	Millet	30	Fruits	Banana/Plantain	102
	Oat	26		Orange	60
	Rye	15		Grapes	60
Oil seeds and oil-legumes	Soybean	189		Apple	58
	Cottonseed	56	Tubers	Mango	26
	Coconut	53		Potato	311
	Rapeseed	36		Cassava	189
	Groundnut	36		Sweet potato	122
	Sunflower	28		Yams	40
Sugar crops	Sugarcane	1 333			
	Sugar beet	234			

examples. All demand a pre-market notification or assessment and acceptance/approval of the novel foods, before the products are placed on the market. These regulations all require that the determination that something is novel is the first step and considered distinct from the safety assessment, which is the second step.

Two main issues immediately come up with such a legislation: the first one is the challenge on how to determine if a food item is traditional or novel, and to decide on the degree of un-familiarity which makes the food item novel. The second challenge is to establish what kind and extent of safety data is needed to make a safety assessment of an acceptable sensitivity and predictability of such a novel plant food. Both challenges carry a strong scientific component but in origin both are management driven in their demands.

The overall approach recommended below consists of a proposal for a management procedure to separate novel plant foods from traditional plant foods and a proposal for a management based scientific assessment policy to establish the safety of those plant foods defined as novel foods.

This 2-step procedure complies with the approaches taken in the risk analysis process as described by [FAO/WHO \(1995, 1997\)](#), the Scientific Steering Committee of EU, [SSC \(2000, 2003a,b\)](#) and the Nordic Working Group on Food Toxicology and Risk Evaluation, NNT ([Fabech et al., 2002](#)). The separation of novel plant foods from traditional plant foods becomes part of the establishment of the *risk profile*, and the scientific assessment policy becomes identical to the management driven establishment of the *risk assessment policy* as the basis for the conduct of the risk assessment.

4.1. Determination of novelty of the plant food as part of the establishment of a risk profile

The establishment of a risk profile is at the first step in the risk management process ([FAO/WHO, 1997](#)). Risk profiling is the process of describing a food safety problem in its societal context in order to identify those elements of the risk relevant to various risk management decisions.

The risk profile is based on available knowledge and is merely to guide the risk assessment. A typical risk profile includes a brief description of the situation, of products or commodities involved, information on present intake/exposures, values expected to be placed at risk, e.g. human health, economic concerns, consumer perceptions of risks and benefits and considerations regarding the societal distribution of risks and benefits.

The decision, whether a plant food is novel (or not), has to emerge from the discussion points listed above as a societal decision taking into account the history and traditions of the country and region. The management perspective is therefore essential for the decision on the novelty of foods derived from plants. The history of (safe) consumption is already recognised as an important part of the background information necessary for this decision in EU, Canada and Australia New Zealand.

The Nordic working group has adopted the Australian/New Zealand approach to divide foods in traditional foods and non-traditional foods and to let a subset of the latter be considered novel foods if 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, the levels of undesirable substances in the product, the known potential for adverse effects in humans, the traditional preparation and cooking methods, or the patterns and levels of consumption of the product ([Knudsen et al., 2005](#)).

The Nordic working group also looked at the possibilities for developing a more generic approach to the process of defining novelty based upon the information regarding the plant sources used for the global food supply ([Knudsen et al., 2005](#)). This approach should be based upon the information from FAO about the worldwide production of different crop plants for food purposes, concluding that a very limited number of food plants meet 95% of the world's food energy needs from plants. Along the same line of thinking the EU research project NETTOX identified 307 food plants in the human diet in the 15 Member States of the European Community in 1998. The idea with the NETTOX list was to include as a start at least all major plants (and mushrooms) used for human consumption in Europe. Since IPGRI at the same time has identified more than 7000 plant species as potential food sources, this demonstrates the future potential for many human populations to be presented for non-traditional or novel plant foods in their area.

On this background the working group has developed the decision tree presented in [Fig. 1](#) with the aim to obtain a rational, logic and simple device for the identification of novel plant foods on a global, regional or local scale ([Knudsen et al., 2005](#)). The decision tree is developed to be used for foods from plants, including plant species, varieties and sub-varieties of plant species.

The following definitions have been applied in this decision tree for the determination of the novelty of food from conventional plants:

- **Plant foods:** Products used as food with a plurality of chemical constituents in a complex, holistic interplay

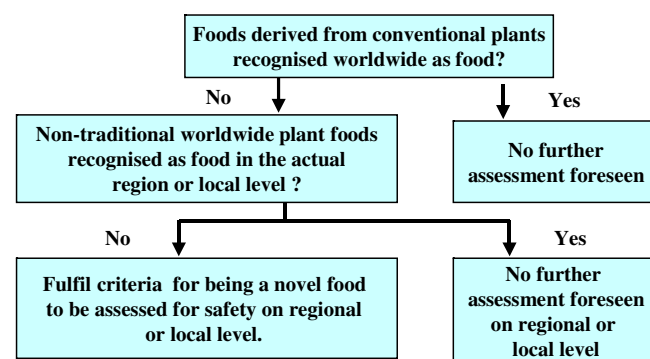


Fig. 1. Decision tree approach for the identification of novel foods from conventional plants for safety assessment.

ranging from intact fruits and vegetables, over complex botanical products like flour and botanical extracts to oils, fibres and proteins. Distinct from pure chemicals with only one chemical entity as the building block.

- **Traditional foods:** Foods with a history of significant human consumption by the broad community for several generations as part of the ordinary diet and thereby generally recognised as safe at the global, regional or local level or by an ethnic group.
- **Non-traditional foods:** Foods with no history of significant human consumption by the broad community for several generations as part of the ordinary diet.
- **Novel foods:** Non-traditional foods for which there is insufficient knowledge in the broad community to ensure safe use, or which have characteristics that raise safety concerns due to composition, levels of undesirable substances, potential for adverse effects, traditional preparation and cooking, and patterns and levels of consumption.
- **Global list of traditional food plants:** A list of plants, identifiable by name and delivering specified plant material used for traditional foods at the global level.
- **Regional lists of traditional food plants:** A set of lists with plants delivering plant material used for traditional foods at the regional level covered by the individual list. “The Region” may be defined on the basis of the five regional dietary patterns described by WHO/FAO in GEMS (WHO, 2003): Middle Eastern, Far Eastern, African, Latin American and European (incl. Australia, Canada and the USA), or as economical or regulatory entities like EU or Australia/New Zealand. When finalised the lists should cover all geographical regions of the world, thereby supplementing each other.
- **Local lists of traditional food plants:** Lists with plants delivering plant material used for traditional foods at the local level. “Local lists” could cover EU, or individual nations like Denmark and China, or an area with a human population of mixed ethnic origin within a region or nation.
- **Ethnobotanical lists of traditional food plants:** Individual lists with plants delivering plant material used for traditional foods by individual ethnical groups. “Ethnobotanical lists” are lists developed to cover well-established plant food eating habits of a defined ethnic entity, e.g. aboriginals in Australia.

At the top of the Decision Tree in Fig. 1 plant foods are divided into the traditional worldwide plant foods and plant foods with no worldwide tradition. Traditional plant foods at this level of the decision tree need no further assessment of their safety. They are by definition intended to be accepted regionally and locally all over the world.

Non-traditional plant foods from the global level of the Decision Tree should then at the regional and local level be subdivided further into plant foods regionally and/or locally accepted as food and those not regionally and/or locally recognised as food. If a non-traditional plant food

from the global level is accepted as food at the regional level, it implies that it is accepted also locally, while a locally accepted food still may be considered novel at the higher regional level.

For the purpose of understanding and evaluating the decision tree approach suggested in Fig. 1, two lists of plants have been prepared as preliminary examples. The first one appearing in Annex 2 is a modified FAO-list of plants (FAOSTAT, 2004) with non-food items excluded. These plants are worldwide recognised as food sources and can thus make the first prototype for a *global list*. It should be mentioned, however, that for some plants on the FAO list it may not be clear whether they should be defined as food or not, like areca nuts (betel) (*Areca catechu* L.), that may not be used in some parts of the world while in others it may be considered as a traditional stimulant or medicine. For risk management purposes, therefore, a final global list of foods will need an international acceptance by risk managers.

The second list in Annex 3 is the prototype for a *regional or local list* consisting of plants with no worldwide recognition as sources for major food items. Basically such a regional or local list as the one in Annex 3 can be generated from a list of all food plants used in that area by subtracting the plants from the modified FAO list in Annex 2. The list in Annex 3 is made from the NETTOX list (NETTOX, 1998) by taking out the Annex 2 plants and represents thus the first prototype of a regional/local list covering food plants used in the EU in 1997 besides the ones already listed in Annex 2. Altogether the food plants on the *global list* and the *regional list* make up the total number of food plant traditionally used in that region.

The use of lists such as FAO list (Annex 2) as a global list and the modified NETTOX list (Annex 3) as a regional or local list in the Decision Tree Approach in Fig. 1 immediately identifies lack of precision. The FAO list used as the basis for the global list in Annex 2 is based on production figures and uses common names for the plant items. Although most plants like maize, rye, oat, brazil nut, tomato, eggplant and carrot include only one species, many items on the list include more than one plant species. Examples of items, which include a group of plants, are wheat (include species of common wheat, durum wheat and spelt), millets (seven or more different botanical small-grained cereal species) and beans (different *Phaseolus* and *Vigna* species). Therefore the consumption of some of the listed plant species may only be very minor and they may have limited history of use. The NETTOX list in Annex 3 is on the other hand based upon single plant species with scientific (Latin) names but it is still not comprehensive in covering all the known plant foods on the market in EU.

However, the lists give a good starting point for identification and evaluation of fruits and vegetables as sources for novel foods at the global, regional and local level of regulation. If the food plant lists are to be more useful or fitted for the evaluation of history of use, such lists should

be based on individual plant species with their scientific names and include information on the plant part(s) normally used for consumption. Recommendations for preparation and cooking procedures would also be of value at this stage. For some plants even specification of the specific plant variety may be of importance since for some species the varieties may differ a lot in relation to safe use (glycoalkaloids in potatoes, lectins in beans).

Foods derived from the plants included in the lists of Annexes 2 and 3 will as a rule-of-thumb not be considered novel food in the EU region unless plant parts not usually used as sources for food are used in the production of food. New food items derived from non-hitherto-consumed parts of traditional food plants will need further assessment at the scientific level using the scientific tools and the scientific information described later. In this way the lists in Annexes 2 and 3 also could be the managerial tool for determining if a plant food is considered novel or not.

It is possible to make a list of plants which potentially may deliver novel food from an EU point of view by comparing the EU list with other regional, local or ethnobotanical lists, e.g. the IPGRI inventory of native American fruits covering 1128 species, 285 genera and 66 families (IPGRI, 2005).

4.2. Establishment of a risk assessment policy for novel plant foods

The individual, scientific safety assessment needs to be preceded by a general decision on a risk assessment policy in order to make the outcome of the safety assessment accepted as the basis for the management decision regarding either the unconditional acceptance of the novel food item on the market, its limited acceptance on the market, or its rejection from the market.

The establishment of a risk assessment policy for novel plant foods begins with science where scientists in the field identify the nature and extent of safety data needed to obtain different degrees of scientific sensitivity and specificity of the risk assessments and thereby predictability/reliability of their risk assessments. Afterwards it is a management task to make a policy decision regarding the data set needed for a premarket assessment.

The risk profile should describe the botanical identity of the source plant and the plant part(s) intended for food use, and identify the gaps in readily available common and scientific knowledge which may prevent the immediate establishment of safe use, taking into account the composition or structure of the plant food, the levels of undesirable substances, the known potential for adverse effects in humans, the traditional preparation and cooking methods, and the patterns and levels of consumption.

Many novel plant foods will have no predetermined specific health target for the safety assessment, eliminating the possibility to immediately focus the whole safety assessment on one or few identified or known chemical targets or biological effects.

The group, therefore, discussed the kind of strategy to recommend for the characterisation of safety of the novel plant food. The proposed scheme is outlined in Fig. 2. It builds upon the traditional elements in a safety assessment: hazard identification at the top (“Data from the Risk Profile”), the column at the right leading to characterisation of hazard, the column at the left leading to the exposure characterisation, and the combined use of the conclusions from those two columns to formulate the final risk characterisation, including recommendations for further actions to take. The full drawn arrows in Fig. 2 indicate the different paths, the case-by-case safety assessment can take depending on the case, while the dotted arrow underlines the iterative element in the assessment process, where new information and additional requests may make the process start over again.

The starting point in the hazard characterisation process in the right column is the history of use, including human experiences regarding safety and nutritional aspects. Depending on the scientific quality of historical data a scientific characterisation of hazards can be performed immediately, or the process has to go through a chemical analytical stage, through wholesomeness testing *in vivo*/*in vitro*, and/or through production of human epidemiological data, as indicated in Fig. 2.

The detailed approach of the safety assessment may differ between novel food items derived from plants already on the *global list* for recognised food plants, novel food from plants on *regional or local or ethnobotanical list(s)*, or novel food from plants that are not on any of the lists. For novel foods derived from not hitherto used tissues of plants already on the global, regional or local lists, there may be many sources of information regarding the presence of toxic or antinutritional substances in these food plants which may facilitate or direct the safety assessment. For other plants not hitherto used as food to an extent that can justify their being on any of the regional lists, local lists or ethnobotanical lists, only limited information may be available to

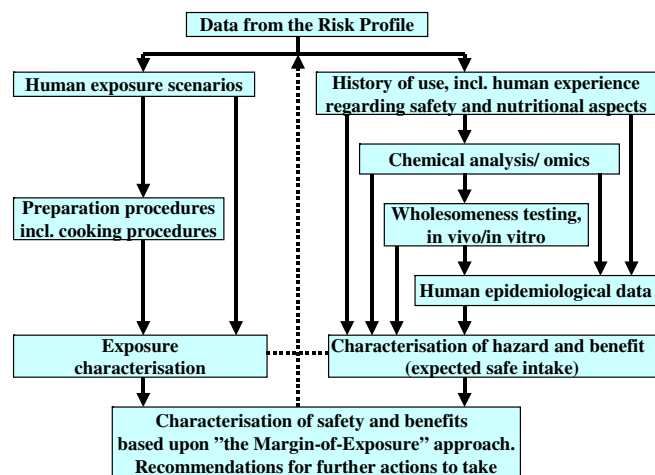


Fig. 2. Safety assessment of novel plant foods and novel plant food ingredients.

guide the first steps in the safety assessment. Here the history of previous use may be of great importance.

The Nordic working group discussed whether it is possible to recommend a defined set of data requirements as a prerequisite for a safety assessment. An alternative could be a reiterated assessment after each step following a hierarchical data generation. In the end the working group recommended a case-by-case approach as illustrated in Fig. 2 with the arrows pointing at the alternative pathways in the iterative safety assessment process. The information needed to conclude the premarket assessment may thus in some cases be the information from all the boxes in Fig. 2, in other cases just information from some of them depending on the nature of the individual novel food. Typically the hazard characterisation will be concluded through a “weight-of-evidence” procedure, where both qualitative and quantitative aspects of the data findings count.

5. Different tools applicable for premarket analysis

The aim of the premarket assessment of novel foods is to demonstrate that the novel food is as safe as traditional counterparts or food items to be replaced in the diet by the introduction of this novel food and as such does not introduce any additional or new risks to the health of the consumer (Howlett et al., 2003; Cellini et al., 2004).

Most of the foods commonly eaten have never been investigated systematically with respect to their impact on consumer health. Generally, they are considered as safe unless a significant risk has been identified in humans. However, it should be emphasised that the absence of evidence of toxicity is not the same as evidence of safety. Without specific investigations, only acute and severe adverse effects are likely to be identified. The demonstration of the safety of a food as part of the overall diet requires specific intake information together with data on health effects. Although case reports, epidemiological observations, and/or experimental human studies may exist for a restricted number of foods (e.g. coffee), this type of information related to human health is lacking for most food plants (Schilter et al., 2003).

The nature and extent of the data required to assess the potential risk associated with a novel food depends largely on the nature of the novel food. Obviously, a plant that has never been consumed before will be a greater challenge for the risk assessor than a novel food very much resembling a traditional food with a long experience of consumption without health problems.

5.1. Characterisation of a plant food

The precise specification of the plant food both from a botanical and chemical point of view is the most important template for trustworthy risk assessment.

5.1.1. Botanical characterisation

Taxonomic identity of the plant should be given according to internationally accepted principles, including com-

plete scientific name (family name, genus, species, author name, subspecies, cultivar/breeding line) and common name (König et al., 2004).

With regard to fruits and vegetables and their products, which have no history of use to a significant degree within a region, a complete scientific taxonomic identification will considerably speed up the identification of possible close relatives to the plant in question, thereby facilitating a prediction of chemical composition of the plant food and an assessment of its safety and nutritional aspects.

One example to demonstrate the necessity of giving extensive information about the identity of a plant is that well-known cabbages, whether red cabbage, cauliflower, Brussels sprouts or broccoli, all belong to the same species *Brassica oleracea*. One group of chemical constituents of Brassicas, the glucosinolates, has been claimed to give rise to adverse as well as health promoting effects. The glucosinolate composition and not least their concentrations vary considerably from one cultivar to the other. Also within cultivars the level of glucosinolates produced may differ, e.g. influenced by several environmental factors, including growing conditions.

Another example would be a species, where ‘ecotypes’ occur, and these differ with regard to chemical composition. Although not being a likely candidate as food plant, the woody nightshade (*Solanum dulcamara* L.) could stand as an example. Depending on where in Europe samples of this species are collected the particular composition of glycoalkaloids change (Andersson, 1999).

It is also important to give information about which part of the plant is intended for food use. The chemical composition often varies substantially between different plant parts. For many food plants only a single plant part is consumed and only that part of the plant is considered safe to eat, e.g. tubers of the potato plant (*Solanum tuberosum* L.).

Additional information to aid the risk assessment could be whether the novel food is collected from nature or the plant is bred in a specific way. If agricultural practices are important, these should be adequately described.

The importance of correct botanical characterisation is underlined by the problems of mis-identification, e.g. by the intoxication caused by using Japanese star anise or bastard anise (*Illicium anisatum* L.) instead of the normally used spice Chinese anise (*Illicium verum* Hook.f.) in a herbal tea in the Netherlands (Johanns et al., 2002).

5.1.2. Chemical characterisation

In most cases each cultivar is delivering one kind of food, a vegetable, a fruit, a grain etc., and this plant food is nutritionally characterised by its content of macronutrients, such as proteins, fats, carbohydrates and fibres, and micronutrients like vitamins and minerals. The chemical characterisation may be further specified by information on the content of specific proteins, individual amino acids, fraction of oils, individual fatty acids, simple and complex carbohydrate, individual sugars and fibres.

The chemical characterisation of the plant food is most perfectly performed in the OECD Consensus Documents, specifically developed to characterise individual plant food items (OECD, 2002). These documents present an excellent background material for the development of the plant food lists recommended in this paper.

Seen from a plant perspective the chemical constituents of plants can arbitrarily be divided into two classes according to function. The *primary* plant metabolites are forming building structures and internal transport systems in the plants or contributing to the energy production in the plants. The *secondary* plant metabolites are not essential to the basic metabolism of plants. They are formed from the primary metabolites and occur in many different chemical forms often specific to a single species or a group of related species, and sometimes as a response to an inducer, e.g. a specific environmental condition or an infection, or as a response to attacking insects (Hegarty et al., 2001). Because of these roles of primary and secondary metabolites in the plants, primary metabolites are most likely to have nutritional importance in the consumer, whereas secondary metabolites are relatively more likely to give rise to adverse effects and to the flavours.

An example of a systematic evaluation of consumed plants is the study of Hegarty and co-workers (2001). These investigators undertook a study of secondary metabolites in Australian bushfoods, assuming these constituents have the strongest potential for toxicity due to the Australian diet. They screened for the presence/absence of alkaloids, cyanogens, oxalates and saponins in fresh and frozen samples of the major bushfood species, and determined the amounts of these compounds present in the foods. The aim of the study was to broaden the knowledge about the chemistry of native plant foods, describe their history of use in the traditional communities, explore the potential to use these foods as a resource for commercial exploration, as well as to indicate areas where further research is required.

It is obvious that knowledge is required on the types and amounts of nutrients, vitamins, and minerals present in a novel food. In addition information is needed on the presence of potential anti-nutrients and natural toxicants. It might also be necessary to identify if the plant is particularly prone to become invaded by minerals and environmental pollutants, as for example selenium and heavy metals, respectively. If knowledge is scarce about the plant species in question, it has been suggested that information on the presence of natural toxins and allergens in related plant species may be used as guidance for identification of classes of compounds most likely to occur in the investigated species (Howlett et al., 2003). If concern with respect to safety of a novel fruit or vegetable has been raised on such a basis, chemical analyses should form the core information on which to base the decision on the kind of further action to take, e.g. performance of toxicological investigations.

A situation that might pertain particularly often to novel foods, is that chemical analytical standards for spe-

cific compounds are not available and, therefore, require chemical synthesis, which may substantially increase the cost of the analytical exercise but may also produce material required for subsequent toxicity testing. If an extensive chemical analysis does not identify compounds that would trigger additional studies, this type of information may be the only data that are needed for the hazard characterisation (See Fig. 2). An example could be a novel food made from a plant part not previously consumed from an otherwise well established food plant.

5.2. History of use as food

Describing the *history of use as food* of a novel plant food is an important introductory part of the safety assessment. For a specific region the *history of use as food* of fruits and vegetables will vary from plant foods that are well known and with a long history of use and no reported negative effects, plant foods that only occasionally have been eaten in that region or other regions before, to plant foods that never have been consumed in any region before.

Therefore the novelty of food plants in a specified geographical region is determined by the *lack* of an established documented *history of use as food* in that region. For the determination of novelty in this respect the lists discussed in Section 4.1 are of crucial importance. These positive lists with plants having a history of use as food can only be established based upon global, regional, and local efforts resulting in the establishment of the lists documenting the claim that the particular plant food with its botanical and chemical identity has a *history of use as food* in that particular regional or local environment. Every list is to be defined by the geographical area it covers. When a plant food is presented as novel in a region, it may be followed by the information on *history of use as food* in another region taken from the positive list of that region.

The term *history of use as food* covers a *description* of the use in different defined geographical areas with information on intake levels, intake patterns, years on the market, different preparation and handling methods and impact on human health, while the term *history of safe use as food* includes a scientific evaluation of the information and implies that this evaluation can lead to a *conclusion* about its safe use (Constable et al., 2007).

The term *history of safe use as food* may be defined as follows:

“History of safe use” for a food is a term for the qualified presumption of safety, where there is evidence for its safety from compositional data and from experience as an ongoing part of the diet for a number of generations in a large, genetically diverse population. This presumption is for a certain context of use (conditions of use, such as part of the plant used and required processing) and allows for minor population predispositions such as intolerance and allergenicity (S. Page, WHO: personal communication 2005).

The assessments of the history of safe use of novel plant foods imply the assessment of scientific data. Since the case-by-case packages are determined by the variety of historical data available, the assessments will need to build upon a broad scientific experience of the expert panel. The principles laid down in the U.S. “Generally Recognised As Safe” (GRAS) concept, which defines a safe substance as “a substance that is generally recognised by experts (qualified by training and experience to evaluate the safety of a substance) to be safe (through scientific procedures or history of common use) under the condition of its use”, may be a good basis for creation of a similar GRAS concept for novel plant foods, where the available historical data is assessed (Knudsen and Ovesen, 1995).

Instead of history of use the term “traditional use” has been suggested. The concept “traditional use” is based upon knowledge and experience in the heritage of a population/culture (but may have very limited scientific documentation), while well-established use in general is based on traditional use supplemented with available scientific data. Traditional use may provide information on acute toxicity but is unlikely to provide information on chronic toxicity. Information on traditional use will also be influenced by the availability of food, the general health of a particular population, and the available health care and health monitoring facilities (Bast et al., 2002).

The safe use of plant foods sometimes depends on special pre-treatment established by “custom and practice” that render it palatable and safe (König et al., 2004). An example here is the necessary inactivation of phytohaemagglutinin in red kidney beans by cooking (CFSAN, 1992).

In the description of *history of use* it is important to remember the context in which the *history of use* is developed, namely on the background of the traditional dietary pattern in the region. From a regulatory point of view, a region would appropriately be defined by national or community borders, e.g. EU. It could also be defined as done by WHO in the *Global Environment Monitoring System - Food Contamination Monitoring and Assessment Programme (GEMS/Food)* (WHO, 2003). Here the global dietary patterns have been divided in five regional dietary patterns, namely the Middle Eastern, the Far Eastern, the African, the Latin American, and the European pattern. The “European” diet includes non-European countries with European-type diets, such as Australia, Canada and the USA. The GEMS/Food document lists about 250 raw and semi-processed food items of both plant and animal origin with average per capita food consumption for each in all five regions. Furthermore by using a cluster analysis approach, thirteen GEMS/Food Consumption Cluster Diets have been produced based on FAO Food Balance Sheets (<http://www.who.int/foodsafety/chem/gems/en/print.html>). Although these diets have been developed with the purpose to predict the dietary exposure to radio-nuclear contamination and pesticides residues, these GEMS diets could equally be used to define regions and to develop regional positive lists for plant foods with their

individual *history of use*, consumption pattern or expected intake level.

As far as possible, published data should be collected and evaluated for their quality and usefulness at the regional or local level, because the national/regional literature in national/regional languages may contain a wealth of information not accessible via global data banks. It is extremely important if such data can be inserted in databases developed to support regional or local positive lists for the food plants. The pre-existence of food plant lists in a region will facilitate producers to introduce such a plant food in another region, where it appears to be considered a novel food. Other sources, including data collection on site, may also be helpful to provide facts and/or guidance for the assessment (Howlett et al., 2003).

Also of importance when addressing the *history of use* of a plant food is to take into consideration that traditional breeding constantly may bring new varieties of a food plant to the market. The food derived from such varieties may vary a lot in composition compared to previous used varieties, but still the information covering the *history of use* for the older varieties will greatly facilitate the process of establishing a *history of safe use*.

Information on local health claims or perception of positive or negative health effects connected to the plant food may be of great help in assessing its safety. A plant that previously has been used for medicinal purposes or has a reputation as a folk remedy in various parts of the world, whether or not consumed as food (or botanical products/extracts covered by the definition of food), may have some physiological effects on health that need to be considered not only as beneficial but also from a safety point of view (Schilter et al., 2003).

Still most of the fruits and vegetables considered novel in one region might be well known with a *history of use*, even *safe use*, in another region. On this background the concept of positive lists for *global, regional, local and ethnobotanical* food plants is introduced in Section 4.1.

Such positive lists shall describe the individual plant food and identify the source plant. Most appropriate, the lists take their starting point in the name of the food plant, which then is subdivided into the individual plant foods derived from that plant. The description shall include the plant names and synonyms for exact identification, specific plant part(s) analysed and the analytical results, sample size, year of sampling. It should also include description of maturity, cultivar, growing conditions, storage conditions, usual processing and food preparation procedures, country of origin, region of origin, season of harvesting. The compositional data of the edible parts shall contain information regarding macro- and micronutrients, inherent toxicants and antinutrients. The individual plant monograph should also contain references to the scientific literature covering nutritional and toxicological data and health promotional appraisal.

When such lists and preferentially also databases with the above-mentioned information have been established

world-wide for each region or each national or economical community, which fit the best, everyone can take advantage of the lists for the assessment first of the novelty, and later of the safety of the different plant foods. The lists are foreseen to facilitate the global trade with plant foods, and the introduction at the regional and local level of regionally novel plant foods, which have a history of safe use in other regions.

5.3. Animal studies in the safety testing of novel plant foods

Toxicological studies in experimental animals have historically been developed for assessing the toxicity of discrete chemical substances. Experimental studies on rodents are indispensable in the testing battery for safety assessment of compounds such as food additives, pesticides, pharmaceuticals and industrial chemicals (WHO, 1987, 1999). Therefore, there are internationally accepted standard approaches for such tests (OECD, 1995). In most cases, the test substance is well characterised, of known purity, of no nutritional value, and human exposure is generally low. It is therefore relatively straightforward to feed such compounds to animals at a range of doses, some several orders of magnitude greater than the expected human exposure levels in order to identify any potential adverse effects of importance to humans. When an adverse non-cancer effect has been identified, the animal study allows the establishment of the highest exposure level at which no overt toxicity occur, the so-called *No-Observed-Adverse-Effect-Level* or NOAEL (WHO, 1987, 1999; ACNFP, 1999; Howlett et al., 2003). The NOAEL is subsequently used to calculate the safe level of intake, the *Acceptable-Daily-Intake* or ADI, by dividing the value for the NOAEL with a safety factor, most often one hundred.

In contrast, novel foods from plants are usually complex mixtures of various compounds, many with the potential to vary in concentration in the individual plant food depending on the plant variety used and the growth conditions. Due to the bulky nature of the food itself and the effect on satiety whole foods can only be fed to animals at lower multiples of the amounts that may be present in the human diet, maximum 100–200 times. Toxic compounds embedded in the novel food may therefore never reach a level in animal studies at which the toxic potential of a constituent is revealed. In addition, a key factor to consider in conducting animal studies on foods is the nutritional composition of the feed. Increasing the fraction of the tested food in the feed above a particular level may distort the nutritional balance of the diet, and may induce adverse effects which are not related directly to the material itself but to induced nutritional imbalance. Picking up any potential adverse effects and relating these conclusively to an individual characteristic of the food can therefore be extremely difficult, unless the studies are well planned and designed with the animal diets well adjusted (ACNFP, 1999; Dybing et al., 2002; Knudsen and Poulsen, 2007). A sensitive and specific approach is to combine the testing of

individual, pivotal compound(s) identified in the novel food with the testing of the whole food, if necessary spiked with the pivotal compound(s), in separate studies (Knudsen and Poulsen, 2007).

The objective of any toxicity testing programmes for novel foods should contribute to the identification of a potential hazard, its dose-response relationship, and the establishment of a reasonable certainty that no harm will result from its intended use as food (Howlett et al., 2003). If applicable, the safety of the novel product should always be compared with the safety of the foods it will replace. Selecting the battery of tests required to establish the safety of novel foods has to be done case-by-case, not least because of the huge variation possible in the extent of novelty of the novel food as compared to traditional foods. Therefore, it is not possible to set 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 a particular novel food the guiding principle 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. The task to identify suitable toxicity studies may sometimes be very difficult. If the toxicity studies are not designed and undertaken with clear and achievable objectives in mind, it is unlikely that they will contribute positively to the safety assessment (Howlett et al., 2003).

Considerations regarding the need for doing animal toxicity studies on the novel plant food in the premarket situation will most likely focus on two main issues: potential toxicity of inherent chemical entities of unknown toxicity identified in the novel food and establishment of the safety of the whole novel food in a repeated dose feeding study in rodents or pigs.

The toxicity testing of distinct chemical entities of course depends upon the availability of those chemicals in isolated form to be mixed in the animal feed. Such a testing procedure will normally start with an acute toxicity testing followed by a 28-day rodent feeding study (Knudsen and Poulsen, 2007). In practice, if toxicokinetic studies are to be performed, they will only be possible for defined chemicals and simple mixtures and are not useful for complete foods, unless it focuses on a defined constituent (Howlett et al., 2003).

Experiences from the testing of chemicals have demonstrated that well-designed 90-days rodent feeding studies with measurement of biomarkers for growth and behaviour as well as measurement of biochemical and macro- and microscopic biomarkers are of sufficient duration to give rise to biological alerts for most chemicals that would also give toxicological effects in chronic exposure studies (Munro et al., 1999), or lead to immunotoxicity, neurotoxicity and reprotoxicity (Kroes et al., 2000, 2004). Therefore in cases where a repeated dose animal feeding study on the novel plant food is considered essential to provide information on the absence of potential adverse effects, the 90-day

subchronic toxicity study in the rat is suggested as the first choice for a sentinel study to assess the safety or to determine the need for further studies of the novel plant food (Knudsen and Poulsen, 2007).

The scope of the animal toxicity study should normally be to include the full range of experimental parameters appropriate for this type of protocol (Howlett et al., 2003). To ensure the scientific validity of such a rodent feeding study, great attention and focus should be devoted to the design of the diet embedding the novel food (Knudsen and Poulsen, 2007). It is suggested that a 90-day study in pigs may provide a better biological filter in the safeguard of human health due to the more humanlike design of the gastrointestinal tract in this animal (S. Page, WHO, personal communication).

A main challenge in the optimal design of repeated dose animal feeding studies for the safety assessment is the identification of appropriate comparators to the novel foods for the control group. In some cases the choice is straightforward with the selection of fruits or vegetables closely related to the novel ones. In other cases the comparator may be the food item, which is going to be replaced in the human diet by the novel food. Finally in some cases no comparator can be identified and the novel food has to be assessed on its own. This may be the case for many novel foods where it is not clear what specific food item or group of foods it will replace.

The levels of the novel food to be incorporated in the animal diet may either be one level, namely the highest level tolerated (calculated from a preceding short-term study and the compositional data) when there is a good comparator, or two levels, namely comparable to expected human intake and the highest level tolerated, when there is no obvious comparator. In the first case the good comparator allows direct calculation of the Margin-of-Exposure between the predicted intake of the novel plant food and the known safe intake of the comparator, while the calculation in the second case depends upon the existence of experimental data illustrating that the expected human intake is safe.

If the repeated dose feeding study becomes the pivotal study for the hazard characterisation, the dose level used will be the one to compare with the expected human intake established in the exposure characterisation. The Margin-of-Exposure established in this manner then becomes the basis for the risk characterisation.

5.4. Testing of novel foods *in vitro* for toxicity and mutagenicity

In vitro methods are relatively cheap and have a high throughput. However, results from *in vitro* tests may only be indicative of toxic effects as these test systems rely on reconstituted purified proteins or cell components, or cell lines cultured artificially. They are only to a limited extent representative of the functioning of such cell components or cells in living organisms. *In vivo* tests are therefore

required to confirm observations on absence or presence of toxic activity from *in vitro* tests (König et al., 2004).

In vitro genotoxicity studies will often be useful only for defined chemicals or simple mixtures. In general, the testing of whole food extracts in genotoxicity studies is inappropriate as the experimental condition is likely to result in artefacts making interpretation difficult. Based on knowledge from the literature, however, single components of complex novel foods may be identified and could be investigated in such studies. For complex foods, some assurance of the absence of a potential for genotoxicity may be gained by appropriate “directed” investigations of bone marrow cells or peripheral lymphocytes undertaken as an additional complementary element of repeated feeding studies in rodents (Howlett et al., 2003).

In the context of novel foods, it should be recognised that many botanical materials contain naturally occurring compounds that may test positive in genotoxicity tests *in vitro*. Although such results are indicative of that botanical material having a genotoxic effect, this might not necessarily be the case. Most compounds that have turned out positive in *in vitro* tests have been negative in *in vivo* assays performed to confirm that mutations are induced also during this condition (Bast et al., 2002). Positive *in vitro* results should, however, be investigated with *in vivo* studies, unless the positive result can be attributed to an identified component known to be safe *in vivo* (EMA, 1999).

5.5. Test of novel foods for allergenicity

Food allergies are adverse reactions to otherwise harmless food or food components characterised by a response of the body's immune system to specific protein(s) in foods (FAO/WHO, 2001). This response could be looked upon as abnormal, as only a minor fraction of the population (with disposition) would react in this way to the protein. The prevalence of food allergy in the Western world is up to 8% in children but only 2% in adults (Sampson and Burks, 1996). Although food allergy is 3.6 times more frequent in children compared to adults it is confirmed that there is a preponderance of severe cases in adults (Morisset et al., 2003).

The most common type of food allergy is mediated by allergen-specific immunoglobulin E (IgE) antibodies. IgE-mediated reactions are known as immediate hypersensitivity reactions because symptoms occur within minutes to a few hours after ingestion of the offending food. In IgE-mediated food allergies, exposure to a specific food and its proteins in addition to reacting with antibodies elicits further development of food allergen-specific IgE antibodies.

True food allergies also encompass delayed hypersensitivity reactions whose mechanisms are less clear. Such reactions include cell-mediated reactions that involve sensitised lymphocytes in tissues rather than antibodies. In cell-mediated reactions, the onset of symptoms occurs more than 8 hours after ingestion of the offending food (FAO/WHO, 2001).

It is not realistic to strive for absolute absence of risk for allergenicity. Instead the general point of view is, that the aim should be to ensure that a novel food is at least as safe as its traditional counterpart, the food item it will substitute in the diet. With this in mind, the objective with regard to allergenicity is to establish whether the novel food has an increased potential to induce sensitisation or to elicit allergic reactions than the food product it is compared to (Kimber and Dearman, 2002). Recommendation for labelling should be part of the consideration for reducing the risk.

Food allergies are caused by a wide variety of foods of which the most important plant products are peanuts, soybeans, wheat and tree nuts. Allergic reactions to fresh fruits and vegetables may be expressed as an oral allergy syndrome (OAS). Symptoms of OAS are typically mild, and mostly confined to the oropharyngeal region. Some of the most significant allergens from foods giving rise to OAS are unstable to heating and digestion. However, OAS in patients allergic to fruits and vegetables may, in some individuals, be followed by a systemic reaction (FAO/WHO, 2001).

Novel food items may give rise to cross-reactivity to well-known food or pollen allergens. Such cross-reactions between new and well-known allergens can be studied by various methods: serological methods, skin prick tests, or by open challenge or double blind placebo controlled food challenge of allergic patients as was done with the nangai nut in the studies by Sten et al. (2002) and Frémont et al. (2001).

In the rare cases when the amino acid sequence of proteins in novel foods are known, these sequences could be tested by bioinformatic methods to predict whether the protein is likely to be an allergen or not (Codex Alimentarius, 2004). As none of the test methods available today is able to predict whether a protein is an allergen or not in the absence of the amino acid sequence, there is a growing consensus that an appropriate validated animal model for characterisation of allergenic potential is needed (FAO/WHO, 2001; König et al., 2004). At present animal models for predicting and characterising (protein) allergenicity are based upon assessment of induced antibody responses and/or the frequency of responders in the test groups. A continued research into the immunobiology of protein allergy with particular emphasis on the identification of molecular markers that can be used to distinguish protein allergens from non-sensitising proteins is required (König et al., 2004).

5.6. New “omics” methods

Although many issues remain to be resolved and significant challenges lie ahead, it is expected that information obtained from genomics, transcriptomics, proteomics, and in particular metabolomics will be extremely useful in the identification, characterisation and profiling of the novel fruits and vegetables as well as the plant as the source for the novel food.

It can also be predicted that particularly the outcome from metabolomic studies will have a significant impact on the case-by-case approach to be taken in toxicological assessment procedure in the future. One can predict that the information gathered from experiments using these technologies will form the basis for improved methods to assess the impact of chemicals on human health (Eisenbrand et al., 2002) but this is an issue with implications much broader than just safety testing of novel plant foods.

5.7. Human data

Human experience, but normally not formal human scientific studies, is an essential part of the data collection in the *history of use*. The human experience on the intake of a certain food in a region different from the one, which has deemed the food to be a novel food, is normally just an empirical observation that the food in question has been eaten in this and that way for generations in that region. It will normally be coupled with information on how it is prepared, how much is eaten, and whether the food in question has had any special claims linked to it. This kind of information is not following the rules for the performance of scientific studies.

There is no doubt that clinical studies in humans as well as epidemiological data from retrospective and prospective human studies are likely to achieve a much greater role in assessment of the safety of novel foods than in other areas of safety testing. Provided the *in vivo* animal studies demonstrate no adverse effects, human studies should be considered in order to confirm the absence of metabolic and physiological disturbances. A greater emphasis could be placed on availability of toxicokinetic studies to complement animal data. Additional mechanistic studies may be appropriate to investigate unexpected adverse effects.

Human studies may also be used to examine bioavailability or human metabolism when the safety of a compound is established e.g. in traditional toxicological studies. For novel plant foods already eaten to a significant degree by humans somewhere, there will be no ethical constraints about performing the relevant human studies in such places.

Whether specific subgroups of a population might be more *sensitive* to a potential hazard associated with a novel food might be studied in more details. More *susceptible subgroups* of a healthy population to certain risks may include infants, pregnant women, nursing mothers, and possibly the elderly. In many cases such studies can be performed without ethical concerns in regions where the food in question already is an accepted component of the diet and therefore not considered novel.

Studies in humans should not form a routine requirement for the premarket safety assessment but when they are available, they can contribute to it by providing confirmation of the absence of adverse effects. Population studies carried out post-launch in the target group of the general population (i.e. after the satisfactory completion of a safety

assessment) may be helpful in providing confirmation of anticipated usage patterns and exposure levels.

5.8. Nutritional aspects

An evaluation of the nutritional characteristics of a novel food is an important 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. A basis for this evaluation may be provided by the information embedded in the *history of use* or it may be a combination of analytical data, recommendations intended for the marketing of the novel food and specifically designed human studies (see the section above).

Key components of novel foods are in most cases nutrients in the particular food that may have a substantial nutritional impact on the consumer. These constituents may be macro-nutrients (fats, proteins, carbohydrates) or micro-nutrients (minerals and vitamins). Novel foods may also contain anti-nutrients that inhibit or block pathways in the human metabolism, or impair digestion. Anti-nutrients may reduce nutrient utilisation, typically proteins, vitamins, or minerals, thereby decreasing the nutritive value of foods (König et al., 2004).

5.9. Exposure assessment

The exposure assessment of novel fruits and vegetables (as of any other novel food) should be undertaken to enable calculation of the Margin-of-Exposure for users under the intended conditions of use.

The intended or anticipated use of the novel fruit or vegetable will provide information of absolute necessity for the assessment of whether that use is safe or may constitute a risk to the consumer. It is of great importance for the outcome of the risk characterisation, whether the novel food is intended or anticipated to be consumed only a few times throughout a lifetime, or it is foreseen to be consumed in kilos per month. Often the sales arguments will tell if the novel food is mainly intended to preserve a good health in general or prevent specific chronic diseases in smaller dosages, is a new interesting spice for cooking, or is meant to replace a major traditional food component, and thereby indicating the volume to be sold. Whilst experience in the region, from which the novel fruit or vegetable originates, surely can provide helpful information, consumption patterns must be considered in the local context of the novel use proposed. A food traditionally consumed only at special occasions or exclusively in combination with another material may cause problems when consumed in larger quantities or in a different combination (Howlett et al., 2003).

The exposure assessment should also consider the appropriate ways of preparing and cooking the novel plant food. Some are to be eaten raw, some are to be milled to

flour and go through baking processes, some are to be peeled and cooked, dried and fried and some are to be extracted, treated with acids or bases, dried or fried. All these processes greatly influence the contents and digestive availability of inherent toxicants, macro- and micronutrients of the individual novel food as assessed in the hazard characterisation.

The primary objective of a food exposure assessment is to estimate the aggregated intake levels of the particular food or food constituent. This includes the determination of an estimated daily intake and the theoretical maximum daily per capita intake (König et al., 2004). Exposure assessments to specific foods may often lack precision because of a wide inter-individual variation in food consumption within and across different populations. In consequence, it is important to gather information on food consumption both at the population level (per capita intake) and at the individual level.

Furthermore, estimates should take into account variation amongst demographic subgroups of a population. Thus, it may be necessary to stratify dietary intake assessments of specific foods according to age, gender, socio-economic status, location, and ethnic origin depending on the outcome of the human studies on the novel food in question.

5.10. Risk characterisation and safety

The risk characterisation is based upon the outcome of the hazard characterisation and the exposure assessment. It assesses the safety and nutritional properties of the defined plant food characterised by its botanical origin and chemical composition. The Nordic working group recommends that the risk characterisation or – more correctly – the safety of the individual novel food is defined by its Margin-of-Exposure as calculated from the estimated daily safe intake divided by the likely human daily exposure (Knudsen et al., 2005). This value can then be used by the risk managers to guide the further decisions on the use of the novel plant food in the general food supply, and – if properly indicated at the food packaging – even by the individual consumer in order to guide his/her choice for a diet that meets the individual expectations and needs.

6. The necessity of a continued interactive exchange of concepts and ideas between management and science in this field

Plant foods that are traditional in one country or region may be novel in another country or region. The EU legislation makes it necessary to distinguish between the traditional plant foods used in the European community on one side and the novel plant foods on the other side because the novel plant foods according to the EU legislation need to go through a premarket assessment procedure. Since the EU legislation is pretty new, from 1997, the legal and scientific instruments for this process are not fully developed yet, and an interactive exchange of concepts

and ideas between management and science is urgently needed.

On that background this paper presents a proposal for a set of criteria for determining whether a plant food is traditional or novel and a proposal for an approach for the safety assessment of such plant foods with no or limited documented history of safe consumption as presented in the preceding sections.

During the development of this proposal a number of issues has underlined the need for an interactive process between science and management. There are many unique, still immature concepts in the assessment process, which need attention both from the scientific and managerial angle, and many new instruments still need to be developed and refined in science and management to make the process a success for all.

Although the regulations of novel foods in Canada, Australia/New Zealand and Europe make sense in their purpose to protect consumers against new foods with potential adverse effects, they all have the same inherent problem namely that in the practical execution of the legislation there is a fairly large room for the individual interpretation of the term *novel* and for the case-by-case decision, whether or not a plant food falls under the legislation.

From the historical experience it is clear that on one hand evidence exists that traditional plant food products might have adverse effects on human health, but on the other hand this problem seems to be manageable taking into account both the high number of traditional plant food products already on the market and the high number of novel plant food products already introduced. However, both due to the high speed by which new foods can be introduced on the market today and due to the expectations from the consumers regarding high quality of their food, the novel food regulation has been introduced. High quality in this respect encompasses acceptable assurances about safety (including informed potential for allergenicity) and well established nutritional properties of the novel plant food as part of the overall diet and qualified guidance on proper use of the novel plant food explaining preparation and cooking procedures, honouring its taste and flavour. An argument for not being too restrictive in the regulation of fruits and vegetables is the fact that in contrast to e.g. food additives these new products as long as they are in their original shape as fruits and vegetables usually are very visible for the consumers who can on the basis of the available information make an informed choice of their own.

Thus the regulation with an approval procedure of plants used for food presents a lot of challenges:

- The present regulation is based on terms like “novel food”, “history of safe use”, “insufficient knowledge”, “use in significant degree” etc. which in many cases are ill-defined and cause doubt about what should be approved and what should not.
- One basic problem with the sentence “regulation of novel food should be focusing on the food plants with insufficient knowledge to enable safe use” (formulation from the Australia/New Zealand guidelines) is that – although it makes sense from a scientific point of view – “insufficient knowledge” is not easily or not clearly defined. The authorities may easily end up in a situation, where every food plant and its individual food products may need to be evaluated by the authorities for their safety. Therefore one of the first tasks is to clarify the extent of the evaluation and the approval procedure needed from a management point of view.
- It is recommended that the evaluation and approval take the botanical plant species as a starting point rather than the trivial trade name for the food such as kiwi or beans. However, a plant species may encompass many different varieties that also need to be considered on their own.
- Many plant foods defined as novel in one region are already common in another region where each of them as an additional complication may be derived from different plant varieties due to years of traditional breeding. In considering the individual food item *history of use* and or its *history of safe use*, the size of the “window” for the assessment needs to be defined taking into account which varieties of the plant species, if not all, are to be covered by the approval process. The distinction between food from highly bred varieties of a plant species and foods from the wild relatives might be essential in defining the novelty and carrying out the safety assessment.
- Traditional breeding, including the use of techniques such as crossing and chemically or physically induced mutations combined with selection pressure, performed after an approval may lead to considerable changes in the composition of the food from the plant. Here it is important to define the “window” e.g. species and variety for which the approval is valid. In cases where certain key components such as toxic substances or vitamins have been identified in the safety assessment process, the term for the approval could be that the content of these key components in the food should not go beyond certain defined limits. For other cases the “window” for approval might be broader and give room for traditional breeding without any specified limits. In such cases the plant that is the source for the approved novel food can be regulated as any other traditional bred plant species used for food.
- *History of safe use* is an important criterion that may lead to approval of a food from a plant without further investigation. An attempt to define when *history of safe use* is fulfilled from a scientific view might easily end up with so high demands for scientific documentation that it is never readily obtainable even for well-known plant foods. Only few plant foods will have a *history of safe use* based on hard core scientific evidence such as epidemiological surveillance. Premarket approval of novel

plant foods may therefore need to apply a less scientific stringent procedure as in the Canadian regulation, where the case is qualified for assessment when *history of use* over several generations (i.e. 100 years) from other regions is evident, and adverse effects, preparation before consumption, cultivation or harvesting procedures, amounts likely to be consumed, and composition are reported.

- Some of the novel foods are intended for marketing with claims supposed to support their sale. In some cases the arguments are claims for maintaining a good health and/or preventing chronic diseases, in other cases the claims promise to cure diseases. In the latter situation the borderline to medicine may be rather thin, and therefore the intension to market such a product as a novel food rather than a medicine should be carefully considered as part of the approval procedure.

The new concepts and principles for risk assessment and risk management of novel plant foods introduced in this paper are:

- The two-step management procedure for establishing the novelty and for committing resources for safety assessment, and
- The use of a worldwide net of global, regional, local and ethnobotanical lists of food plants to guide the decision on novelty at the first step and to enable the safety assessment at the second step.

At the first step of the two-step management procedure the management establishes a *risk profile* with input from e.g. stakeholders, scientists in the field and consumer representatives taking into account the product itself, information on expected intake, *history of use*, values at risk, e.g. human health, other potential consequences, consumer perception of risks and benefits, and societal distribution of risks and benefits. The plant lists discussed below are an integrated element of the *history of use*. The discussions at this step should lead to the conclusion whether the plant food under consideration is traditional at the regional level or local level or a traditional ethnic food in the area, or actually a novel plant food, which needs a safety assessment according to the regulation.

At the second step of the 2-step management procedure the management decides on the general *risk assessment policy* for plant foods defined as novel foods at the first step. *Risk assessment policy* in this context means that the authorities based upon scientific advice and based upon an overall societal value judgment of pros et cons define the extent and sequence of the scientific data which should form the basic mandatory demand for data to be made available for the scientific risk assessors in the premarket assessment phase. It is the authorities (= the management) who need to take the societal responsibility for the decision on availability of data for the assessment, since the resources to create the data cannot be committed by the scientists anyway, and since the sci-

entific imagination of scientists for further request of scientific data is unlimited both due to their scientific wish to improve the assessment but also due to their professional desire to be able to take full scientific responsibility for the reliability of the safety assessment. In most cases the resources for creating the basic scientific data may need to come from the applicant. In the end the outcome of the risk assessments in terms of sensitivity, specificity, and the resulting predictability is totally dependent on the initially decided, managerial risk assessment policy.

For a smooth introduction of the novel fruits and vegetables from one region to another, the Nordic working group recommends to use the “*history of use*”-concept as the core ingredient of the premarket submission (Knudsen et al., 2005). To the extent that the data submitted by the applicant can support the claim that a product has a *history of safe use*, the submission is accepted and no further data requested at this point. The working group supports the Canadian approach with *history-of-use* over several generations as an excellent guide to the development of a general framework for both the global, regional and local risk assessment policies for novel plant foods.

To support and ease the availability of the standardised and high quality “*history of use*” data for the premarket submissions, the working group recommends the development of a worldwide set of lists with recognised food plants covering the global, regional and local levels world-wide. The data given for each plant on the individual list should be identical to the data establishing the *history of safe use* of the fruits, roots or other plant parts as human food in that region or geographical area, the list is covering. When a plant food from a plant already on one regional list is to be introduced as a novel plant food in another region, the data documenting its safe use in the first region can be used both for the submission by the applicant in the second region and by the authorities and their experts in that region. It is obvious that the lists have to build on reliable, high quality information and exactly referenced sources in order to make it possible for the scientific assessors to perform a proper safety assessment.

Such lists do not exist at the present time, but the lists presented in Annexes 2 and 3 give some hints regarding the wider perspectives of the concept recommended by the working group (Knudsen et al., 2005). The list modified from FAO in Annex 2 represents commercial plants and is based on production figures. This may cause some bias due to differences in use (e.g. as spices or for nutrition/energy), and differences between reported production and actual intake. Not all countries can give exact information on the commercial production, and the production from plants grown in home gardens or collected from the wild may be underestimated. However, it is expected that the plants (or plant products) on the FAO list all have a *history of safe use* as food used in ways and at levels well established in the worldwide food intake.

Each regional list should contain (at best) those plant food items that are commonly used in that region and

therefore in general have a long *history of use* and at least the potential for providing sufficient data to fulfil the criteria for having a *history of safe use*, data which in turn may facilitate the introduction of such plant foods to regions where they have not been eaten before. The modified NETTOX list in Annex 3 covering about 300 plants used as food sources in the EU area in 1997 is probably the best example of a regional/local plant list available at present. The NETTOX list with all its background data (not presented in details in this paper) is the one coming closest to the type of list, which may be considered a regional list. In Section 3 three examples of ethnobotanical surveys, which may be turned into ethnobotanical lists, are presented. They all contain candidates for types of plant foods indefinitely novel in EU.

Looking at the plant potential for introduction of novel plant foods, e.g. in Europe, there are over 1100 edible fruits recognised for food use in South America, 782 species of edible plants in Peru alone, and up to 7000 other plant species used in the human food supply around the world as explained in Section 3. The 101 plant species on the NUS list in Annex 1 gives also some hints in that direction, although many of the plants are not to be considered novel (48 of the plants are on the NETTOX list). It is stated on the web site of IPGRI that the intention of the NUS list is to draw attention to plants with a potential to securing food and income in some poor, rural communities. However, it can be expected that many of these potential novel food plants in some regions with few starvation problems will fall into the category of plant foods being sold based on their claims for health promoting capabilities. Such plant food products may trigger considerations that the scientific basis for such marketing should be documented in order to assure against negative effects of over-use.

The paradigm for the safety assessment of novel plant foods and novel plant food ingredients with all types of data sources is presented in Fig. 2. Based upon the discussion in Section 4.2, it is clear that the well described *history of use* possibly picked directly from one of the food plant lists will be sufficient to establish *history of safe use* for another region, where that plant food is new. Therefore, new studies (chemical studies, animal studies, human studies, exposure studies) beyond those already cited in the *history of use* may not be needed in the premarket situation for most novel fruits and vegetables. Of course such studies will be needed, if the cited *history of use* cannot lead to the establishment of *history of safe use* due to shortcomings in the characterisation of the plant species, in the compositional data and historical evidence of food use, due to the nature and severity of possible adverse effects and the character of physiological effects, due to insecure safety consequences of the cultivation, harvesting, processing and preparation methods, and/or due to the information regarding possible amounts of the novel plant food to be eaten. A similar situation with a need for basic chemical studies, animal studies, human studies and exposure studies exists if the novel plant food is derived from a not traditionally eaten part of a traditional

food plant, or if the novel plant food is derived from a plant, which has never been the source of human food anywhere.

This paper and the recommendations of this paper only address the novelty and safety of human foods derived from plants. It is to be foreseen that similar considerations and approximately similar recommendations could be developed to address the novelty and safety of mushrooms for human consumption.

7. Overall conclusions and recommendations

The European Union, Australia/New Zealand and Canada have introduced a pre-market notification or assessment and approval of novel foods in their regulation. The managerial and scientific instruments for the enforcement of this regulation are still under development.

A special area in this respect is the area of plant foods, where mutually accepted concepts and principles for risk assessment and risk management of novel plant foods are urgently needed to ensure a sufficient global production of safe and nutritious food and a smooth international trade based on mutual acceptance of these foods.

The Nordic working group has analysed the present regulatory situation and has identified the definitions of *novelty* and *safety* in relation to plant foods as the main challenges both globally, regionally and locally.

The working group recommends the introduction of a two-step management procedure, where the aim is to establish *novelty* at the first step, and to define extent and commit resources for the *safety assessment* at the second step.

Furthermore it is recommended to develop a worldwide net of global, regional, local and ethnobotanical lists of traditional food plants to guide the decision on novelty at the first step and to enable the safety assessment at the second step.

For a smooth introduction of the so-called novel fruits and vegetables from one region to another the working group recommends to use the “*history of use*”-concept as the core ingredient of the premarket submission. To the extent that the data submitted by the applicant can support the claim that a product has a *history of safe use*, the submission can be accepted as such and no further data requested at this point.

This paper describes “the-state-of-the-art” and gives recommendations in an area of the food safety arena, where only few concepts and ideas are fixed yet by administrative practices and scientific “rules-of-thumb”. Each definitive conclusion needs to be taken with caution, since all potential consequences need to be taken into account and no one forgotten, because these conclusions in the end have great perspectives for the global food supply and the global trade with food commodities and may change the basis for the physical and cultural survival of large and small communities.

Therefore the working group recommends interactive exchanges of concepts and ideas between management and science in this field as a high priority at the local, regional and global levels as well as between these levels.

Conflict of interest statement

There is no conflict of interest. The paper is based upon the work by a working group under the Nordic Working Group on Food Toxicology and Risk Evaluation, which was supported by the Nordic Council of Ministers. The present group of authors are identical to the ones preparing the written material for the Nordic Working Group.

Acknowledgement

This work was financially supported by the Nordic Council of Ministers. The authors thank Dr. Leena Mannonen, Ministry of Trade and Industry, Finland, Dr. Christer Andersson, National Food Administration, Swe-

den, Dr. Arne Mikalsen, Norwegian Scientific Committee for Food Safety, Norway, as well as the Nordic Working Group on Food Toxicology and Risk Evaluation for excellent discussions and support in the process of developing the concept and principles.

Annex 1. Examples of NUS in the regions

From <http://www.ipgri.cgiar.org/nus/home.htm>. The column “Americas” contains no marks but instead the page contain a link to a inventory list of native fruits from America (http://www.ciat.cgiar.org/ipgri/fruits_from_americas/frutales/fruits_from_america.htm) (Coppens D'Eeckenbrugge and Ferla, 2000).

Botanical name	Common name	Europe	Asia Pacific Oceania	Central West Asia North Africa	Sub Saharan Africa	Americas
Cereals and pseudocereals						
<i>Brachiaria deflexa</i>	Guinea millet				×	
<i>Digitaria exilis</i>	Fonio				×	
<i>Eleusine coracana</i>	Finger millet		×			
<i>Fagopyrum</i> spp.	Buckwheat	×	×			
<i>Pennisetum glaucum</i>	Pennisetum				×	
<i>Secale cereale</i>	Rye	×		×		
<i>Setaria italica</i>	Foxtail millet		×			
<i>Stipa lagascae</i>	Stipa			×		
<i>Triticum</i>	Hulled wheat	×		×		
<i>monococcum/dic.lspelt</i>						
Legumes						
<i>Kerstingiella geocarpa</i>	Kersting's groundnut				×	
<i>Lathyrus</i> spp.	Grass pea		×			
<i>Lupinus</i> spp.	Lupin	×		×		
<i>Macrotyloma uniflorum</i>	Horse gram		×			
<i>Mucuna</i> spp.	Velvet bean				×	
<i>Phaseolus angularis</i>	Adzuki bean		×			
<i>Phsophocarpus</i>	Winged bean		×			
<i>tetragonolobus</i>						
<i>Plectranthus esculentus</i>	Coffee potato				×	
<i>Sphenostylis stenocarpa</i>	African yam bean				×	
<i>Trigonella foenum graecum</i>	Fenum-greek			×		
<i>Tylosema esculentum</i>	Marama bean				×	
<i>Vigna subterranea</i>	Bambara groundnut				×	
Vegetables						
<i>Abelmoshus esculentum</i>	Okra		×			
<i>Allium</i> spp.	Shallot, chives, leek, onion, garlic	×				
<i>Amaranthus</i> spp.	Amaranth				×	
<i>Brassica</i> spp.	Brassicas	×		×		

Annex 1 (continued)

Botanical name	Common name	Europe	Asia Pacific Oceania	Central West Asia North Africa	Sub Saharan Africa	Americas
<i>Capparis</i> spp.	Caper	×		×		
<i>Chicorium</i> spp.	Chicory	×		×		
<i>Chorchorus olitorius</i>	Chorchorus				×	
<i>Citrullus lanatus</i>	Water melon				×	
<i>Cleome gynandra</i>	Cat's whiskers				×	
<i>Cucurbita moschata</i>	Pumpkin		×			
<i>Cynara cardunculus</i>	Cardon	×				
<i>Eruca/Diplotaxis</i> spp.	Rocket	×				
<i>Hibiscus sabdariffa</i>	Roselle				×	
<i>Malva</i> spp.	Mallow	×		×		
<i>Scolymus</i> spp.	Spanish oyster/golden thistle			×		
<i>Sechium edule</i>	Chayote		×			
<i>Solanum melongena</i>	Egg plant		×			
<i>Solanum nigrum</i>	Black nightshade		×			
<i>Valerianella locusta</i>	Corn salad	×				
Fruits and nuts						
<i>Adansonia digitata</i>	Baobab				×	
<i>Artocarpus</i> spp.	Bread fruit, jackfruit		×			
<i>Butyrospermum kirkii</i>	Shea butter tree				×	
<i>Carissa edulis</i>	Natal plum				×	
<i>Ceratonia siliqua</i>	Carob			×		
<i>Cordeauxia edulis</i>	Yeeb nut				×	
<i>Cydonia oblonga</i>	Quince			×		
<i>Durio zibethinus</i>	Durian		×	×		
<i>Dyosphyros kaki</i>	Japanese persimmon		×			
<i>Ficus carica</i>	Fig			×		
<i>Garcinia mangostana</i>	Mangosteen		×			
<i>Irvingia gabonensis</i>	Dika nuts				×	
<i>Litchi chinensis</i>	Litchi		×			
<i>Metroxylon sagu</i>	Sago palm		×			
<i>Nephelium lappaceum</i>	Rambutan		×			
<i>Phoenix dactylifera</i>	Date palm			×		
<i>Physalis alkekengi</i>	Chinese lantern	×				
<i>Pistacia vera</i>	Pistachio			×		
<i>Plyllanthus</i> spp.	Indian gooseberry		×			
<i>Pomegranate</i>	Punica granatum			×		
<i>Prunus</i> spp.	Wild <i>Prunus</i> spp.			×		
<i>Schlerocarrya birrea</i>	Marula				×	
<i>Tamarindus indica</i>	Tamarind		×			
<i>Treculia africana</i>	African breadfruit				×	
<i>Zizyphus</i> spp.	Jujube		×	×		
Beverages, stimulants, medicinal, aromatic						
<i>Artemisia</i> spp.	Absinthe			×		
<i>Cola</i> spp.	Cola nut				×	
<i>Coriander</i> spp.	Coriander		×	×		
<i>Crocus sativus</i>	Saffron	×		×		
<i>Glycyrrhiza glabra</i>	Liquorice	×				
<i>Origanum</i> spp.	Oregano			×		
<i>Raphia</i> spp.	Wine palm				×	
<i>Rhaphanus sativus</i>	Horse radish	×				

(continued on next page)

Annex 1 (continued)

Botanical name	Common name	Europe	Asia Pacific Oceania	Central West Asia North Africa	Sub Saharan Africa	Americas
<i>Rosmarinus</i> spp.	Rosmarin			×		
<i>Thymus</i> spp.	Thyme			×		
<i>Zingiber officinale</i>	Ginger		×			
Industrial						
<i>Carthamus</i> spp.	Safflower		×	×		
<i>Dioscorea zingiberensis</i>	Yam		×			
<i>Guizotia abyssinica</i>	Niger		×			
<i>Laurus nobilis</i>	Laurel	×		×		
<i>Rhus coriaria</i>	Sumac			×		
<i>Sesamum indicum</i>	Sesame		×	×	×	
<i>Stipa tenacissima</i>	Esparto			×		
<i>Vetiveria zizanioides</i>	Vetiver grass					
Forage and browse						
<i>Atriplex halymus</i>	Saltbush			×		
<i>Dactylis glomerata</i>	Cock's foot			×		
<i>Hedysarum</i> spp.	Sulla	×		×		
<i>Lathyrus</i> spp.	Grass pea		×	×	×	
<i>Leucaena leucocephala</i>	Leucaena		×			
<i>Panicum</i> spp.	Panicum		×			
<i>Salsola</i> spp.	Thistle			×		
Forest trees						
<i>Abies</i> spp.	Fir	×		×		
<i>Acacia</i> spp.	Acacia			×	×	
<i>Juniper</i> spp.	Juniper	×		×		
<i>Pistacia</i> spp.	Wild pistachio	×		×		
<i>Quercus</i> spp.	Oak	×		×		
Roots and tubers						
<i>Coleus dysentericus</i>	Frafra potato				×	
<i>Colocasia esculenta</i>	Cocoyam		×		×	
<i>Dioscorea</i> spp.	Yam		×		×	
<i>Pastinaca sativa</i>	Parsnip	×				
<i>Sphenostylis stenocarpa</i>	African yam bean				×	

Annex 2. Draft global list based on the FAO-list of global plant food production

Developed on the basis of: <http://faostat.fao.org/faostat/collections?subset=agriculture>

	Item	Megaton
1	Sugar Cane	1.333.253
2	Maize	638.043
3	Rice, Paddy	589.126
4	Wheat	556.349
5	Potatoes	310.810
6	Sugar Beets	233.487
7	Soybeans	189.234
8	Cassava	189.100

Annex 2 (continued)

	Item	Megaton
9	Barley	141.503
10	Sweet Potatoes	121.853
11	Tomatoes	113.308
12	Watermelons	91.790
13	Bananas	69.286
14	Cabbages	65.956
15	Grapes	60.883
16	Sorghum	59.584
17	Apples	57.967
18	Seed Cotton	56.097
19	Coconuts	52.940
20	Onions, Dry	52.547

Annex 2 (continued)

	Item	Megaton
21	Yams	39.913
22	Cucumbers and Gherkins	39.599
23	Rapeseed	36.146
24	Groundnuts in Shell	35.658
25	Plantains	32.974
26	Millet	29.806
27	Eggplants	28.994
28	Sunflower Seed	27.740
29	Cantaloupes & other Melons	26.749
30	Oats	26.269
31	Mangoes	25.563
32	Carrots	23.321
33	Chillies & Peppers, Green	23.248
34	Tang. Mand. Clement. Satsuma	20.950
35	Lettuce	20.810
36	Beans, Dry	19.038
37	Pears	17.191
38	Olives	17.169
39	Cauliflower	15.948
40	Rye	14.851
41	Peaches and Nectarines	14.788
42	Pineapples	14.616
43	Garlic	13.696
44	Lemons and Limes	12.452
45	Spinach	11.862
46	Peas, Dry	10.248
47	Triticale	10.245
48	Plums	10.110
49	Green Corn (Maize)	9.066
50	Taro (Coco Yam)	8.939
51	Peas, Green	8.914
52	Coffee, Green	7.796
53	Palm Kernels	7.503
54	Chick-Peas	7.123
55	Dates	6.749
56	Papayas	6.342
57	Asparagus	6.288
58	Beans, Green	5.933
59	Okra	4.940
60	Grapefruit and Pomelos	4.697
61	Broad Beans, Dry	4.033
62	Cow Peas, Dry	3.722
63	Cocoa Beans	3.257
64	Tea	3.207
65	Strawberries	3.199
66	Lentils	3.093
67	Pigeon Peas	3.053
68	Avocados	3.040
69	Sesame Seed	2.942
70	Apricots	2.529
71	Pimento, Allspice	2.482
72	Persimmons	2.430
73	Linseed	2.091

Annex 2 (continued)

	Item	Megaton
74	Cashew Nuts	2.034
75	Buckwheat	2.008
76	Cherries	1.872
77	Almonds	1.679
78	Cashewapple	1.671
79	String Beans	1.625
80	Lupins	1.593
81	Walnuts	1.446
82	Artichokes	1.171
83	Figs	1.087
84	Sour Cherries	1.055
85	Broad Beans, Green	1.052
86	Chestnuts	1.036
87	Ginger	1.029
88	Kiwi Fruit	996
89	Chicory Roots	939
90	Mate	912
91	Hazelnuts (Filberts)	698
92	Currants	688
93	Areca Nuts (Betel)	669
94	Safflower Seed	648
95	Mustard Seed	632
96	Melon seed	580
97	Pistachios	542
98	Quinces	392
99	Anise, Badian, Fennel	387
100	Raspberries	384
101	Pepper, White/Long/Black	367
102	Yautia (Cocoyam)	357
103	Cranberries	342
104	Kapokseed in Shell	341
105	Fonio	264
106	Blueberries	238
107	Kolanuts	221
108	Gooseberries	173
109	Cinnamon (Canella)	106
110	Hops	97
111	Brazil Nuts	72
112	Nutmeg, Mace,	69
	Cardamons	
113	Peppermint	61
114	Poppy Seed	59
115	Quinoa	52
116	Bambara Beans	44
117	Vanilla	6

Annex 3. Draft regional plant list based on the NETTOX food plant list

This regional food plant list for EU is the NETTOX food plant list from 1997 exempted the plants on the FAO list in [Annex 2](#).

English	Latin names
Alligator pepper, guinea grains	<i>Acer saccharum</i> Marsh.
Lesser galangal	<i>Aframomum melegueta</i> (Rosc.) K. Schum.
Dill	<i>Alpinia officinarum</i> Hance
Angelica	<i>Anethum graveolens</i> L.
Cherimoya	<i>Angelica archangelica</i> L.
Pond apple	<i>Annona cherimola</i> Mill.
Soursop	<i>Annona glabra</i> L.
Bullock's heart	<i>Annona muricata</i> L.
Noble chamomile, roman chamomile	<i>Annona reticulata</i> L.
Celery, celeriac	<i>Anthemis nobilis</i> L.
Breadfruit, breadnut	<i>Apium graveolens</i> L.
Orache, garden orache	<i>Artocarpus communis</i> J.R. et J.G.A. Foster
Carambola, starfruit, caramba	<i>Atriplex hortensis</i> L.
Malabar spinach, Ceylon spinach, Indian spinach	<i>Averrhoa carambola</i> L.
European barberry	<i>Basella alba</i> L.
Chard, swiss chard, leaf beet, spinach beet	<i>Berberis vulgaris</i> L.
Borage	<i>Beta vulgaris</i> L. ssp. vulgaris var. cicla L.s.l.
Caraway	<i>Borago officinalis</i> L.
Coffee chicory	<i>Carum carvi</i> L.
Chinese cinnamon, Chinese cassia	<i>Cichorium intybus</i> L. cv sativum
Batavia cinnamon, padang cassia	<i>Cinnamomum aromaticum</i> Nees
Ceylon cinnamon	<i>Cinnamomum burmanii</i> Bl.
King mandarin tree	<i>Cinnamomum zeylandicum</i> Schaeff.
Spoon-wort, scurvy-grass	<i>Citrus nobilis</i> L.
Coriander	<i>Cochlearia officinalis</i> L.
Cornelian cherry, cornel tree	<i>Coriandrum sativum</i> L.
Saffron, crocus	<i>Cornus mas</i> L.
Cumin, cummin	<i>Crocus sativus</i> L.
Common turmerio, Turmeric plant, Indian saffron	<i>Cuminum cyminum</i> L.
Zedoary	<i>Curcuma longa</i> L.
Sere-grass, lemongrass, West Indian lemongrass	<i>Curcuma zedoaria</i> (Bergius) Rosc.
Cardoon	<i>Cymbopogon citratus</i> (D.C.) Stapf.
Earth almond, yellow nutsedge	<i>Cynara cardunculus</i>
Water chestnut, matting reed, Chinese water chestnut	<i>Cyperus esculentus</i>
Cardamon plant, cluster	<i>Eleocharis dulcis</i> (Burm. F.) Trinius ex Henschel
Rocket salad	<i>Elettaria cardamomum</i> (L.) Maton
Surinam cherry, Brazil cherry	<i>Eruca sativa</i> Mill.
	<i>Eugenia uniflora</i> L.

Annex 3 (continued)

English	Latin names
Marumikunquat, round kunquat	<i>Fortunella japonica</i> (Thumb.) Swingle
Kunquat, kunquat maruoni	<i>Fortunella margarita</i> (Lour) S.
Wild strawberry	<i>Fragaria vesca</i> L.
Scarlet strawberry, Virginia strawberry	<i>Fragaria virginiana</i> Mill.
Liquorice	<i>Glycyrrhiza glabra</i> L.
Cotton	<i>Gossypium</i> Sp.
Topinambur, Jerusalem artichoke	<i>Helianthus tuberosus</i> L.
Roselle	<i>Hibiscus sabdariffa</i> L.
Hyssop	<i>Hyssopus officinalis</i> L.
Chinese anise, star anise tree	<i>Illicium verum</i> J.D. Hook
Water Spinach	<i>Ipomoea aquatica</i> Forsk.
Juniper	<i>Juniperus communis</i> L.
Hyacinth bean, bonavist bean, lablab bean	<i>Lablab purpureus</i> (L.) Sweet
Delicious lactarius	<i>Lactarius deliciosus</i> Fr.
Prickly lettuce	<i>Lactuca serriola</i> Turner L.
Bottle gourd, calabash gourd	<i>Lagenaria siceraria</i> (Molina) Standl
Chickling vetch, grasspea, kaasari	<i>Lathyrus sativus</i> L.
Sweet bay, laurel, bay tree	<i>Laurus nobilis</i> L.
Boletus	<i>Leccinum scabrum</i> Fr.
Lovage, garden lovage	<i>Levisticum officinale</i> W. Koch
Lemon verbenia	<i>Lippia triphylla</i> (L'Hér.) Kuntze
Acerola	<i>Malpighia punicifolia</i> L.
Sapodilla, chicle	<i>Manilkara zapota</i> (L.) van Royen
Balm, lemon balm	<i>Melissa officinalis</i> L.
Spearmint	<i>Mentha spicata</i> L.
Spearmint	<i>Mentha spicata</i> L. emend L.
African cucumber, balsam epar, balsam apple	<i>Momordica charantia</i> L.
Sweet basil, common basil	<i>Ocimum basilicum</i> L.
Sweet majoram	<i>Origanum majorana</i> L.
Wild marjoram, European oregano	<i>Origanum vulgare</i> L.
Guaraná	<i>Paullina cupana</i> H.B.K.
Cape gooseberry	<i>Physalis peruviana</i> L.
Allspice, Jamaica pepper	<i>Pimenta dioica</i> (L.) Merr.
Anise	<i>Pimpinella anisum</i> L.
Purslane	<i>Portulaca oleracea</i> L. ssp. sativa (Haw.) Celak.
Cherry-plum tree, myrobalan-plum tree	<i>Prunus cerasifera</i> Ehrh.
Japanese plum	<i>Prunus salicina</i> Lindl.

Annex 3 (continued)

English	Latin names
Brasilian guava, Guinea guaava, guisaro	<i>Psidium guineense</i>
Archil, orchil, angola weeb	<i>Rorippa Nasturtium-aquaticum</i> (L.) Hayeck.
Dog rose, wild rose	<i>Rosa canina</i> L.
Rosemary	<i>Rosmarinus officinalis</i> L.
Cloudberry	<i>Rubus chamaemorus</i> L.
Blackberry	<i>Rubus fruticosus</i> L.
Raspberry	<i>Rubus ideaus</i> L.
Sage	<i>Salvia officinalis</i> L.
Brazilian peppertree	<i>Schinus terebinthifolius</i> Raddi
Sesame, beniseed	<i>Sesamum indicum</i> L.
Chinese artichoke, Japonesse artichoke,	<i>Stachys affinis</i> Bunge
Ringed boletus	<i>Suillus luteus</i> Fr.
Clove tree	<i>Syzygium aromaticum</i> (L.) Merr. & L.M. Perry
Rose apple, jambos	<i>Syzygium jambos</i> (L.) Alston
Dandelion	<i>Taraxacum officinale</i> Weber
New Zealand spinach	<i>Tetragonia tetragonioides</i> (Pall.) Kuntze
Wild thyme, creeping thyme	<i>Thymus serpyllum</i> L.
Garden thyme, common thyme	<i>Thymus vulgaris</i> L.
Small-leaved lime tree, winter linden tree	<i>Tilia cordata</i> Mill.
Large -leaved lime tree, summer linden	<i>Tilia platyphyllos</i> Scop.
Water chestnut, caltrops	<i>Trapa natans</i> L.
African breadfruit	<i>Treculia africana</i> L.
Fenugreek	<i>Trigonella foenum-graecum</i> L.
Indian cress, garden nasturtium	<i>Tropaeolum majus</i> L.
Truffle	<i>Tuber melanosporum</i> Vitt.
Nettle, stinging nettle	<i>Urtica dioica</i> L.
	<i>Vaccinium uliginosum</i> L.
Cowberry	<i>Vaccinium vitis-idaea</i> L.
Cornsalad, lamb's lettuce	<i>Valerianella locusta</i> (L.) Laterrade
Adzuki bean	<i>Vigna angularis</i> (Willd.) Ohwi et Ohashi
Black gram	<i>Vigna mungo</i> (L.) Hepper
Chinese date	<i>Ziziphus ziziphus</i> L. Meikle

References

- ACNFP, 1999. Annual report. Ministry of Agriculture, Fisheries and Food and Department of Health, pp. 55–65.
- Andersson, C., 1999. Glycoalkaloids in tomatoes, eggplants, pepper and two Solanum species growing wild in the Nordic countries. TemaNord, 599.

- Bast, A., Chandler, R.F., Choy, P.C., Delmulle, L.M., Gruenwald, J., Halkes, S.B.A., Keller, K., Koeman, J.H., Peters, P., Przyrembel, H., de Ree, E.M., Renwick, A.G., Vermeer, I.T.M., 2002. Botanical health products, positioning and requirements for effective and safe use. *Environ. Toxicol. Pharmacol.* 12, 195–211.
- Brack Egg, A., 1999. Diccionario enciclopédico de plantas útiles del Perú. PNUD/CBC, Lima, Peru.
- Bublin, M., Mari, A., Ebner, C., Knulst, A., Scheiner, O., Hoffmann-Sommergruber, K., Breiteneder, H., Radauer, C., 2004. IgE sensitization profiles toward green and gold kiwifruits differ among patients allergic to kiwifruit from 3 European countries. *J. Allergy Clin. Immunol.* 114, 1169–1175.
- Cellini, F., Chesson, A., Colquhoun, I., Constable, A., Davies, H.V., Engel, K.H., Gatehouse, A.M.R., Kärenlampi, S., Kok, E.J., Leguay, J.-J., Lehesranta, S., Noteborn, H.P.J.M., Pedersen, J., Smith, M., 2004. Unintended effects and their detection in genetically modified crops. *Food Chem. Toxicol.* 42, 1089–1125.
- CFSAN, 1992. Phytohaemagglutinin. In: Foodborne Pathogenic Microorganisms and Natural Toxins Handbook (Bad Bug Book); Center for Food Safety & Applied Nutrition, US Food & Drug Administration. URL: <http://www.cfsan.fda.gov/~mow/chap43.html>.
- Codex Alimentarius, 2004. Foods Derived from Biotechnology. FAO/WHO, Rome, pp. 47–51 (Annex: Assessment of possible allergenicity).
- Constable, A., Jonas, D., Cockburn, A., Davi, A., Edwards, G., Hepburn, P., Herouet-Guicheney, C., Knowles, M., Moseley, B., Oberdorfer, R., Samuels, F., 2007. History of safe use as applied to the safety assessment of novel foods and foods derived from genetically modified organisms. *Food Chem. Toxicol.* 45, 2513–2525.
- Coppens D'Eeckenbrugge, G., Ferla, D.L., 2000. Fruits from America. An Ethnobotanical inventory. IPGRI (International Plant Genetic Resources Institute). URL: http://www.ciat.cgiar.org/ipgri/fruits_from_americas/frutales/fruits_from_america.htm.
- 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.
- 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.
- EMA, 1999. Ad hoc Working Group on Herbal Medicinal Products.
- European Commission, 1997. Commission recommendation of 29 July 1997 concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients and the preparation of initial assessment reports under Regulation (EC) No. 258/97 of the European Parliament and of the Council. Official Journal L 253:0001–0036.
- Fabech, B., Bryhni, K., Forshell, L.P., Georgsson, F., Gry, J., Hansen, B.T., Hallström, H., Hatakka, M., Holene, E., Kapperud, G., Kristinsson, J., Majjala, R., Nielsen, N.L., Nordström, U., Schultz, A.C., Solheim, C., Thorkelsson, Á.E., 2002. A Practical approach to the application of the risk analysis process. Illustrated with two examples caffeine and campylobacter. TemaNord 510, 5–159.
- FAOSTAT, 2004. Agricultural Data. URL: <http://faostat.fao.org/faostat/collections?subset=agriculture>.
- FAO/WHO, 1995. Application of Risk Analysis to Food Standard Issues. Report of the Joint FAO/WHO Expert Consultation. Geneva, Switzerland, 13–17 March 1995. WHO, Geneva.
- FAO/WHO, 1997. Risk Management and Food Safety. Report of a Joint FAO/WHO Consultation. Rome, Italy, 27–31 January 1997. FAO, Rome.
- FAO/WHO, 2000. Safety aspects of genetically modified foods of plant origin. Report of a joint FAO/WHO Expert Consultation on Foods Derived from Biotechnology. Geneva, Switzerland, 29 May – 2 June 2000. World Health Organization, Geneva.

- FAO/WHO, 2001. Evaluation of Allergenicity of Genetically Modified Foods. Report of a Joint FAO/WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology, 22–25 January 2001. Food and Agriculture Organisation of the United Nations, Rome.
- Frémont, S., Moneret-Vautrin, D.A., Nicolas, J.P., 2001. Allergenicity of the nan-gai nut. *Allergy* 56, 581.
- FSANZ, 2004a. Australia New Zealand Food Standards Code, standard 1.5.1 Novel Foods Including Amendment 70 (FSC 12), 29 April 2004. URL: <http://www.foodstandards.gov.au/foodstandardscode/>.
- FSANZ, 2004b. General information to assist in applying to amend the Australian New Zealand Food Standards Code – Novel foods Updated April 2004, URL: http://www.foodstandards.gov.au/_src-files/Novel_Food_Guidelines_June_2004.pdf.
- Getahun, H., Lambein, F., Vanhoorne, M., Van der Stuyft, P., 2003. Food-aid cereals to reduce neurolathyrisms related to grass-pea preparations during famine. *Lancet* 362, 1808–1810.
- Getahun, H., Lambein, F., Vanhoorne, M., Van der Stuyft, P., 2005. Neurolathyrisms risk depends on type of grass pea preparation and mixing with cereals and antioxidants. *Trop. Med. Int. Health* 10, 169–178.
- Health Canada, 1994. Guidelines for the safety assessment of Novel Foods. URL: http://www.hc-sc.gc.ca/fn-an/alt_formats/hpfb-dgpsa/pdf/legislation/novele_e.pdf.
- Health Canada, 1999. Regulations Amending The Food and Drugs Regulations (948 - Novel Foods) – October 27, 1999. URL: http://www.hc-sc.gc.ca/fn-an/alt_formats/hpfb-dgpsa/pdf/gmf-agm/schedule-annexe948_e.pdf.
- Hegarty, M.P., Hegarty, E.E., Wills, R.B.H., 2001. Food safety of Australian plant bushfoods. Rural Industries Research and Development Corporation, New Plant Products Research and Development, Queensland, Australia.
- Hermann, M., 2004. The amendment of the EU Novel Food Regulation: opportunity for recognizing the special status of exotic traditional foods; Discussion paper, June 2004, International Plant Genetic Resources Institute (IPGRI).
- Howlett, J., Edwards, D.G., Cockburn, A., Hepburn, P., Kleiner, J., Knorr, D., Kozianowski, G., Müller, D., Peijnenburg, A., Perrin, I., Poulsen, M., Walker, R., 2003. The safety assessment of Novel Foods and concepts to determine their safety in use. *Int. J. Food Sci. Nutr.* 54 (Suppl), S1–S32.
- IPGRI (International Plant Genetic Resources Institute), 2004. Conserving and increasing the Use of Neglected and Underutilized Crop Species. Examples of NUS in the Regions. URL: <http://www.ipgri.cgiar.org/nus/home.htm>.
- Janick, J., 1999. New crops and the search for new food resources. In: Janick, J. (Ed.), *Perspectives on New Crops and New Uses*. ASHS Press, Alexandria, VA, pp. 104–110.
- Johanns, E.S., van der Kolk, L.E., van Gemert, H.M., Sijben, A.E., Peters, P.W., de Vries, I., 2002. Én epidemie van epileptische aanvallen na drinken van kruiden thee. *Ned. Tijdschr. Geneesk.* 146, 813–816.
- Kimber, I., Dearman, R.J., 2002. Approaches to assessment of the allergenic potential of novel proteins in food from genetically modified crops. *Toxicol. Sci.* 68, 4–8.
- Knudsen, I., Ovesen, L., 1995. Assessment of novel foods: a call for a new and broader GRAS concept. *Regul. Toxicol. Pharmacol.* 21, 365–369.
- Knudsen, I., Poulsen, M., 2007. Comparative safety testing of genetically modified foods in a 90-day rat feeding study design allowing the distinction between primary and secondary effects of the new genetic event. *Regulatory Toxicology and Pharmacology* 49, 53–62.
- Knudsen, I., Søborg, I., Eriksen, F., Pilegaard, K., Pedersen, J., 2005. Risk assessment and risk management of novel plant foods. Concepts and principles. *TemaNord* 588, 11–108.
- Kroes, R., Galli, C., Munro, I., Schilter, B., Tran, L.-A., Walker, R., Würtzen, G., 2000. Threshold of toxicological concern for chemical substances present in the diet: A practical tool for assessing the need for toxicity testing. *Food Chem. Toxicol.* 38 (2–3), 255–312.
- Kroes, R., Renwick, A.G., Cheeseman, M., Kleiner, J., Mangelsdorf, I., Piersma, A., Schilter, B., Schlatter, J., van Schothorst, F., Vos, J.G., Würtzen, G., 2004. Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. *Food Chem. Toxicol.* 42 (1), 65–83.
- Kunkel, G., 1984. Plants for Human Consumption an Annotated Checklist of the Edible Phanerogams and Ferns. Koeltz Scientific Books, Königstein, Germany.
- König, A., Cockburn, A., Crevel, R.W.R., Debruyne, E., Grafstroem, R., Hammerling, U., Kimber, I., Knudsen, I., Kuiper, H.A., Peijnenburg, A.A.C.M., Penninks, A.H., Poulsen, M., Schauzu, M., Wal, J.M., 2004. Assessment of the safety of food derived from genetically modified (GM) crops. *Food Chem. Toxicol.* 42, 1047–1088.
- Lucas, J.S.A., Lewis, S.A., Hourihane, J.O'B., 2003. Kiwi fruit allergy: a review. *Pediatr. Allergy Immunol.* 14, 420–428.
- Lucas, J.S.A., Grimshaw, K.E.C., Collins, K., Warner, J.O., Hourihane, J.O'B., 2004. Kiwi fruit is a significant allergen and is associated with differing patterns of reactivity in children and adults. *Clin. Exp. Allergy* 34, 1115–1121.
- Mlingi, N., Poulter, N.H., Posling, H., 1992. An outbreak of acute intoxication from consumption of insufficiently processed cassava in Tanzania. *Nutr. Res.* 12, 677–678.
- Munro, I.C., Kennepohl, E., Kroes, R., 1999. A procedure for the safety evaluation of flavouring substances. *Food Chem. Toxicol.* 37, 207–232.
- Morisset, M., Boulègue, M., Beaudouin, E., Pirson, F., Rancé, F., Gallen, C., Moneret-Vautrin, D.-A., 2003. Anaphylaxie alimentaire sévère et léthale cas rapportés en 2002 par le réseau d'allergovigilance. *Rev. Fr. Allergol. Immunol. Clin.* 43, 480–485.
- Morris, S.C., Lee, T.H., 1984. The toxicity and teratogenicity of Solanaceae glycoalkaloids, particularly those of the potato (*Solanum tuberosum*): a review. *Food Tech. Australia* 36, 118–124.
- Myers, N., 1983. A wealth of wild species: storehouse for human welfare. Westview Press, Boulder, Colo.
- NETTOX, 1998. Nettox List of Food Plants. Information on inherent food plant toxicants, report 2. Danish Vet. Food Adm; Søborg, Denmark.
- OECD, 1995. Guidelines for the Testing of Chemicals. Organisation for Economic Cooperation and Development, Paris.
- OECD, 2002. Consensus Document on Compositional Considerations for New Varieties of Maize (Zea Mays): Key Food and Feed Nutrients, Anti-nutrients and Secondary Plant Metabolites. Series on the Safety of Novel Foods and Feeds, No. 6. Organisation for Economic Cooperation and Development, Paris. URL: [http://www.olis.oecd.org/olis/2002doc.nsf/LinkTo/env-jm-mono\(2002\)25](http://www.olis.oecd.org/olis/2002doc.nsf/LinkTo/env-jm-mono(2002)25).
- Pilegaard, K., Eriksen, F.D., Soerensen, M., Gry, J., 2007. EuroFIR-NETTOX Plant List. European Food Information Resource Consortium (EuroFIR). ISBN 0 907 667 570.
- Rao, S.L.N., 2001. Do we need more research on neurolathyrisms? *Lathyrisms Lathyrisms Newslett.* 2 2–4.
- Sampson, H.A., Burks, A.W., 1996. Mechanisms of food allergy. *Annu. Rev. Nutr.* 16, 161–177.
- Schlatter, B., Andersson, C., Anton, R., Constable, A., Kleiner, J., O'Brien, J., Renwick, A.G., Korver, O., Smit, F., Walker, R., 2003. Guidance for the safety assessment of botanicals and botanical preparations for use in food and food supplements. *Food Chem. Toxicol.* 41, 1625–1649.
- Siddique, K., Hanbury, C., 2005. “Ceora”: Australia's first grasspea variety. CLIMA (Centre for Legumes in Mediterranean Agriculture) newsletter, April 2005.
- Slanina, P., 1990. Assessment of health-risks related to glycoalkaloids (“Solanine”) in potatoes: a Nordic view. Report from the Nordic Working Group on Food Toxicology and Risk Assessment. *Vår Föda* 43 (Suppl), 1–15.
- Spencer, P.S., Roy, D.N., Ludolph, A., Hugon, J., Dwivedi, M.P., Schaumburg, H.H., 1986. Lathyrisms: evidence for role of the neuroexcitatory amino acid BOAA. *Lancet* 328, 1066–1067.

- SSC, 2000. First Report of the Scientific Steering Committee on the Harmonisation of Risk Assessment Procedures. European Commission, Health & Consumer Protection Directorate-General. URL: http://europa.eu.int/comm/food/fs/sc/ssc/out83_en.pdf Appendices: http://europa.eu.int/comm/food/fs/sc/ssc/out84_en.pdf.
- SSC, 2003a. Second Report of the Scientific Steering Committee on the Harmonisation of Risk Assessment Procedures. European Commission, Health & Consumer Protection Directorate-General. URL: http://europa.eu.int/comm/food/fs/sc/ssc/out361_en.pdf.
- SSC, 2003b. Final Report on Setting the Scientific Frame for the Inclusion of New Quality of Life Concerns in the Risk Assessment Process. Adopted 10–11 April 2003. URL: http://europa.eu.int/comm/food/fs/sc/ssc/out357_en.pdf.
- Sten, E., Stahl Skov, P., Andersen, S.B., Torp, A.M., Olesen, A., Bindslev-Jensen, U., Poulsen, L.K., Bindslev-Jensen, C.A., 2002. Allergenic components of a novel food, Micronesian nut Nangai (*Canarium indicum*), shows IgE cross-reactivity in pollen allergic patients. *Allergy* 57, 398–404.
- Weiss, E., Wetterstrom, W., Nadel, D., Bar-Yosef, O., 2004. The broad spectrum revisited: evidence from plant remains. *Proc. Natl. Acad. Sci. USA* 101, 9551–9555.
- WHO, 1987. Principles for the safety assessment of food additives and contaminants in food. No. 70. WHO, Geneva.
- WHO, 1999. Principles for assessment of risk to human health from exposure to chemicals. No. 210. WHO, Geneva.
- WHO, 2003. GEMS/FOOD Regional Diets – Regional Per Capita Consumption of Raw and Semi-processed Agricultural Commodities. URL: http://www.who.int/foodsafety/chem/gems_regional_diet.pdf.
- Wilson, E.O., 1992. *The Diversity of Life*. Penguin, London.
- Zohary, D., Hopf, M., 2000. *Domestication of Plants in the Old World: The Origin and Spread of Cultivated Plants in West Asia, Europe and the Nile Valley*, third ed. Oxford University Press, New York.