Health Council of the Netherlands

The safety assessment of novel foods (2)

Gezondheidsraad
Health Council of the Netherlands

To the Minister of Health, Welfare and Sport

Subject : presentation of advisory report *Safety Assessment of Novel Foods (2)*
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Dear Minister,

From 1999 to 2004 the Health Council's Committee on Safety Assessment of Novel Foods (VNV) carried out a large number of dossier assessments. In 2005 the work of this committee was transferred to the Medicines Evaluation Board. To conclude its work at the Health Council, and to supplement its 2002 report *Safety Assessment of Novel Foods*, Publication No. 2002/05VNV), I hereby present you with the report on *Safety Assessment of Novel Foods (2)* by the VNV, following consultation with the Standing Committee on Nutrition.

Yours faithfully,

(signed)
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to:

the Minister of Health, Welfare and Sport

No. 2007/23E, The Hague, October 25, 2007

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Contents

Executive summary

From 1999 to 2004, the Health Council's Committee on the Safety Assessment of Novel Foods (VNV) carried out dossier assessments in the context of European Regulation 258/97. In addition to advisory reports on specific products, in 2002 this Committee published an advisory report on an assessment framework for novel foods. The present advisory report supplements that previous document. Here, the emphasis is on topics associated with the implementation of the regulation, and on developments in the field.

What is a novel food?

The Committee has highlighted the fact that there is still considerable debate about when products should or should not be characterised as novel foods. According to the regulation, products are not novel foods if they have a long and safe tradition of use for dietary purposes. According to the Committee, this should only apply to instances of documented use within the European Union. If one of the member states declares that a food was consumed in significant quantities on its territory prior to 1997, and if it can provide evidence to support this claim, then all of the other member states tend to accept this.

Many products are being developed that involve the addition to foods, in concentrated form, of components that occur naturally in foods. The VNV Committee takes the view that – dependent on the size of the concentration increase involved and on the nature of the ingredient in question – such products

should sometimes be designated as novel foods. In certain cases, the composition of foods of animal origin can be modified in a controlled way, through changes made to cattle feed. The Committee believes that if there have been substantial changes to the nutritional value of the end products, to the levels of undesirable substances that they contain or to their metabolism, then these too should be regarded as novel foods.

On several occasions, the Committee was confronted with proposals for the use of ingredients that had previously been used in food supplements. The Committee believes that such use does not indemnify these ingredients against testing in accordance with the new food legislation. According to the current regulation, new strains developed by means of traditional improvement methods are not considered to be novel foods. The Committee feels that this is inappropriate, however, as the use of such methods brings about substantial changes in the end product.

The Committee urges that the efficacy of specific bio-active compounds should not be disengaged from the issue of safety. New uses for existing ingredients – such as micronutrients and dietary fibre – in special categories of foods, such as foods especially developed for medical purposes and infant formulas, deserve further assessment.

Requirements for a notification dossier

New sources are sometimes found for familiar foods or ingredients. This may involve a different species of animal, plant or micro-organism. Such cases often involve the notification procedure, in which it must be established that the product in question is substantially equivalent to a food that has already been approved. The Committee feels, however, that an authorisation procedure should be mandatory when a new source is used, except in the case of products that are highly purified. In such cases, a notification should be sufficient.

The Committee notes that, in practice, different European member states vary considerably in their approach to the option of granting products admission to the market by means of the notification procedure. The requirements for a notification dossier should therefore be harmonised at European level. The Committee has put forward a number of suggestions to this end. The notification procedure centres around the judgement of whether or not there is substantial equivalence to foods that have already been approved. However, it is the Committee's view that notification requests should automatically involve a broad check of the entire body of current legislation pertaining to the food in question, such as procedures concerning hygiene and contaminants. According to the

current regulation, foods that are created through the use of a substantially novel production process can only be assessed by means of an authorisation procedure. However, it is the Committee's view that a notification would be appropriate if the end product can be shown to be substantially equivalent to an existing product.

Requirements for an authorisation dossier

On the basis of its experience, the Committee has worked out the requirements to be imposed on dossiers for the authorisation of various categories of novel foods. These requirements must nevertheless be harmonised at European level. For the purposes of this advisory report, separate consideration is given to the assessment of any allergenic properties that a product might possess. This is because, in the Committee's view, the methods for doing so have not yet been fully put into practice. Further research into the cross-reactivity of allergenic proteins from various sources can serve as the basis for an improved pre-marketing assessment of the allergenic potential of novel foods. Incidentally, the Committee feels that any market introduction of novel foods with allergenic properties should be linked to adequate flanking measures. Given the scientific restrictions associated with the pre-marketing assessment, there should be a systematic registration system for reports of the occurrence of allergic reactions to foods.

The importance of market monitoring

In its 2002 advisory report, the Committee expressed its views on the options for the post-launch monitoring of novel foods. Subsequent developments have shown that the market monitoring of specific bio-active compounds, such as plant sterols, affords some insight into the ways in which these products are used. The Committee endorses the recommendations made by the National Institute for Public Health and the Environment (RIVM) in this field. It is delighted that the new European traceability legislation will enable more tightly focused measures to be taken in the event of incidents.

The Committee is fully cognizant of the fact that the interests of food safety are viewed in the perspective of positive health effects of foods. However, it states that the high level of food safety that has already been achieved must be maintained. It takes the view that the current practice of pre-marketing assessment of the safety of novel foods contributes to this. This Committee has now been relaunched, following the transfer of this work to the Medicines

Evaluation Board Agency (CBG) on 1 January 2005. In this way, it continues to play a part in the European assessment procedure for novel foods.

Chapter 1

Introduction

In 1997 the European Parliament and the Council laid down a Community Assessment Procedure for novel foods in Regulation (EC) 258/97.[22] European recommendation 97/618/EC was published the same year: this sets out what information dossiers submitted for an assessment must contain.[7] In a request for recommendations of 18 August 1999, the Minister of Health, Welfare and Sport – also on behalf of the State Secretary for Agriculture, Nature and Food Quality – asked the Health Council to organise the implementation of the Regulation in the Netherlands. The full text of the request for recommendations is appended as Annex A.

The Health Council Committee on Safety Assessment of Novel Foods (VNV) set up for this purpose, further developed the assessment framework for novel foods, based on its practical experience of dossier assessment. It reported on its methodology and discussed particular concerns regarding three categories of novel foods in its 2002 report on Safety Assessment of Novel Foods.[31] The membership of the committee is set out in Annex B.

The present report supplements the 2002 report, in particular considering aspects of the assessment procedure that affect the evaluation and revision of the European legislation on novel foods. Article 14 of Regulation (EC) No. 258/97 lays down that the Regulation shall be evaluated after five years of experience in practice.[22] The European Commission is to submit a report to the European Parliament and the Council on its implementation. The present report is intended

as input to the consultation process that the European Commission (DG SANCO) began in 2002, when it drew up a discussion document in which it touched upon certain issues and put forward various options for improving the situation.[6] It invited those concerned to come up with alternative suggestions, and not to restrict their comments to those aspects of the Regulation mentioned in the document.

Following a period of stagnation, the procedure for revising the legislation has been resumed during the past year. Foods consisting wholly or partly of genetically modified organisms and foods produced using genetically modified organisms (GMOs) now have their own legislation on approval and traceability,[25-28] making them exempt in principle from the rules in the Novel Foods Regulation. Regulation (EC) No. 1829/2003 mentions an exception, however: the Novel Foods Regulation still applies if a characteristic has not been taken into consideration during the GMO licensing procedure, resulting in the product being assigned to one of the remaining categories of novel foods.

It is not clear to the VNV how this will be interpreted in practice. Its comments on the 'genetically modified foods' category relate mainly to market monitoring and allergenicity, whereas most attention is being paid to novel foods with specific bioactive components, exotic novel foods and food ingredients from new sources and new processes.

The report is organised as follows. Chapter 2 discusses the interpretation of the law on novel foods: the VNV has noted that there is often controversy as to whether or not a particular product should be regarded as a novel food. This chapter also discusses other procedures for special categories of foods. Chapter 3 deals with the system of applying for notifications: the main issues here, in the VNV's opinion, are when it is appropriate to use this procedure, and, when applicable, what information the dossier should contain. Chapter 4 considers the dossier requirements for authorisations, and can be regarded as supplementing the 2002 report on Safety Assessment of Novel Foods. Chapter 5 gives an update on safety following the introduction of a novel food. In Chapter 6 the VNV concludes its recommendations with a look at the future.

This report is based on the VNV's six years' experience of assessing dossiers and designing the scientific assessment framework for novel foods at the request of the Ministers of Health, Welfare & Sport and Agriculture, Nature & Food Quality. During the 1999-2004 period, the Health Council published 32 reports which were drawn up by the VNV (see Annex C). Since 1 January 2005 the VNV's reports have been published by the Medicines Evaluation Board's Novel Foods Unit.

Chapter 2

What is a novel food?

2.1 The demarcation in the law

The Novel Foods Regulation applies to the marketing within the European Community of foods and food ingredients which have not hitherto been used for human consumption to a significant degree.[22] It distinguishes between the following categories:

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

The Regulation also states that the Standing Committee on the Food Chain and Animal Health may decide whether a food or food ingredient falls into one of the categories. In practice, providing each other with information and asking about

foods and ingredients which have not been defined as either novel or existing foods is an almost daily activity among the competent authorities, national assessors and enforcers.

2.2 Determining status

The first question that needs to be answered when determining the status of a product is whether the food or ingredient was used for human consumption to a significant degree within the European Community before 15 May 1997. In practice, if the government of one country supports the fact that the product was on the market before May 1997, the other Member States will accept this. However, if there are still serious doubts regarding the safety of a product, requiring a safety dossier under the Novel Foods Regulation is not the way, and a different course of action needs to be taken.

Foods that have been discussed and on which a decision has finally been made, are listed in the Novel Food Catalogue, which is maintained by European Commission officials: this states which countries support significant consumption before 1997, or alternatively that the food in question has been designated as novel. The Catalogue avoids repeated arguments about the same product, but as the list is not published, the information is not directly available to applicants. The aim, however, is to publish a simplified version on the European Commission website in 2007. As a result of the accession of new Member States to the European Union, it is anticipated that the status of some food ingredients may be changed and the list of discussed foods and ingredients will grow in size.

The second question that often arises when determining the status of products is whether ingredients that have a history of being used in food supplements should be regarded as novel foods, as firms sometimes wish to use them in foods as well. Assessors, however, do not regard use in food supplements as being synonymous with ‘used for human consumption to a significant degree’. In the Netherlands, food supplements are covered by the Commodities Act, whereas in some other countries they are covered by specific legislation or regarded as medicinal products.

The Committee on Safety Assessment of Novel Foods takes the view that using a product as an ingredient in a food supplement restricts its consumption to a sub-group of the population that is far from representative of the population as a whole. Moreover, there are many ill-defined ingredients in use in supplements on which little safety information is available. If by using a product more widely

a producer or trader lends it the status of a novel food, that firm must submit safety data. Meanwhile the Standing Committee on the Food Chain and Animal Health has adopted a position that is in line with this approach.[43] There is also a current debate about the addition, in concentrated form, of naturally occurring components. The VNV continues to take the view that whether an ingredient should be regarded as novel needs to be decided on a case-by-case basis, depending on the increase in concentration and the nature of the ingredient.

The third type of questions raised when determining status concern the interpretation of the terms used to define categories of novel foods. The term 'new or intentionally modified primary molecular structure', for instance, is problematic in the case of an ingredient that has identical properties to an existing ingredient, but comes from another source and therefore does not have a completely identical molecular structure. If firms want the VNV to adopt a position on such cases, they are usually asked to produce a dossier. The conventional counterpart can of course readily be used as a comparison, and all that needs to be done is to gauge the result of the difference – which may be minor.

Also much discussed is the category definition 'foods and food ingredients consisting of, or isolated from plants, and food ingredients isolated from animals, except for foods and food ingredients obtained by traditional propagation or breeding practices and having a history of safe food use'. In practice the VNV uses the species boundary in this case as the criterion for a novel vegetable or animal ingredient (see the inset on exotic fruits). New varieties developed by means of traditional improvement methods are thus excluded from the 'novel' category. This is unjustified in some cases, however. The VNV is thinking for example of the requirement to test each new potato variety for solanine content, while being aware that the industry also runs these tests. The VNV is also thinking of methods such as chemical mutagenesis and irradiation, which are regarded as conventional improvement techniques, but which entail a risk of unintentional effects. Systematic information on the nature and risk of unintentional effects therefore needs to be obtained.

It is not clear why the list of exceptional cases has been expanded to include those 'having a history of safe food use'. Could that include use outside Europe? This has been at issue in the case of e.g. Actinidia (kiwi), Morinda citrifolia (Noni), Amelanchier alnifolia (saskatoon berry) and Theobroma grandiflorum, and in general in relation to exotic vegetables and fruits. The VNV considers that the 'use' must have been in Europe (see the inset on exotic fruits).

Lastly, the VNV is frequently consulted on the definition of a new production process. Here again the VNV cannot really adopt a position unless there is a

dossier indicating whether or not a seldom-used process gives rise to significant changes in the composition or structure of the foods or food ingredients which affect their nutritional value, metabolism or level of undesirable substances. Some firms would like the VNV to make its opinion known where the new process does *not* result in a novel food. It is still possible to change the composition of animal products significantly by altering the composition of feedstuffs without the need to file an application under the Novel Foods Regulation. The VNV takes the view that products that should be regarded as novel foods can be developed in this way. Whether this is the case depends on the change in concentration and the nature of the components.

Exotic fruits

Fruits from other parts of the world are increasingly available on the European market, e.g. via the Internet. It is important for sellers to realise that even if a fruit has a history of consumption by the local population elsewhere, it is still regarded as a novel food in Europe. Whether the fruit in question has a positive image in its area of origin makes no difference to its status in Europe.

The **Noni** (Morinda citrifolia), for instance, is a fruit that comes from Hawaii, Tahiti and French Polynesia, among other places. It became clear from evaluating it as a novel food, and through a series of notification applications, that it was not so much the juice of the fruit itself as the primary production process that raised questions: lead content was a problem with more than one producer, for instance, as was the microbial quality of the juice. It was also found that the tree bark and twigs of the noni can contain anthraquinones: these should not be present in the juice, so it is important to ensure that these parts of the plant are not processed.
Another debate concerned **Cupuaçu** (Theobroma grandiflorum), a plant species related to cocoa. Although Cupuaçu and cocoa are related, they are different enough to warrant separate assessment, especially since there are differences in the parts of the plant used. The flesh of the Cupuaçu is used in ice cream, fruit juice, chocolates, creams, jellies and cakes; the beans are used for similar purposes as those of the cocoa plant. When drawing up a safety dossier, the way a new product is used in other parts of the world and its relationship to a fruit already consumed in Europe is useful information which can make it easier to assess.

The **saskatoon berry** (Amelanchier alnifolia), a berry that has a history of large-scale consumption in Canada, was initially regarded as a novel food. The Finnish authorities stated that it had been used for human consumption to a significant degree in Finland before May 1997. To be precise, ten growers had harvested and sold six to eight tonnes per hectare from a five-hectare plantation, starting in 1995. Is this significant? The VNV considers this to be a reasonable argument for the product. Additional arguments put forward by Finland were that other berries had not caused health problems and that the Canadian population is similar to that of northern Europe. The VNV does not accept these arguments: the other berries are from different plant species, and while the fact that the Canadian population has been consuming the berry without problems can serve as information in the dossier, this would not have obviated the need for assessment if no history of consumption in Finland had been demonstrated.

The **kiwi** (Actinidia) was certainly introduced to Europe before 1997, but in summer 2004 a new type (known as the 'golden kiwi') that had not been declared as a novel food, was found in supermarkets. 'A kiwi is a kiwi' was the oft-heard maxim. Taxonomy is inconclusive as to whether these are different species (Actinidia deliciosa and Actinidia chinensis) or varieties of the same species. The two types of kiwi differ not only in appearance and taste, but also in their allergen profiles.[3] The VNV considers that an opportunity was missed in terms of image-building, in that such a large-scale introduction of a new species or variety of a fruit known to be allergenic was not discussed in advance with the competent authorities.

2.3 Special categories of foods

Certain special categories of foods are covered by specific legislation. This is often accompanied by appendices listing substances that are allowed to be used in the foods in question, but the lists are usually not exhaustive. If a producer wishes to use an ingredient that is not on the lists of permitted ingredients for those foods, then the producer must first check whether the substance falls into one of the categories of novel food ingredients, in which case the Regulation procedure for novel foods has to be followed.

2.3.1 *Food supplements*

The Commodities Act defines food supplements as 'food or drink products that are intended as a supplement to the normal diet, provide a concentrated source of one or more micronutrien*ts or other substances with a nutritional or physiological effect, and are traded in measured small unit quantities intended for ingestion'. The Food Supplements (Commodities Act) Decree is an interpretation of European Directive 2002/46 on the approximation of laws of the Member States in this area.[20] An Annex to the Directive lists vitamins and minerals and the chemical compounds in which these are permitted to be used. The Directive further requires minimum and maximum levels to be laid down for the presence of vitamins and minerals in food supplements, based on scientific recommendations. Medicinal claims are not permitted. There are types of vitamins and minerals that are not on the list but that were already on the market in food supplements when the Directive entered into force: for these products a safety dossier had to be submitted to the European Commission by a Member State before 12 July 2005. If the European Food Safety Authority (EFSA) does not then make a negative recommendation, the substance may be used in food supplements in the Member State until 31 December 2009. The European Commission is to produce a proposal for the revision and enlargement of the list annexed to the European Directive on food supplements, also for substances other than vitamins and minerals, by 12 July 2007.

2.3.2 *Enriched foods*

Enriched foods are foods to which micronutrients (vitamins and minerals) have been added but whose main purpose is not to provide micronutrients. Enriched foods are covered by the Addition of Micronutrients to Foods (Commodities Act) Decree: these products may only contain micronutrients listed in the Appendix to the Decree. In the case of enriched foods to which a substance has been added that is not on the Decree list, the producer must apply to the Minister of Health for an exemption, demonstrating that the product is not harmful.

A recently published European Regulation on the enrichment of foods (European Community, 2006) states that the European Commission is to draw up

* The Commodities Act defines micronutrients as nutrients essential to the functioning of the human organism that the body cannot produce itself and therefore have to be ingested in small quantities in the diet.

a Register of permitted vitamin formulations and mineral compounds, with conditions for their use. Vitamins and minerals already used in enriched products in a Member State on the date that the Directive enters into force, may be used in that Member State for a maximum of seven years thereafter, provided the Member State submits a safety dossier within three years of its entry into force and the EFSA does not make a negative recommendation on the substance. In addition, substances other than vitamins and minerals used for enrichment and which the EFSA suspects may be harmful, are placed on a list of substances to be investigated. Producers and other interested parties may submit data to the EFSA on these substances demonstrating that they are safe in use: it will then be decided within four years whether use of the substance is to be permitted generally, permitted with restrictions or prohibited.

The VNV has been asked several times for an opinion on the qualification 'micronutrient' in the case of compounds such as conjugated linoleic acid and zeaxanthin, but these questions are beyond its mandate. The VNV notes that so far it has been able to assess the safety of novel foods satisfactorily aside from their effects (if any). It does however consider it desirable for the scientific basis for effects to be assessed and the results of the two assessments combined at some point.

2.3.3 *Foods for particular nutritional uses*

The 'foods for particular nutritional uses' category covers products such as infant formulae and follow-on formulae, baby food, foods for energy restricted diets, dietary food for special medical purposes, foods for sportspeople and foods for diabetics. There is a general European Framework Directive (89/389/EEC, amended by Directives 96/84/EC and 1999/41/EC),[11,15,17] and there are separate European Directives on some of these categories of foods*. In the Netherlands this legislation is implemented in the Products for Particular Nutritional Uses (Commodities Act) Decree and a number of Commodities Act Regulations.

Later on in this report we consider foods for infants and young children and dietary food for special medical purposes, for which there are separate lists of nutrients that may be added. The other types of foods for particular nutritional uses are covered by a list annexed to European Directive 2001/15/EC (amended by Directive 2004/5/EC).[18,21] The Dutch Addition of Substances to Foods for Particular Nutritional Uses (Commodities Act) Decree is based on this Directive.

* An overview can be found on the European Commission website: http://ec.europa.eu/comm/food/food/labellingnutrition/nutritional/index_en.htm.

The recital in the European directive includes the following text: “A number of nutritional substances such as vitamins, minerals, amino acids and others may be added to foods for particular nutritional uses in order to ensure that the particular nutritional requirements of the persons for whom those foods are intended are fulfilled [...].” The Annex to this Directive lists the substances that may be added to foods for particular nutritional uses: vitamins, minerals, amino acids and substances such as carnitine and taurine, nucleotides and choline and inositol. Other compounds may be used, but substances that are essentially new must undergo assessment as novel foods. Trade in products which do not comply with this Directive has been prohibited since 1 April 2004. Products for particular nutritional uses that are not listed in the categories under the Directive must be notified to the competent authority of the Member State by the producer or importer, and a label must be submitted. The competent authority can then require scientific data to be submitted, which prove that the product is safe and fulfils the target group’s particular nutritional requirements. The VNV notes that here too the national assessment body can be called upon to adjudicate.

Foods for infants and young children

Substances and quantities that may and may not be used are covered by European Directive*s12,14 (and subsequent amendments to these Directives) and in the Netherlands by the Commodities Act Regulations on Infant Formula and Baby Food, which are based on the former. Only nutrients listed in the Appendix may be added in the production of processed cereal-based foods for infants and young children. In addition to the substances listed in the Appendix to the Infant Formulae (Commodities Act) Decree, other food components may be used ‘where appropriate’ in infant formulae and follow-on formulae (Article 7 of the Infant Formulae (Agricultural Quality) Decree 1994), provided it has been demonstrated based on generally accepted scientific data that these substances are suitable to fulfil the target group’s particular nutritional requirements. It is important, in the VNV’s view, that the scientific data be checked.

Dietary foods for special medical purposes

European Directive 1999/21/EC on dietary foods for special medical purposes[16] defines three types of dietary foods used under medical supervision: standardised, nutritionally complete foods; nutritionally complete foods

* Meanwhile a revised Directive has been published (2006/141/EC).

specifically for medical therapy; nutritionally incomplete foods specifically for medical therapy. The Directive lays down rules on what must be stated on the label. The Annex to the Directive contains tables of rules for levels of vitamins, minerals and trace elements, distinguishing between products for infants and products for other users.

Article 3 of the Directive states:

The formulation of dietary foods for special medical purposes shall be based on sound medical and nutritional principles. Their use, in accordance with the producer's instructions, should be safe, beneficial and effective in meeting the particular nutritional requirements of the persons for whom they are intended, as demonstrated by generally accepted scientific data.

The Dutch Dietary Food for Special Medical Purposes (Commodities Act) Regulation implements the European Directive. When marketing a dietary food for special medical purposes for the first time, the producer must submit a specimen label to the Food and Consumer Product Safety Authority.

Arginine
At the end of 2003, two medical nutrition products for intensive care patients were withdrawn on the basis of Canadian findings concerning arginine. A meta-analysis found that adding arginine to food for intensive care patients had no effect on mortality or complications due to infections. Some previously published studies had shown that the use of arginine in patients with sepsis was associated with increased mortality. New evidence-based Canadian guidelines advise against enteral nutrition with added arginine. L-arginine and L-glutamine are permitted in medical nutrition in Europe: these substances are explicitly listed in the European and Dutch legislation. As with all medical nutrition, it must be possible to show satisfactorily that the food is safe, beneficial and effective. If a substantially new ingredient is used, the safety assessment procedure for novel foods must be followed.

TGF-ß2
This protein is obtained from casein (in the processing of cow's milk). It is already being used in medical nutrition for patients with Crohn's disease, where the TGF-ß2 level is said to be the same as in unpasteurised cows

milk. This product is offered on a particular firm's website, stating that a doctor's prescription is not required for medical nutrition, but that it must be used under medical supervision. Another firm wishes to offer TGF-ß2 for a different type of patients at a concentration 1,250 times higher than in cow's milk, pointing out that this concentration is still lower than that in mother's milk. The question remains whether this intended use of TGF-ß2 makes it a novel food.

2.3.4 *Herbal preparations*

Herbal preparations consist of herbal substances or preparations thereof, such as extracts, and are covered by the Herbal Preparations (Commodities Act) Decree. An Appendix to this lists herbs that may not be traded as goods; there is no 'whitelist'. Producers and traders are expected to have objective data indicating the effects or properties, and showing satisfactorily that the herbal preparation has a history of safe use in foods. Herbs and plants that have not previously been used for human consumption to a significant degree in the EU, are covered by the legislation on novel foods.

Herbal preparations must not be confused with herbal medicines, which are defined separately in European Directive 2001/83/EC on medicinal products for human use[19] as: "Any medicinal product containing as active ingredients one or more herbal substances or preparations thereoff. These products are covered by the pharmaceuticals legislation. The Directive also gives separate definitions of 'herbal substance', 'preparation from a herbal substance', and 'traditionally used herbal medicinal products.

2.3.5 *Food additives*

In short, additives are substances that are not as such normally consumed as foods or used as food ingredients, and that are added to foods for technical reasons. Directives 89/107/EEC and 94/34/EC provide the basis for the European legislation on these products,[10,13] and are implemented in the Food Additives (Commodities Act) Decree, where the full definition of additives can be found. The Directive describes what categories of additives there are, and lays down general criteria for their use. Separate Directives are drawn up on colourings,

sweeteners and the other additives as a group. The Commodities Act also distinguishes between these categories of additives, and covers them in separate regulations or decrees. Additives may only be used if they are listed in the appendices to these texts. A Member State may permit an additive that is not on the list (but that does belong in one of the listed categories) for a maximum period of two years. An official check of foods in which the additive is used must then be carried out. The Member State must inform the other Member States and the European Commission of the decision, and may file an application for the additive to be added to the whitelist, along with a dossier justifying and explaining its use. Additives are assessed by the EFSA for use in the EU. Their approval is decided by the Standing Committee on the Food Chain and Animal Health. This also applies to sweeteners and colourings.

2.3.6 *Flavourings*

Flavourings are defined in the Flavourings (Consumer Goods Act) Decree. They do not include substances that impart only a sweet, acidic or salty taste. The Flavourings (Commodities Act) Decree implements EU Directive 88/388/EEC*. [9] The associated Substances in Flavourings (Commodities Act) Decree lays down maximum levels for certain flavourings in foods. There is also a European Register of flavourings for use in foods declared in the Member States. These flavourings are to be assessed as set out in Regulation (EC) No. 1565/200023, so as to arrive at a European whitelist of permitted flavourings.

* An overview can be found at the website: http://ec.europa.eu/comm/food/food/chemicalsafety/additives/comm_legisl_en.htm

Chapter 3

Notifications

3.1 Criteria for notification

Under the notification procedure a ‘novel’ product can be placed on the European market immediately, provided it is similar to a novel food on which a European Decision has already been issued, or similar to an existing food. The firm notifies the European Commission, providing relevant product data indicating that it is a substantially equivalent product. So far the practice in the EU has been that a product is only placed on the market if the notification is supported by at least one Member State. This is why in practice this accelerated procedure takes place through the competent authority of one of the European Member States (the Ministry of Health, Welfare and Sport in the Netherlands), with which the firm files its notification application. If the assessment authority (the Novel Foods Unit of the Medicines Evaluation Board in the Netherlands) takes the view that the ‘novel’ product is sufficiently similar to an existing food and the competent authority adopts this view, the other Member States are notified of this through the European Commission. The procedure described here is laid down in Article 5 of European Regulation 258/97 on novel foods and novel food ingredients.

3.2 What data should the notification dossier contain?

A dossier should contain certain data on the basis of which substantial equivalence with an existing product can be assessed. As regards information on the history of the source, human exposure and toxicology, it is sufficient, in principle, to refer to the existing product (an already approved novel food or an existing food). The dossier should also contain the following data:

- product specification: a good description of the composition of the food or food ingredient. Analyses of the composition of several product batches must show that the product is consistent
- source identification:
  (a) It must be demonstrated that the product is from the same organism (species) as the already approved novel food or the existing food
  (b) If the source differs at species level (or the relationship is even less close), market approval cannot be arranged through a notification procedure, unless it is a highly refined product consisting of only a limited number of chemical compounds
  (c) If the source material is from another variety of the same species, a precise description must be supplied with all the relevant information on safety aspects (e.g. secondary plant substances, potential allergens).
- description of the production process, including quality assurance (e.g. GMP, *Good Manufacturing Practice*)
- level of undesirable substances. This includes not only chemical and microbial contaminants, but also any harmful substances and toxins from microorganisms that are naturally present
- intended use; description of use(s) and expected intake: the applicant must state the quantity that is expected to be consumed on a daily basis
- nutritional value, metabolism: if the product composition is the same, this information will already be known from the already approved novel food or the existing food.

Micro-alga (Odontella aurita)
The Member States have received the opinion of the French authority on the micro-alga Odontella. When considering Odontella, the French authority looked at the available data on composition (fatty acid profile, minerals, amino acids), use (flavour enhancer in products such as soups, hence low consumption), pesticide residues (below the limit), phycotoxins (absent), external contaminants (absent, except arsenic, which is removed), and microbial quality (adequate). This appears to be in order. The notification, however, is supported with the argument that this micro-alga, as qualified above, is very similar to macro-algae such as brown algae (Pheophyta), red algae (Rhodophyta) and green algae (Chlorophyta), which have a history of use as foods in France. The VNV can well imagine that different families of algae are similar, but it wonders whether the similarities provide sufficient basis for the qualification 'substantially equivalent', and hence for a notification. After all, these are different species of organisms that are not even related at genus level. To clarify: the phylogenesis and taxonomy of living organisms are based on the following classification, in order of increasing relatedness: class, family, genus, species, variety. The question is whether there can be substantial equivalence between organisms of two different species, let alone at the level of different genera or families. The VNV objects to the use of the notification procedure in cases of this kind. In the form of a safety dossier, however, the data supplied by the applicant could be used in an authorisation procedure.

Argan oil (Argania spinosa)
This case concerns not the organism as a whole, but the oil, a processed food. The French note the similarities with other vegetable oils: as regards the fatty acid profile, for instance, the oil is similar to peanut oil and sesame oil (but not to olive oil, as the applicant claims). The amount of tocopherol also seems to be similar to that in sesame oil. The phytosterols, on the other hand, do not seem to be similar to those in peanut oil or sesame oil, but to the oil in spinach, while the triterpene alcohols seem similar to those in other plants, such as lettuce. This oil has a strong taste, as is the case with, for instance, hazelnut oil. Here too, the qualification 'substantially equivalent' seems forced. This oil displays similarities with other edible vegetable oils and contains components that occur in leafy vegetables, that is all. These are totally different families, genera, species and varieties. The comparisons can be used for safety assessment, but they do not justify the qualification 'substantially equivalent'.

Tea seed oil (Camellia furfuracea)
In this case, the Dutch VNV has been asked to evaluate the applicant's claim of substantial equivalence: the applicant notes the similarities with olive oil. Here too, the fundamental problem is that the olive belongs to a completely different plant family than tea. The fatty acid profiles do seem somewhat similar, but there are undoubtedly differences in the carotenoids, tocopherols and phytosterols. The production method in China also needs to be considered.

3.3 'Substantial equivalence' of foods often debatable

The VNV is unhappy with the use of the term 'substantial equivalence' in the case of foods consisting of organisms from different classes, families, genera or species, or in the case of foods that are derived from them and have a complex composition. Accordingly, it is not in favour of the procedure adopted in the case of the notifications of the micro-alga Odontella aurita and of Argan oil (Argania spinosa). The applicant for the notification for tea seed oil (Camellia furfuracea) should follow the authorisation procedure. The VNV also considers that the requirements for a notification dossier should be harmonised at European level in line with the points put forward. When dealing with a notification request, the whole of the legislation in force on that food should be reviewed in general, including the rules on hygiene, contaminants and composition. This is not the decisive factor in the assessment of substantial equivalence, however.

Chapter 4

Dossier requirements for authorisations

4.1 What data should the authorisation dossier contain?

Novel foods that cannot be regarded as substantially equivalent to foods that have already been approved must be subjected to the authorisation procedure, which comprises more steps than the notification procedure. An initial assessment of the safety of the product in one of the Member States is followed by a round of second assessments by the other Member States. If the Member States' opinions differ, a decision to approve or reject the product has to be taken at European level. The Member States vote on this in the Standing Committee on the Food Chain and Animal Health, if necessary after having obtained a scientific recommendation from the EFSA. The assessment system used by the VNV has been discussed in detail in a previous report;[31] this Chapter supplements that discussion.

According to the European Commission recommendations (97/618/EC),[7] the dossier should contain the following components:

1 administrative data on the applicant
   If the applicant is not the producer of the novel food or ingredient, the dossier must clearly indicate who the supplier is
2 general description of the new product or new process used
3 specification of the information required based on the structured schemes (decision trees)

4 evaluation and conclusion
5 summary of the dossier.

As regards point 3, the dossier should contain the following components:

- product specification: a good description of the composition. Analyses of the composition of several product batches must show that the product is consistent
- description of the production process, including quality assurance (e.g. GMP)
- precise description of the source of the novel food or food ingredient: this means all the relevant information on safety aspects
- description of the uses of the food or food ingredient
- data on expected human consumption: in the case of a food ingredient, for instance, an estimate of the total consumption of the various products in the proposed range. Measures to prevent consumers from ingesting more than the safe limit should be proposed if necessary
- data on prior exposure in humans (including, for instance, the intake in daily nutrition) and the effects on health
- data from nutritional (physiological) research
- microbiological information
- toxicological data: results of toxicological research on the novel food or food ingredient, and information on the level of undesirable substances
- data on possible allergic reactions
- data on safety trials in humans
- data on post-market monitoring: it should be considered whether pre-market research should be conducted and whether the product should be monitored after market launch.

Research data may be obtained from the applicant's own research and independent research commissioned by the firm, and may include published reports in the scientific literature.

4.2 Considerations for particular categories of novel foods

The previous section lists the components that a dossier should contain according to the European Commission recommendations. The ensuing sections briefly comment on some points that need to be considered in the case of certain categories of novel foods. Detailed information on the categories 'genetically modified products', 'exotic products' and 'bioactive components' can also be found in the 2002 report on Safety Assessment of Novel Foods.[31]

4.2.1 *Exotic products*

Exotic novel foods are products that are consumed elsewhere in the world, outside the European Union (EU). Points that should be considered in the dossier to be submitted are:

- awell-documented history of safe use outside the EU. This information can serve as an indication of the absence of toxicity (acute or worse). Depending on the nature of the product and the information available, data from new safety trials on laboratory animals and/or humans may be required
- the absence of contaminants should be discussed in a description of the production chain. This chain control should include the reproducibility of the production process and the hygiene aspects
- additional toxicological research may be necessary, depending on the nature of the product and the target group
- possible shifts in dietary habits. It should be considered whether the new exotic product will be consumed instead of a traditional food in the same category, whether this will have consequences for the population's dietary habits, and if so, what consequences.

4.2.2 *Specific bioactive ingredients*

Specific bioactive ingredients can be: minerals, vitamins, antioxidants, carbohydrates with special properties, long-chain polyunsaturated fatty acids, whey protein concentrates. Also, if a new bioactive ingredient is added to a food supplement or food for a particular nutritional use, such as medical food or infant formula, this new ingredient is covered by the European legislation on novel foods and should therefore be declared for assessment. There are ingredients that have so far only been used in food supplements. If an ingredient of this kind is to be used in foods, this must also be declared for assessment.

Points that should be considered in the dossier to be submitted are:

- the composition of the end-product. The VNV assesses the composition of the product, irrespective of how the bioactive ingredients are added (they may be added directly to the end-product or earlier in the production chain, e.g. in the feed of an animal from which the novel food is derived)
- the absence of indirect adverse effects. It must not jeopardise the resorption of other nutrients; it must not have an effect on the intake of other nutrients

- any consumption research must pay particular attention to the potential danger of overdose or accumulation. Data from food consumption surveys are important here (attention should be paid to differences in dietary habits in different geographical areas and populations in Europe)
- additional toxicological research may be necessary, depending on the nature of the ingredient and the target group
- when carrying out safety trials on volunteers, the biomarkers chosen will depend very much on the type of ingredient
- active market monitoring may be necessary to supplement these trials. A limitation of pre-market research in humans is that it never fully reflects the diversity of the population. Assumptions regarding level of intake can be verified by monitoring use under free conditions: this is particularly important in the case of a specific bioactive ingredient that has a physiological effect beyond the effect of the food as such.

4.3 Allergenicity

The safety assessment of a proposed novel food should include possible allergic reactions to consumption by persons with particular sensitivities. In the past, particular attention has been paid to this aspect in the case of foods from genetically modified organisms (GMOs), for which a standardised assessment procedure has been developed.

The vast majority of the current generation of commercial GMOs are well-known food plants to which a new property has been added by inserting a relatively small piece of DNA from another organism, resulting in the production of one or more proteins. It has been demonstrated that this technique can in principle result in the addition of an allergenic protein to a plant in the case of a genetically modified soya with a protein from the Brazil nut.[38] This product has consequently not been commercialised.

International guidelines have been drawn up on the pre-market assessment of allergenic properties of GMOs.[4,5] These are based on knowledge of any allergenic properties of the parent plant and the organism from which the transferred DNA is taken. In addition, the amino acid sequence of the new proteins is compared with that of the known allergens, and the researchers check, using in vitro digestion experiments, whether the new proteins are unresponsive to digestive enzymes, which could be an indication of allergenic properties. The use of laboratory animal models has also been proposed, but the question is whether there is already a practical method that could be used to achieve this goal. Lastly, it has been proposed that serum pools from allergy patients could be

used to check for possible allergic reactions. There is a distinction here between specific screening (for a particular allergen) and targeted screening (for several groups of known allergens). VNV's assessments of GMOs have not yet included this method.

It is also important to assess the possible allergenic properties of other novel foods that contain large numbers of different proteins. This is the case, for example, with exotic fruits, certain seeds or a fungus-based protein preparation. Some such products have been demonstrated to produce allergic reactions in particularly sensitive persons when consumed: we now know, for instance, that there are people who display an allergic reaction after eating kiwi[36] and that incorporating lupin flour in bread can cause a reaction in people with peanut allergy.[30,35]

Various methods that are used to assess possible allergenicity in GMOs are not applicable to complex novel foods of this kind, as they contain very large numbers of proteins of which the amino acid sequences are generally not known. The remaining methods, on the other hand, have not been sufficiently operationalised, in the VNV's view. The VNV therefore considers that researchers should be encouraged in particular to develop and validate suitable laboratory animal models and in vitro methods (such as serum screening). The idea of a targeted serum screen is now ripe for development, taking into account knowledge on the relationship between organisms that have been identified as allergenic as well as knowledge on the relationship between allergenic proteins from different organisms, in relation to cross-reactivity.[2]

An important point here is that a number of allergens can often occur in a single source, causing different reactions in patients. The VNV also considers that not enough attention is being paid to differences in sensitivity between populations, even within Europe.

In certain cases a novel food could be allowed onto the market despite the fact that its use could produce allergic reactions in some consumers. The VNV would emphasise that in this case an appropriate flanking policy is needed, e.g. regarding consumer information. It also recommends examining whether systematic recording of reports of allergic reactions is feasible. This would be worthwhile because, based on current scientific knowledge, a pre-market safety assessment cannot rule out allergenic properties of a novel food with one hundred percent certainty. Subjective complaints, on the other hand, need to be confirmed clinically before a conclusion can be drawn.

Chapter 5

Safety following introduction

5.1 Market monitoring

European Novel Foods Regulation 258/97 is accompanied by a European Commission recommendation (97/618/EC)[7] on the scientific aspects and presentation of the information required to support applications for the marketing of novel foods and food ingredients. The recommendation says: “In some circumstances it is envisaged that plans should be provided for post-market surveillance for possible long term effects of the novel food.”

The authorities are also responsible for monitoring food safety in a broader context. In its initial framework recommendation on novel foods, the VNV proposed a market monitoring system with four central elements:

- a complaints line
- on-going monitoring of intake data on foods by the authorities and the industry jointly
- long-term epidemiological prospective cohort research into the relationship between chronic illnesses and nutrition
- active market monitoring of novel foods containing specific bioactive ingredients by the industry (PLM, post-launch monitoring).[31]

TNO had already developed a PLM concept for the industry.[44] Since then suggestions have been made in the scientific literature for PLM on functional foods, also to measure their effects.[45] As regards novel foods of genetically

modified origin, it should be emphasised yet again that PLM is only worthwhile if there are specific indications of possible problems.[34,40] In 2004 the National Institute for Public Health and the Environment (RIVM) published a report focusing on the authorities' market monitoring of functional foods.[40] The report dealt with the sequencing of existing elements, and indicated the possibilities of extending components and establishing connections. The RIVM envisages responsibilities for the authorities, particularly in (a) actively identifying problems and carrying out exposure research, (b) gauging the relevance of exposure, (c) quantifying exposure, (d) quantitatively weighing up the health loss and gain, and (e) putting forward legislation and regulations where necessary. The authors of the RIVM report suggest that this be done by an independent expert committee. The VNV endorses these RIVM recommendations.

5.2 Market monitoring by the industry

Sometimes approval of a product is made contingent on post-launch monitoring after it comes onto the market. The purpose of this is to provide additional information on use by consumers. So far this has been the case with a group of foods with specific bioactive components known as 'functional foods'. With this type of food in particular, high intake may not be desirable, as there have been no long-term studies of high consumer intake. Sometimes ingestion by very young children or pregnant women is not desirable, because little or no research has been done on the subject. There is no indication that the novel food is harmful to these groups, however, as in that case it would not have been approved, or more pre-market research would have been required. Still, it may be known that the level of a biomarker changes in the case of high intake. PLM could also be used to observe product-related health problems experienced by consumers.

The conclusions that can be drawn from the PLM studies carried out so far on cholesterol-lowering ingredients, are that they are consumed mainly by people in the target group, and that many consumers are not methodical enough to use the product on a daily basis. Moreover, the optimum amount is often not reached.

Phytosterols
Phytosterols and phytostanols are vegetable substances that are added to reduce blood cholesterol level. Market approval of a particular type of phytosterols in yellow fat spreads has been made contingent on post-launch monitoring. This requirement was adopted by the European Scientific Committee on Food, which also assessed the results. The study showed that

the product was bought mainly by over-45s in one or two-person households, with no children living at home. There has been no specific research into the extent to which children consume the product. The European Committee concludes: "However, the similarity between consumption by one-person households and larger households suggests the predominant use is by one person per household, presumably to try to control elevated blood cholesterol levels. Given the extensive exposure to the product in Europe the number of health-related calls received from the consumers has been small. No evidence was obtained from PLM on occurrence of adverse health effects from the current intake of marketed spread-containing phytosterol esters."[42] The firm's PLM study did not look at the blood cholesterol levels of the consumers who buy the product. Generally speaking, one in three Dutch people have an excessive cholesterol level (higher than 5 mmol/L); most of them aged over 45. The firm has undertaken to once again carry out post-launch monitoring when it extends its product range.

Phytostanols
The Dutch competent authority required post-launch monitoring following the introduction of margarines and yoghurt containing certain phytostanols. Phytostanols are not regarded as a novel food ingredient because they were already on the market in Finland before Regulation (EC) No. 258/97 came into force. In the Netherlands, however, the Health Council and the Ministry of Health, Welfare and Sport wanted information on the consumption of these products for the same reasons as in the case of phytosterols. The firm concerned commissioned independent research from TNO. The research method used here provided more information on the backgrounds of the individual users than that used in the study of phytosterols mentioned earlier. A substantial majority of the participants in the study, characterised as 'loyal users', consumed the margarine on their own initiative. The vast majority of users knew about their personal cholesterol levels from regular checkups.

In its recommendations, as a precaution against over-consumption, the VNV has constantly urged reducing the product range and providing standardised, unambiguous portion packages and clear instructions and labelling. It stands by this view, as the range of products containing plant sterols and plant stanols in

Europe has expanded considerably, and there are no research results confirming that they are safe in the case of chronic exposure.

5.3 Assessing signals

The VNV has looked into the possibilities of quantifying the post-launch cycle of genetically modified maize and soya. A quantified supply chain from producer to consumer would provide a basis for a well-founded risk assessment if there are any complaints about these novel foods.

The VNV has examined whether genetically modified maize and soya and derived products can be monitored right up to their use in individual foods and intake by consumers. It has explored the current feasibility of gauging the value of signals that there could be something wrong with a genetically modified food. The information that a dossier on a genetically modified food would need to contain is set out in detail in the first framework recommendation in Chapter 3:[31] namely nutritional and toxicological data, biomolecular characterisation and expected consumption. If there are complaints, a comparison between the quantities of maize and soya eaten by laboratory animals and consumer exposure could be important: if the safety research shows no adverse effects from high intakes of the novel protein and the novel food in laboratory animals, and there is no indication from molecular biological research that an unintended change in composition takes place, then there is not likely to be any effect from low intakes in humans.

For laboratory animals, the VNV took NOAELs (no-observed adverse effect levels) from – or calculated them from – producers' dossiers (see Annex D). These data relate to the daily intake of soya protein and maize protein by laboratory animals at which they experience no adverse effects. To gauge consumer intake, the VNV used producers' estimates and data from the food consumption survey. It should be noted, however, that this was based on a worst-case scenario. Based on the data available, the VNV calculated MOEs (margins of exposure) by dividing the NOAEL by the quantity consumed by humans.

The applicants' computations show that there is a wide margin between the quantities of novel proteins that consumers could be exposed to and the highest tested doses that showed no adverse effects in laboratory animals. This comparison, however, has to be based on the information supplied by applicants. The VNV has found that it is not really possible at present to monitor these plants and the derived foods using directly accessible data such as data banks and sites of industry organisations. Recent legislation is expected to improve this situation substantially. Now that the European Regulations on genetically modified foods

and the General Food Regulation (EC/178/2002)[24] have come into force, there is an obligation to provide a unique identification code for each genetically modified variant of a plant, and the traceability of all foods through the supply chain has been assured since 1 January 2005. In the event of incidents, this provides a much more targeted way of assessing health problems or signals, and taking measures if necessary. The information on labels, however, will only be of limited usefulness.

The VNV would note the following here: when signals involve, for instance, reports of allergic reactions that have not occurred hitherto, in the case of soya these could also be caused by proteins in conventionally improved soya, for which no safety dossier needs to be submitted before it comes onto the market (see the example of kiwis in 2.1).

Chapter 6

The future

In recent years, Europe has invested a good deal in achieving a high level of food safety and transparency in the food chain.[33] The positive effects of food on cardiovascular disease and type 2 diabetes have been in the spotlight recently.[37,41] As a result, some people consider that food safety has enjoyed (and is enjoying) an exaggerated amount of attention. However right it may be to put things in perspective, it is not desirable to abandon the high level of food safety that has been achieved.[37] The current system of pre-market assessment of the safety of novel foods contributes to this level of safety.

We continue to use nutrition and other means to achieve longer life and better quality of life. In Western society this has resulted in the development of foods with specific bioactive components. In addition to slow-absorbing carbohydrates and medium and short-chain fatty acids, there are antioxidants to combat ageing, immune-active proteins, modified microorganisms to supplement the normal intestinal flora, and appetite-inhibiting functional foods coming onto the market.[39] Endeavours to achieve a good nutrient profile for complex vegetable and animal foods will continue through improvement and gene modification. The VNV believes that these innovations call for a sharp lookout to be kept for possible food safety risks (and effects). In other parts of the world, attempts at improvement will focus on other types of products, which also call for our attention, given the global nature of food supply. In the VNV's opinion, the current European legislation and the global CODEX agreements should in principle be adequate.

Elsewhere in this report recommendations are given on revising the European legislation at a practical level. Another question is what role the European Food Safety Authority (EFSA) should play in the assessment procedure in the future. In order to perform the function of the Dutch assessment authority, the VNV has been assigned to the Medicines Evaluation Board.

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Annexes

Annex **A**

Request for advice

On 18 August 1999 the Minister of Health, Welfare and Sport wrote as follows to the Chair of the Health Council (letter ref. GZB/VVB 993428):

European Union Regulation (EC) 258/97 on novel foods and novel food ingredients has been in force since May 1997, making safety assessment part of a Community procedure.

The possibility of having the assessment carried out by the Health Council has already been discussed with you, and I would therefore ask you, also on behalf of the State Secretary for Agriculture, Nature Management and Fisheries, to organise the safety assessment for a number of years during this initial phase of the implementation of European Regulation (EC) 258/97. Assigning this task to the Health Council makes sense in view of the experimental nature of the assessment in the first few years, as this is a new kind of assessment, including some new categories of foods and food ingredients: namely a pre-launch safety assessment of foods of genetically modified origin and ‘functional foods’ (nutriceuticals) in particular. I also trust that the independent scientific advice from the Health Council will further strengthen confidence in the Dutch opinion on the part of the European Commission and the other Member States.

My policy is to achieve the greatest possible openness and transparency in the procedure adopted and the assessment, so as to give consumers confidence in the safety of the novel foods. I would ask the Health Council to contribute to this, e.g. by allowing access to the dossiers for which applications are filed, while of course protecting confidential company data, and publishing the criteria used to assess safety.

Minister of Health, Welfare and Sport
(signed)
Dr. E. Borst-Eilers

Annex **B**

The Committee

- Prof. L.M. Schoonhoven, *chair until 1 January 2004*
  Emeritus Professor of Entomology; Wageningen University and Research Centre
- Prof. E.G. Schouten, *chair from 1 January 2004 to 1 January 2005*
  Professor of Epidemiology; Wageningen University and Research Centre
- Prof. C.A.F.M. Bruijnzeel-Koomen
  Professor of Dermatology and Allergology; University Medical Center Utrecht
- Dr. M.M.C. Gielkens, *advisor*
  Committee on Genetic Modification-Ministry of Housing, Spatial Planning and the Environment (COGEM-VROM), The Hague
- B. van der Heide, *advisor*
  Ministry of Health, Welfare and Sport, The Hague
- E.J. Kok
  Toxicologist; Institute of Food Safety (RIKILT), Wageningen
- Dr. C.F. van Kreijl
  Molecular biologist; National Institute for Public Health and the Environment (RIVM), Bilthoven
- Prof. P. van der Laan
  Professor of Statistics, Eindhoven University of Technology

- Dr. B. Loos, *advisor*
  Committee on Genetic Modification-Ministry of Housing, Spatial Planning and the Environment (COGEM-VROM), The Hague
- Dr. F. Nagengast
  Gastroenterologist; Radboud University Nijmegen Medical Centre
- Dr. J.M.A. van Raaij
  Nutritional physiologist; Wageningen University and Research Centre; National Institute for Public Health and the Environment, Bilthoven
- Prof. G. Schaafsma
  Professor of Nutrition, TNO Nutrition, Zeist
- Dr. G.J.A. Speijers
  Toxicologist; National Institute for Public Health and the Environment (RIVM), Bilthoven
- Prof. W.J. Stiekema
  Professor of Bioinformatics; Wageningen University and Research Centre
- R. Top, *advisor*
  Ministry of Health, Welfare and Sport, The Hague
- Prof. W.M. de Vos
  Professor of Microbiology; Wageningen University and Research Centre;
- Dr. R.A. Woutersen
  Toxicologist, TNO Nutrition, Zeist
- Dr. M. Rutgers, *scientific secreary*
  Health Council, The Hague
- Dr. C.M.A. van Rossum, *scientific secreary*
  Health Council, The Hague
- Dr. J.A.G. van de Wiel, *scientific secreary until 1 December 2004*
  Health Council, The Hague

The current composition of the VNV can be found on the website of the Medicines Evaluation Board's Novel Foods Unit: http://www.nieuwevoedingsmiddelen.nl.

Annex **C**

Reports till 1 January 2005

1999/01VNV	Herbicide-resistant maize (GA-21)
1999/02VNV	Oliezuurverrijkte soja (260-05) [only in Dutch]
1999/03VNV	Fractions of cereal brans
1999/04VNV	Bacterial dextran
1999/05VNV	Fytostanolesters [only in Dutch]
1999/06VNV	Lemna minor Horst 1 [only in Dutch]
2000/01VNV	Salatrims
2000/02VNV	Bt11-maize (pZO1502)
2000/03VNV	Herbicide-resistente soja (GTS 40-3-2) [only in Dutch]
2000/04VNV	Coagulated potatoe protein and -hydrolysates
2000/05VNV	Trehalose
2001/01VNV	Phytosterols
2001/02VNV	Genotoxicity of phytosterol(esters)
2001/03VNV	Noni juice
2001/04VNV	Phytosterols (2)
2002/01VNV	Maize-germ oil with phytosterols and vitamin E
2002/02VNV	Rapeseed oil with phytosterols and vitamin E
2002/03VNV	Docosahexaenoic acid rich oil
2002/04VNV	Herbicide-tolerant maize (NK603)
2002/05VNV	Safety assessment of novel foods
2002/06VNV	Iodine-enriched eggs

2002/07VNV	Dycylglyerol oil
2003/01VNV	Phytosterols (3)
2003/02VNV	*Camellia furfuracea var. furfuracea*
2003/03VNV	Betaine
2003/04VNV	Insect-resistant and herbicide-tolerant maize (1507)
2003/05VNV	Palmolein
2004/01VNV	Isomaltulose
2004/02VNV	Lycopene
2004/03VNV	Noni juice(2)
2004/04VNV	Noni juice(3)
2004/05VNV	Chia seed

More recent advisory reports have been issued under the responsibility of the Novel Foods Unit of the Medicines Evaluation Board (MEB). They can be found at the website http://www.nieuwevoedingsmiddelen.nl.

Annex **D**

Calculated margins of exposure for GMOs

Margin of exposure for maize and maize protein

NOAEL*s for the intake of maize and maize protein in laboratory animals can be found in the dossiers of Monsanto (GA 21 and NK 603 maize) and Novartis (Bt 11 maize). NOAELs are stated for acute and subchronic exposure to maize and maize protein in the diet. By the end of the study laboratory animals were consuming approximately 1/0.5877 = 1.7 grams of maize protein per kg of body weight per day. This intake was taken as the NOAEL. For the intake in humans, the producers' calculations used the average intake and the intake in humans in the 'heavy users' category. In some cases the producers used the 90 percentile for this, in others the 95, 97.5 or 99 percentile, so the figures are not necessarily comparable. The MOEs have been rounded off and indicate an order of magnitude. GA21 maize (herbicide-tolerant).

When calculating the margin of exposure for GA21 maize, Monsanto assumed a subchronic NOAEL (in rats) of 23.5 g/kg/day (see 5.3.1). This was divided by the expected average human intake of GA21 maize (0.015 g/kg/day), yielding an MOE of 23.5/0.015 = 1567 (rounded off to 1600) for adults and 23.5/0.03 = 783 (rounded off to 800) for children. The people in P97.5 have a margin

* To clarify: the term NOAEL is used here in the sense of the highest tested dose at which no adverse effects were observed, without limiting it to a particular type of study design.

of 23.5/0.113 = 208 (rounded off to 200) for adults and 23.5/0.171 = 137 (rounded off to 150) for children.

MEPSPS protein from GA21 maize (herbicide-tolerant)

To calculate the margin of exposure to the novel protein mEPSPS, Monsanto used the following computation: the subchronic NOAEL (in rats) for mEPSPS of 75 µg/kg/day was divided by 0.05 (average intake of mEPSPS in adults), yielding a margin of exposure (MOE), with respect to laboratory animals, of 1500. The margin for children, given average intake, is 750. The people in P97.5 have a margin of exposure of 1040 (rounded off to 1000) for adults and 680 (rounded off to 700) for children with respect to laboratory animals. According to the producer, this is a worst-case scenario, as the rats in the trial were given undenatured mEPSPS, and 80% of the protein in foods will probably be denatured by the various processes.

Margin of exposure for soya protein

CP4 EPSPS protein from GTS 40-3-2 soya (herbicide-tolerant)
The Monsanto dossier on GTS 40-3-2 soya found an acute NOAEL for exposure to CP4 EPSPS protein. No value was found for the NOAEL of soya protein, so a calculation was done based on data in the dossier.

In a 15-week trial, the final weight of BN rats averaged 178.5 ± 6.03 grams. The rats ingested 6.8 grams of food per day consisting of 30% soya. The soya consumption was approximately 0.3 x 6.8 = 2 grams of soya per day. In terms of body weight this was approximately 11.4 grams of soya per kg per day. The soya was preheated to 100ºC for 30 minutes. Soya beans cooked in salt contain 21.5 g of protein per 100g (NEVO (Dutch Food Composition Database) table). The consumption of soya protein was approximately 11.4 x 0.215 = 2.5 grams of soya protein per kg per day.

In the same trial the final weight of mice was 24.2 ± 0.91 grams. The mice ingested 2.77 grams of food per day. The proportion of soya in the food was 30%. The daily intake of soya was approximately 0.3 x 2.77 = 0.8 grams of soya. In terms of body weight, this was approximately 34.3 grams of soya per kg per day. The daily intake of soya protein was approximately 34.3 x 0.215 = 7.4 grams of soya protein per kg per day.

Monsanto does not give an estimate of human consumption of soya or soya protein. The genetically modified soya contains CP4 EPSPS protein, but the dossier does not state quantities; other sources give quantities of up to 300 µg/g.

The article by Harrison et al. (1996) estimates the maximum human consumption of CP4 EPSPS (from soya, tomato, potato and maize) at 0.3-0.44 mg/kg/day.

As there are no data on human exposure in the producer's dossiers, it is impossible to calculate the margin of exposure to total soya protein. The margin of exposure to CP4 EPSPS protein is based on an acute NOAEL (in mice) of 572 mg/kg/day (see 3.3.1). According to Monsanto, this dose is over 1,000 times higher than the highest expected human intake of CP4 EPSPS from soya and other sources. Human exposure to CP4 EPSPS is based on the data in.[32] The margin of exposure for intake of CP4 EPSPS is 572/0.44 = 1300.