Herbicide-resistant maize (GA-21)

Assessment of safety for the consumer, in accordance with European Regulation 258/97 concerning novel foods and novel food ingredients

Letter to the Dutch Minister of Health, Welfare and Sport

On December 21, 1999, professor JGAJ Hautvast, Vice-president of the Health Council of the Netherlands wrote as follows to the Minister of Health, Welfare and Sport:

Herewith I present you an advisory report that is prepared in response to your request, also on behalf of the State Secretary for Agriculture, Nature Management and Fisheries for advice regarding the safety of herbicide resistant maize (GA-21) for the consumer. This advise is a so called first assessment in the context of European Regulation EC 258/97 concerning novel foods and food ingredients. The assessment is carried out by the Committee on the Safety assessment of novel foods of the Health Council of the Netherlands.

This advisory report is also presented to the State secretary for Agriculture, Nature management and Fisheries.

signed
professor JGAJ Hautvast

Herbicide-resistant maize (GA-21)

Assessment of safety for the consumer, in accordance with European Regulation 258/97 concerning novel foods and novel food ingredients

Health Council of the Netherlands:
Committee on the safety assessment of novel foods

to:

the Minister of Health, Welfare and Sport

the State Secretary for Agriculture, Nature Management and Fisheries

Number 1999/1VNV, The Hague, December 21, 1999

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Contents

Chapter 1

Introduction

In August 1998, the Minister of Health, Welfare and Sport requested the opinion of the provisional Committee on the safety assessment of novel foods about the safety for consumers of a novel maize variant and foods and food ingredients made from it. The maize comes from a plant (GA-21), that, through genetic modification, produces an altered biosynthesis enzyme, thereby making it resistant to the herbicide 'Roundup Ready' (glyphosate). The provisional Novel Foods Committee considered the file and, to obtain clarification and additional information, contacted the producer, Monsanto (Mon98, Mon98a), the company that also submitted the application for permission to market the product. The committee could not finish the assessment.

On January 1st, 1999 the file was passed to the Committee on the safety assessment of novel foods of the Health Council of the Netherlands, hereafter referred to as 'the committee'. The committee considered the file for the first time on February 11th and formulated a further question about the profile of the secondary plant metabolites (Mon99). In June 1999, the applicant confirmed the analyses and the committee received the results on October 20th (Mon99a). The committee completed its assessment in December 1999. This advisory report represents its findings.

Chapter 2

Completeness and correctness of the file

2.1 Administrative data

Name and address of the applicant and producer of the novel food are as follows: Monsanto Company, represented by Monsanto Europe SA, 270-272 Avenue de Tervuren, 1150 Brussels, Belgium.

2.2 General description of the food

The application concerns the marketing and trading on the European market of GA-21 maize for immediate consumption and for further processing into foods and food ingredients.

The producer has split its original application to the Dutch competent authority into two parts. Monsanto first requests authorization, in accordance with article 4 of Regulation (EC) 258/97 (EC97), for the entire grain kernel and the food ingredients derived from it. Secondly, the producer requests the committee's opinion about the substantial equivalence of certain food ingredients derived from the plant to conventional ingredients. This concerns maize oil and starch hydrolysates, such as syrups and sugars. In the case of substantial equivalence, it is permitted with a notification to market these products immediately, in accordance with article 5 of Regulation (EC) 258/97. The committee chose to assess the safety of genetically modified maize kernels for consumption and considers these findings applicable to maize derived products.

2.3 Classification of the food for assessment

The file contains arguments for classification in class 3.1, one of the six main classes and sub-classes of novel foods, as referred to in table 1, in section I of Recommendation 97/618 of the European Commission (97/618/EC) (EC97a). This application concerns a genetically modified plant, the conventional variant of which has a history of safe use in the European Union. The committee concurs with this classification.

2.4 Information about the food

The applicant specifies the information that is essential for assessing the suitability for consumption of a food in class 3.1 on the basis of the subjects prescribed in EC Recommendation 97/618:

I Specification of the novel food (NF)
II Effects of the production process applied to the novel food
III History of the organism used as a source of the NF
IV Effect of the genetic modification on the properties of the host organism
V Genetic stability of the genetically modified organism (GMO) used as NF source
VI Specificity of the expression of novel genetic material
VII Transfer of genetic material from the GMO
IX Anticipated intake and extent of use of the NF
X Information from previous human exposure to the NF or its source
XI Information on the nutritional value of the NF
XII Microbiological information on the NF
XIII Toxicological information on the NF.

The applicant goes through the flowcharts for each subject in a clear manner and refers to appendices or the references for the data used. The committee considers the molecular-biological, nutritional and toxicological information to be sufficient for making a consumer safety assessment The original data on the presence of modified DNA and protein in certain food ingredients was inadequate but was supplemented by the applicant at the committee's request (Mon98a). The analytical methods used were also extensively documented in the second instance (Mon98a). For the underpinning of the substantial equivalence of the modified and conventional maize kernels, the committee considers it important to have information about the secondary plant metabolites, in addition to the data on macro- and micro-nutrients. The applicant has

conducted analyses to determine the levels of furfural, p-coumaric acid, ferulic acid, raffinose and phytic acid (Mon99a).

2.5 Brief summary from the applicant

The file contains a brief summary that has been sent to the EC Member States, as required by article 6, subsection 2, Regulation EC 258/97. See annex D.

2.6 Other assessments

The molecular-biological aspects of this novel food have already been extensively assessed by the Netherlands Committee on Genetic Modification, at the request of the Ministry of Housing, Spatial Planning and the Environment, within the scope of Directive 90/220/EEC (EC90).

Monsanto has also notified the Ministry of Agriculture, Nature Management and Fisheries about the file, within the scope of the voluntary check on the safety of animal feed. The State Institue for Quality Control of Agricultural products assessed the animal feed safety.

The permission to treat this maize in the field with Roundup Ready rests with the Board for the Authorization of Pesticides, which also establishes a residue tolerance for foods derived from the maize.

2.7 Labelling proposal from the applicant

The file contains a labelling proposal in compliance with EC Regulation 1139/98, which is concerned with the compulsory inclusion in the labelling of certain foods, produced using genetically modified organisms, of information that differs from that for which provisions are included in EC Directive 79/112 (EG79, EG98). In the Netherlands, the labelling proposal is being discussed in the Regular Commodity Act Consultations and is not further discussed in this advisory report.

Herbi -resistant maize (GA 21)

Chapter 3

Interpretation and evaluation of the data presented

3.1 I Specification of the novel food (NF)

The application concerns a maize line into which a modified gene (mEPSPS gene) is introduced, thereby making the plant resistant to the use of the herbicide glyphosate. EPSPS is an enzyme that is important for the biosynthesis of aromatic amino acids. It occurs in plants and micro-organisms. The mEPSPS protein hardly differs from the ordinary EPSPS protein, but has far less affinity for glyphosate. In a maize field treated with glyphosate, the maize plants will suffer less than the weeds because the metabolism of the maize plants is hardly affected.

The maize is mainly used to make food ingredients for the food industry, such as oil, meal and starch hydrolysates (sugars and syrups).

The committee believes enough is known about maize to assess this variant's safety. The specification of this maize line is such that the data supplied in the file is considered representative of products that are marketed under the name ‘Round up Ready maize line GA-21’.

3.2 II Effects of the production process applied to the NF

The applicant indicates that maize kernels undergo various processes before being used for the preparation of food. After milling, grain flakes, meal and oil are obtained and -

with further processing - flour, syrups and ethanol. These industrial food production processes are the same for new and conventional variants.

3.3 III History of the organism used as a source of the NF

The source of the new food plant is a conventionally cultivated maize line known as *Zea mays* N/A AT (indicating the gender, species, subspecies and variant respectively). A single, mutated gene is added to the maize genome. The applicant convincingly shows that maize has long been a widely cultivated plant and is used throughout the world.

3.4 IV Effect of the genetic modification on the properties of the host organism

Roundup Ready maize line GA-21 is made using the NotI-fragment of the pDPG434-plasmid. This fragment contains a promoter (rice actin), an intron (rice actin), the modified EPSPS maize gene and a terminator (NOS 3'). It is inserted in embryo cells of the maize variant N/A AT. Transformed callus cells were selected by application of glyphosate.

The applicant shows with the data provided that the introduced genetic modification is not only the intended difference but also the only difference from the conventional maize lines. The way of inserting the modified gene and the characterization of the modified line do not cause the committee to ask further questions or to observe any lack of clarity.

3.5 V Genetic stability of the genetically modified organism (GMO) used as NF source

The applicant demonstrates that the GMO is sufficiently stable under normal conditions. The applicant bases this on the pattern of inherited glyphosate tolerance over six generations of GA-21 progeny. This pattern is characteristic of a monogenic property. The gene's presence and stability in plants of different generations has been confirmed by DNA analyses.

3.6 VI Specificity of the expression of novel genetic material

The applicant describes the expression of the mEPSPS gene in maize kernels and other parts of the plant. The analysis of the composition shows that, as expected, the expression results in the production of the intended protein.

3.7 VII Transfer of genetic material from the GMO

The applicant refers to the literature and argues that there is no published evidence that plant genes are being transferred to other organisms. The applicant says horizontal transfer is so unlikely that this facet is considered irrelevant in the risk assessment.

The Committee does not concur with this. Humans have large daily intakes of plant and animal DNA. It is conceivable that parts of this DNA, in the form of intact gene fragments, could enter the small intestine where they could be transferred to the resident microflora. If this already occurs, in practice there will be little, if any, expression of these genes, because no good promoter is coupled to them. In by far the majority of cases, if these genes were to be expressed they would not provide the bacteria concerned with any competitive advantage or the host with any disadvantage. A problem could occur in the case of the transfer of antibiotic-resistance marker genes to a consumer's intestinal flora if that is under selection pressure because of the use of antibiotics. An antibiotic-resistance marker gene is no longer present in GA-21 maize.

3.8 IX Anticipated intake and extent of use of the NF

Maize is widely used for foods. Sufficient information is available about the intake and frequency of use. The proposed genetic modification is of agronomic interest and it is unlikely that the current consumption patterns of maize and derivative products will change.

3.9 X Information from previous human exposure to the NF or its source

Conventional maize has a long history of safe use in the United States and Europe. The novel maize variant has been on the market in the United States since early 1998.

3.10 XI Information on the nutritional value of the NF

The applicant has performed nutritional analyses of the maize kernels for protein, fat, carbohydrates, fibre, dry matter, moisture content, amino acid composition, fatty acid profile, calcium and phosphor. The rest of the plant has also been studied. This was done using plants of maize line GA-21 and the non-transgenic line but also using other local maize lines. These plants were cultivated in 1996 at five different locations in the United States, and in 1997 at another seven locations in the US and four in Europe. From each line at each location, a sample was made up for analysis. The composition

of the new maize line proved not to differ from that of the conventional control line, nor did it differ from what is reported in the literature on this subject (Jug76, USDA93, Wat82, Wat87). The data of samples from five different locations were combined to determine the average level and distribution of a nutritional component. Nutritionally, there is no difference between the conventional maize and maize line GA-21.

The committee concurs with this conclusion.

3.11 XII Microbiological information on the NF

No other micro-organisms are expected to occur on the new maize or any derivative products nor is a different microbial metabolism expected.

3.12 XIII Toxicological information on the NF

The applicant provides a sufficiently extensive file on the plant's safety. The degree of substantial equivalence of the two genetically modified lines to the conventional parent line is underpinned by the comparison of the nutritional composition (see 3.10) and by more detailed analysis of five secondary plant metabolites. The concentrations have been determined of furfural (Ada97, Fer91, Lee96), raffinose (Aun93, Nac97, Vor98), phytic acid (Har95, Har99) p-coumaric acid and ferulic acid (Cli99, Rad98, Ros95). The concentration of furfural was below the limit of detection. The other concentrations in the GMO lines were not significantly different from those in the conventional plant, except for *p*-coumaric acid. This concentration was significantly higher in one of the two GMO lines. The applicant argues that this difference is small (0.029 versus 0.022 percentage by weight (dry weight) or 29 mg/100g for the GMO line and 22 mg/100g for the control line), and falls within the variation of other commercially available maize variants. Moreover, there are no differences in the concentrations of ferulic acid, which is only two enzymatic steps away from *p*-coumaric acid via the general phenyl propanoid pathway. The committee concurs with this.

After determining the substantial equivalence of the rest of the plant with the conventional parent line, the studies focused on the expression product of the modified gene. This covered both toxicity and allergenicity.

Research was conducted on the acute toxicity of the mEPSPS protein in mice. The EPSPS protein was produced in micro-organisms to enable a sufficient amount to be used in the animal studies. The highest dose used was not the maximum amount that can be included in the food package without resulting in unbalanced nutrition (see recommendation 97/618/EC), but 500 times the maximum expected intake by humans. The committee considers this safety factor to be large enough.

Clinical observations were made and recorded. Tissues and organs were examined macroscopically and microscopically. Nutritional intake and weight increase were determined. No adverse effect was observed for the tested doses. The protein is rapidly broken down by gastric juices. Based on these data it was concluded that in terms of the introduced protein, GA-21 maize is safe. No toxicological information is available on the maize kernel as a whole. This is not necessary, because of the extent of substantial equivalence with the parent maize line.

Maximum exposure of humans to the mEPSPS through consumption of maize products is estimated to be no more than 0.04 mg/kg body weight per day for young children (estimate based on data on the English, German and average European nutritional pattern). It is assumed here that no protein is broken down while processing the maize into foods and food ingredients. The mEPSPS concentration in GA-21 maize is put at 0.001% of the fresh weight, twice as much as the concentration found in maize kernel analyses conducted by the producer.

It has been convincingly demonstrated that foods derived from this maize will not result in allergic reactions. No correspondence with the mEPSPS protein has been found in databases on known allergens. Moreover, the protein is broken down rapidly and the intake is low.

The Committee's opinion is that, insofar as the gene and the expression product of the modified gene in the novel food or food ingredients derived from it are present, there is no reason to expect any toxicity or allergenicity. Therefore there is no question of risk groups in the population.

Chapter 4

Conclusion and recommendations

The safety file that the applicant has complied on maize line GA-21 contains molecular-biological, nutritional and toxicological information. The composition of the modified maize line differs from that of a conventional line with regard to the mEPSPS gene and the expression product of the modified gene. There are no indications that genetic modification in the plant results in adverse pleiotropic effects. The modified EPSPS protein has not proved to be toxic or allergenic in the concentrations that occur. Variations in the other maize components studied remain within the values cited in the references and have no health consequences.

The committee considers this information to be complete and accurate, insofar as it is relevant for the safety assessment. The data submitted have been interpreted and evaluated correctly, in accordance with the state of the art in science.

The committee's opinion is that consuming GA-21 maize and the foods and food ingredients produced from it is as safe for humans as consuming maize and maize products that have not been genetically modified.

The committee points out that applicants would be helped by specific instructions regarding the number of samples, locations and years that are required for quantitative analyses. The committee will work out this recommendation and present it in international gremia involved with the implementation of the EU Regulation on Novel foods.

The Hague, December 21, 1999,
for the Committee
(signed)

JAG van de Wiel,	LM Schoonhoven,
Secretary	Chairman

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A Request for advice

B The committee

C EU procedure

D Executive summary of the dossier

Annexes

Annex **A**

Request for advice

On 18 August 1999, the Minister of Health, Welfare and Sport wrote as follows to the President of the Health Council (under reference GZB/VVB 003428):

Since May 1977, Regulation (EC) 258/97 concerning novel foods and novel food ingredients has been in force in the European Union. Under the Regulation, the safety of novel foods has to be assessed as part of a community procedure.

Following discussions regarding the possibility of the Health Council making such assessments, the State Secretary for Agriculture, Nature Management and Fisheries and I wish the Council to take reponsibility for safety assessment for a period of several years during the fist phase of implementation of European Regulation (EC) 258/97. It is considered appropriate the the Health Council should initially take on this role because the assessment activities will be of an experimental nature, involving both a new form of assessment (i.e. pre-marketing assessment) and, in many cases, new categories of foodstuff (primarily foodstuffs with a genetically modified basis and functional foods or nutraceuticals). We also feel that if assessments are made by a body with the Council's independent scientific status, this will support the validity of the Netherlands'opinion in the eyes of the European Committee and other member states.

My wish is to make the procedure and the assessment as open and transparent as possible, so as to enhance consumer trust in the safety of novel foods. I would like the Health Council to support this objective by, for example, allowing perusal of applicants (insofar as consistent with the need to protect the conficen-

tiality of commercially sensitive information) and publishing the criteria upon which safety assessments are made.

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

Annex **B**

The committee

- Dr LM Schoonhoven, chairman
  emeritus professor of entomology; Wageningen University and Research centre
- Dr JEN Bergmans, advisor
  Committee on Genetic Modification, The Hague
- Dr A Brouwer
  professor of environmental toxicology; Free University, Amsterdam
- Dr CAFM Bruijnzeel-Koomen
  professor of dermatology/allergology; Academic Hospital Utrecht
- Dr EJ Kok
  toxicologist; State Institute for Quality Control of Agricultural Products, Wageningen
- Dr CF van Kreijl
  molecular biologist; National Institute of Public Health and the Environment, Bilthoven
- Dr R Top, advisor
  Ministry of Health, Welfare and Sport; The Hague
- Dr F Nagengast
  gastro enterologist; Academic Hospital Nijmegen
- Dr JMA van Raaij
  food physiologist; Wageningen University and Research centre

- Dr EG Schouten
  professor of epidemiology; Wageningen University and Research centre
- Dr GJA Speijers
  toxicologist; National Institute of Public Health and the Environment, Bilthoven
- Dr WJ Stiekema
  professor of bioinformatics; Wageningen University and Research centre
- Dr WM de Vos
  professor of microbiology; Wageningen University and Research centre
- Dr JAG van de Wiel, executive secretary
  Health Council of the Netherlands, The Hague

Administrative assistance: C Brussee; Health Council of the Netherlands, The Hague.

Annex **C**

EU-procedure

When manufacturers bring novel foodstuffs onto the market, consumer safety has to be assured. In 1997, a European Directive (EC97) came into force, laying down the procedure for approving the market introduction of novel foodstuffs. The procedure recognises various actors. The applicant must decide whether a product is a novel foodstuff, i.e. a substance that has not previously been available for human consumption to any substantial extent within the European Union and is not substiantially equivalent to any existing product (If a foodstuff is substiantially equivalent to any existing product, it is sufficient to inform the authorities of its market introduction). Foodstuff additives, aromas and extracts are excluded from the provisions of the directive, since they fall within the scope of an established assessment regime. Before marketing a novel foodstuff, the applicant must compile a safety dossier that complies with the Recommentations of the European Commission (EG97a). These Recommendations are based on reports by a number of bodies that have studied the issue of novel foodstuffs, in particular the OECD (OECD93, OECD96) and the WHO/FAO (WHO91, FAO96). The Health Council of the Netherlands has also considered the question (GR92). Since publication of the EU recommendations, international efforts have been made to clarify and adapt the latest scientific knowledge in the field (SSC99, SCF99, OECD98).

Having compiled a dossier in line with the guidelines, the manufacturer has to submit it to the competent authority in the country where the product is to be marketed first. This dossier is assessed by the national authority. In the Netherlands, this is the Minister of Health, Welfare and Sport, who is advised by the Health Council. The

President of the Health Council has created a Committee on the Safety assessment of novel foods (VNV) to advise the minister on behalf of the Council.

On the basis of the scientific state of the art, the committee has to decide whether the information provided by the manufacturer is accurate and complete and whether the manufacturer's conclusions are sound. The committee then draws up a report on its findings for the minister; this report must also comply with the European Recommendation (EC97a, part III). After considering the report, the minister formulates the Netherlands'opinion regarding the foodstuff in question, which is discussed at European level in the Standing Committee for Food. All other European member states are invited to express a 'second opinion' regarding the dossier and the first opinion. The Permanent Committee then arrives at a final judgement. If a dossier is particularly contentious, the European Commission calls upon the Scientific Committee for Food for advice. If consensus still cannot be reached, the issue is referred to the European Council of Ministers.

Annex **D**

Executive summary of the dossier