Bt11-maize (pZO1502)

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 April 27, 2000, 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 regarding the safety of Bt11 maize (pZO1502) for the consumer. This advice is a so called first assessment in the context of European Regulation EC 258/97, concerning novel foods and novel 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

Bt11-maize (pZO1502)

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

No. 2000/02VNV, The Hague, April 27, 2000

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Contents

Executive summary, conclusions and recommendations

The safety file compiled by the applicant for the sweet maize line Bt11 contains molecular biological, nutritional and toxicological information. The reference is a standard sweet maize line that has a history of safe use in the European Community. The modified maize line differs in composition from a conventional line in relation to the *pat*-gene and the *Btk* gene and the expression products. Both genes are originating from bacteria. The *pat*-gene confers resistance to the herbicide glufosinate ammonium. The *Btk* gene protects the plant from attack by the European corn borer larvae. There are no indications that the genetic modification of the plant results in detrimental, so called pleiotropic effects. The PAT and Bt proteins have proved to be not toxic or allergenic in the concentrations that occur. Variations in the other maize components studied remain within the figures cited in the references and have no health consequences. The Committee considers this information to be both complete and accurate. The data submitted has been interpreted and evaluated correctly, in accordance with the current level of knowledge.

The Committee is of the opinion that the consumption of Bt11 sweet maize and the foods and food ingredients produced from it are just as safe for human consumption as maize and maize products that have not been genetically modified.

The Committee points out that applicants would be assisted by specific instructions regarding the kind of nutrients and secondary plant metabolites and the number of samples, locations and years that are required for quantitative analysis. The Committee will work out this recommendation and present it in international consultations.

Chapter 1

Introduction

On 6 April 1998 Novartis Seeds B.V. sought the opinion of the provisional Committee on the Safety Assessment of Novel Foods (vVNV) regarding the substantial equivalence of foods and food ingredients produced from genetically modified Bt11 sweet maize and conventional maize. In consultation with the Ministry of Health, Welfare and Sport and the vVNV, Novartis decided to change the request to a comprehensive evaluation of the new maize's safety for the consumer in both fresh and processed forms (Nov98). This request was received by the provisional Committee on the Safety Assessment of Novel Foods in November 1998 and was not further discussed by this Committee.

As of 1 January 1999 the file was transferred to the Health Council's Committee on the Safety Assessment of Novel Foods hereinafter referred to as the Committee. On 13 January 1999 this Committee received a request for advice from the Ministry of Health, Welfare and Sport to evaluate the safety of Bt11 sweet maize for the consumer in accordance with Regulation 258/97 of the European Parliament and the Council and the associated recommendations of the European Commission 97/618.

The Committee devoted several meetings to discussing the file. They posed further questions to the company regarding the arguments on which the safety claims concerning the PAT protein were based and requested further analysis of five secondary plant substances (Nov99, Nov00). The Committee completed the assessment in April 2000. This advisory report contains the Committees 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: Novartis Seeds B.V., PO Box 26, 1600 AA Enkhuizen, The Netherlands.

2.2 General description of the food

The application concerns the marketing and trading on the European market of Bt11 sweet maize for immediate consumption, for the consumption of tinned and frozen sweet maize and for the further processing into sweet maize powder. The Committee chose to assess the safety of the genetically modified maize kernels for consumption and believes that the outcomes may also be applied to maize subjected to further processing.

2.3 Classification of the food for assessment

The application concerns the marketing and trading on the European market of Bt11 sweet maize for immediate consumption, for the consumption of tinned and frozen sweet maize and for the further processing into sweet maize powder. The Committee chose to assess the safety of the genetically modified maize kernels for consumption and believes that the outcomes may also be applied to maize subjected to further processing.

2.4 Information about the food

The applicant specifies the information that is essential for assessing the suitability of a food in class 3.1 for consumption in accordance with the selection of themes as prescribed in EC recommendation (97/618/EC):

I	Specification of the novel food (NF)
	Effects of the production process applied to the NF
III	History of the organism used as the 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 the NF source
VI	Specificity of the expression of novel genetic material
VII	Transfer of genetic material from the GMO
IX	Anticipated intake and frequency of use of the NF
X	Information based on 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.

For every theme, the applicant clearly follows each step in the flow charts and refers to the appendices in the dossier or the literature for the data used. The Committee considers the molecular biological, nutritional and toxicological information to be sufficient for making the assessment.

The data for assessing the substantial equivalence and the toxicological information regarding the novel food were initially inadequate but was supplemented by the applicant at the Committee's request (Nov99, Nov00). For the underpinning of the substantial equivalence of the modified and conventional maize kernels, the Committee considers it important for information to be provided about the secondary plant substances, in addition to the information on macronutrients and micronutrients. The applicant has conducted analyses to determine the levels of furfural, *p*-coumaric acid, ferulic acid, raffinose and phytic acid.

2.5 Brief summary from the applicant

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

2.6 Other assessments

The molecular biological aspects of this novel food have already been extensively assessed by the Genetic Modification Committee, at the request of the Ministry of Housing, Spatial Planning and the Environment, within the scope of Directive 90/220/EEC, concerning the intentional introduction of genetically modified organisms into the environment.

Novartis has also notified the Ministry of Agriculture, Nature Management and Fisheries about this file, within the scope of the voluntary check on the safety of animal feed. The National Institute for Quality Control of Agricultural Products conducted the animal feed assessment.

The permission to treat this maize in the field with Basta (glufosinate-ammonium) rests with the Board for the Acceptance of Pesticides, which also establishes a residue tolerance for foods derived from the maize. Until now, the applicant has solely used the insensitivity to glufosinate ammonium as a marker for selecting the genetically modified plants. Within Europe, the use of Basta on maize fields is not permitted.

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 details that differ from those for which provisions are included in EC Directive 79/112. The labelling proposal is being discussed in the Netherlands in the Regular Consumer Goods Act Consultations and is not further discussed in this advisory report.

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 two genes of bacterial origin are introduced. One of the genes originates from the soil bacterium *Streptomyces viridochromogenes*. This gene codes for the enzyme phosphinothricin-N-acetyltransferase (abbreviated to *pat*) which renders the plant tolerant to the herbicide glufosinate ammonium. The pat enzyme converts the herbicide into breakdown products. Glufosinate ammonium disrupts the synthesis of glutamine in plants. Tolerance to glufosinate ammonium is used as a selection marker. If cultivated maize plants are treated with Basta (glufosinate ammonium) the modified maize plants will suffer less than the unmodified plants because their metabolism is scarcely disrupted.

The other gene, the *Btk* gene originates from the soil bacterium *Bacillus thuringiensis*. The gene is modified so that it can be expressed in plants such as maize. The protein thus produced in the plant tissue protects it from being attacked by European corn borer larvae. The Bt protein becomes active in the intestine of these insects and causes pores to be formed in the cell membrane. This leads to a disruption is the osmotic balance resulting in cell lysis.

Sweet maize is consumed in the form of whole maize kernels or as a powder in, for example, soups.

The Committee believes that enough is known about maize to assess this variant's safety. The specification of this maize line is such that the data presented in this file is considered representative of products that are marketed under the name 'Bt11 maize (pZO1502)'.

3.2 II Effects of the production process applied to the NF

The applicant indicates that the maize kernels are cooked, steamed, roasted or blanched prior to consumption. They are sold on the cob, frozen or tinned. Sometimes the maize kernels are dehydrated into a powder form that is then used as a food ingredient. These familiar production processes are the same for new and conventional varieties

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

The source of the novel food plant is a conventionally cultivated maize variety (*Zea mays L.*). Two bacterial genes have been inserted into the genome of the original maize line. The applicant convincingly demonstrates 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

The first Bt11 maize line is produced using the NOTI fragment from the pZO1502 plasmid. This fragment contains a promoter (P35S), an intron (IVS6), the *Btk* gene and a terminator (T*nos*) as well as a promoter (P35S), an intron (IVS2), the *pat* gene and a terminator (T*nos*). After that the modified maize line is conventionally crossed with some well known sweet maize varieties like Jubilee, Bonus and Empire. This resulted in three modified sweet maize hybrids Bt 95-0943, Bt 95-0937, Bt 95-0941.

Using the data provided, the applicant demonstrates that the genetic modification introduced is both the intended and sole difference from the conventional maize lines. The means of inserting the modified gene and the characterization of the modified lines do not give the Committee any reason to make further enquires or to point out 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 glufosinate tolerance and European

corn borer tolerance over four generations of Bt11 progeny. This pattern is characteristic of a monogenic property. The gene's existence 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 both the *Btk* and *pat* genes maize kernels and other plant components. The analysis of the composition shows that, as expected, the expression results in the production of the intended protein. At the point of harvest, the Btk protein is present in all parts of the maize plant. In the kernels it is present at about 1,6 µg per gram of fresh weight. The protein is not detectable in tinned sweetcorn (detection limit was 2 ng Btk protein per gram of fresh weight). The PAT protein is not detectable in maize kernels (detection limit 1 ng/ml extract).

3.7 VII Transfer of genetic material from the GMO

The applicant states that the DNA will be present in some of the food products and ingredients derived from the Bt11 sweet maize but not in others, dependent upon the treatment process. However, the assessment is concerned with the possible risk of this DNA being transferred. The Committee states that human beings 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 large intestine where they would be transferred to the resident microflora. If this already occurs, in practice there will be little, if any, expression of these genes, because the right promoter is not coupled to them. In by far the majority of cases, even 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 only occur in the case of the transfer of antibiotic-resistance marker genes, if the consumer's intestinal flora was also subjected to selection pressure as a result of antibiotic use. An antibiotic-resistance gene is no longer present in Bt11 sweet maize lines.

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 genetic modification is of agronomic importance 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.

3.10 XI Information on the nutritional value of the NF

In total, the applicant has commissioned four different studies to compare the composition of the genetically modified and control plants. A maize kernel consists mainly of starch (71%), protein (10%), oil (4.5%) and fibre (3%) (Wat 87). In the first investigation, nutritional analyses were carried out to determine the moisture level, protein, fat, ash, sugars, total carbohydrate, calories, fibre, vitamins A and C, sodium, potassium, calcium and iron contents. Comparisons were made between three varieties of Bt11 sweet maize and the most similar non-modified varieties (isogenic controls). These were all cultivated at the same location in California in 1996. Ten cobs were harvested from each variety. The company did not commission a statistical analysis due to the small number of samples taken. In general, the Committee is of the opinion that a statistical analysis must be carried out. In this case, given the numbers in the file, it is clear that there are only slight differences in the composition between the conventional and genetically modified maize for the components reported. The applicant does not provide any arguments as to why no studies were carried out on the concentrations of phosphorous, sulphur, chlorine, iodine, zinc, fluorine, manganese, copper, lead, cadmium, chromium, selenium, cobalt and mercury. Notably, phosphorous and sulphur are present in quite high concentrations in maize kernels (Wat87). The Committee would have preferred to have seen a clear argument as to the choice of micronutrients analyzed, yet the data submitted is sufficient for an assessment.

In a second study, moisture, total nitrogen, ash, starch, cellulose, xanthophyll and various fatty acids and amino acids were determined. A homozygous and a heterozygous Bt maize plant were compared with their respective controls. The controls were cultivated in a glasshouse. Approximately 50 cobs were harvested from each variant and a representative sample of 500 g was taken per genotype. The averages of two separate analyses were compared, an acceptable difference having being indicated beforehand. There is a difference in the nitrogen (protein) level between the homozygote Bt maize and its control which is borderline to the acceptable difference of 0.6%. All of the plants contained large amounts of nitrogen, which was possibly due to the application of artificial fertilizers in the glasshouse.

A third study compared maize kernel size and thickness as well as starch, protein, oil, fibre, fatty acid and amino acid profiles, using near infrared spectrometry. From early and late harvest lines two Bt varieties and their controls were cultivated in duplo at

three field locations. At each location two to five cobs were harvested from each variant. For the purpose of the analyses the kernels were processed into powder. There were no relevant differences, except for the protein level in the Bt plants of the early harvest variant, which was significantly lower than that of its controls. The values observed fell well within the values cited in the literature for maize and the Committee, therefore, does not deem it to be a problem (Wat87).

The comparison of fatty and amino acids revealed a difference for four components at the 5% significance level. These were palmitic acid (Bt variant more than the control) stearic acid, cysteine and arginine (control more than the Bt variant). In view of the large variation exhibited by conventional lines, the applicant does not consider these differences as relevant. The Committee concurs with this view.

The fourth study concerns vitamins and minerals. For each variant the average analysis values from three locations were taken. No statistically significant differences between the genetically modified maize line and the isogenic control were found. The Committee is of the opinion that it would be better to include the individual data from each location in the file and this has been requested.

3.11 XII Microbiological information on the NF

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

3.12 XIII Toxicological information on the NF

The applicant provides a sufficiently extensive file on the crop's safety. The degree of substantial equivalence of the two genetically modified lines to the conventional parent line is underpinned by the composition from the nutritional point of view (see XI) and by the further analysis of five secondary plant substances. The concentrations have been determined for furfural (Ada97, Fer91, Lee96), raffinose (Aun93, Nac97, Vor98), myo-inositol/phytic acid (Har95, Har99) and *p*-coumaric acid and ferulic acid (Cli99, Rad98, Ros95). Samples were taken from three modified Bt11 maize lines and the associated non-modified parent lines. All of these were cultivated at one location. No statistically significant differences between the genetically modified and conventional maize lines were found.

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

The manufacturer has correctly limited the toxicological information to the two new proteins that are produced in the maize. The applicant discusses the data concerning the

Bt and PAT proteins found in the scientific literature and then, using mice, carries out a digestive experiment and an acute oral toxicity study for both proteins. Finally, the applicant explains why he finds a chronic study unnecessary.

The Committee concurs with the applicant's arguments and only comments on the digestion and acute oral toxicity tests on the experimental animals. Initially, detailed reports were not included in the file but these were made available at the Committee's request. The study was carried out using a bacterially produced Bt protein that is demonstrably comparable to the Bt protein produced in the maize plant. The digestive test demonstrated that after being incubated in the gastric juice for two minutes, more than 90% of the Bt protein is broken down. The biological activity decreased by 74 – 90%. Incubation with intestinal juice scarcely had any effect. The acute oral toxicity test with the Bt protein was designed in accordance with the EPA guidelines for the testing of biochemical pesticides, which were established in 1982. Three test groups each containing 10 male and 10 female albino mice (race CD-1) and a control group were used. The doses of protein tested for activity were 0, 400, 1000 and 4000 mg/kg of bodyweight. The mice were observed twice daily for possible symptoms of toxicity. Following their sacrifise, the animal's organs were examined. In the Committee's opinion this provided sufficient data which can be accurately interpreted from a toxicological viewpoint. The report contains no indications of toxicity for the product under the test conditions used.

Initially, the arguments for the safety of the PAT protein were not adequately underpinned with references to the literature. At the Committee's request the applicant supplied details that further underpinned the argument. In the Committee's opinion this information was sufficient for both the digestive and acute oral toxicity tests. The tests were carried out with a bacterially produced PAT protein that was comparable to the PAT protein in maize. In the digestive test a rapid degradation in human gastric juice was observed.

For the assessment of the allergenic potential of both the Bt and the PAT proteins the applicant compared the characteristics of these proteins with those of known allergens. Allergens typically have a molecular weight of 10-70 kD, they are protected from breakdown by glycosidation, their breakdown in the gastrointestinal tract is limited, they survive all sorts of refining processes and are present at high concentrations in certain foods. The Bt and PAT proteins have a molecular weight of between 10 and 70 kD but exhibit none of the other allergenic characteristics and have no structural similarity with any allergens.

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

The Hague, 27 April, 2000,
for the committee

signed
JAG van de Wiel,
project director

signed
LM Schoonhoven,
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 993428):

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

conficentiality 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*
  COGEM, 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; RIKILT-DLO, Wageningen
- Dr CF van Kreijl
  molecular biologist; RIVM, Bilthoven
- Dr F Nagengast
  gastro-enterologist; Academic Hospital Nijmegen
- Dr JMA van Raaij
  ood physiologist; Wageningen University and Research centre
- Dr EG Schouten
  professor of epidemiology; Wageningen University
- Dr GJA Speijers
  toxicologist; RIVM Bilthoven
- Dr WJ Stiekema
  professor of bioinformatics; Wageningen University and Research centre

- Dr R Top, *advisor*
  Ministry of Health, Welfare and Sport; The Hague
- Dr WM de Vos
  professor of microbiology; Wageningen University and Research centre
- Dr JAG van de Wiel, *project director*
  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, OEC98).

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 safety assessment 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