Opinion of the Scientific Panel on Genetically Modified Organisms on an application (Reference EFSA-GMO-UK-2004-08) for the placing on the market of products produced from glyphosate-tolerant genetically modified sugar beet H7-1, for food and feed uses, under Regulation (EC) No 1829/2003 from KWS SAAT AG and Monsanto[1]

(Question No EFSA-Q-2004-164)

Opinion adopted on 5 December 2006

SUMMARY

This document provides an opinion of the Scientific Panel on Genetically Modified Organisms (GMO Panel) of the European Food Safety Authority (EFSA) on products produced from genetically modified sugar beet H7-1 (Unique Identifier KM-ØØØH71-4), developed to provide tolerance to glyphosate-containing herbicides. The scope of this application is for food produced from or containing ingredients produced from sugar beet H7-1 and feed produced from sugar beet H7-1. These products are for example sugar, syrup, dried pulp and molasses.

In delivering its opinion the GMO Panel considered the application (Reference EFSA-GMO-UK-2004-08), additional information provided by the applicant (KWS SAAT AG and Monsanto Company) and scientific comments submitted by the Member States.

The sugar beet H7-1 was assessed with reference to its intended use and the risk assessment principles described in the Guidance document of the Scientific Panel on Genetically Modified Organisms for the Risk Assessment of Genetically Modified Plants and Derived Food and Feed. The scientific assessment included a molecular characterisation of the inserted DNA present in sugar beet H7-1 and of the insertion site. The nature and safety of the newly expressed protein in the genetically modified plants was assessed with respect to toxicology and allergenicity. Furthermore, a comparative analysis of agronomic traits and composition was undertaken and the safety of the whole food/feed was evaluated.

The sugar beet H7-1 was developed for glyphosate tolerance by *Agrobacterium tumefaciens*-mediated introduction of the gene *cp4 epsps*, isolated from the soil bacterium *Agrobacterium* sp. CP4, into the sugar beet. The inserted gene encodes a 5-enolpyruvylshikimate-3-phosphate synthase protein (CP4 EPSPS) that, in contrast to the plant's own EPSPS protein, is insensitive to glyphosate-containing herbicides and, therefore, can continue synthesizing aromatic amino acids also in the presence of these herbicides.

Molecular characterisation of the DNA insert showed that sugar beet H7-1 contains one copy of the expected insert and that this is present at a single locus in the nuclear genome of the genetically modified plant. The DNA sequence of the insert and the flanking sequences were provided. The four mismatches observed in the insert sequence have no influence on the CP4 EPSPS protein. Bioinformatic analysis showed that potential fusion proteins would have no homology to known toxins or allergens.

Sugar beet H7-1 was found to contain the CP4 EPSPS protein associated with the new trait of glyphosate tolerance. Besides this deliberate change, this sugar beet showed no marked

[1] For citation purposes: Opinion of the Scientific Panel on Genetically Modified Organisms on an application (reference EFSA-GMO-UK-2004-08) for the placing on the market of products produced from glyphosate-tolerant genetically modified sugar beet H7-1, for food and feed uses, under Regulation 9EC) No1829/2003 from KWS SAAT and Monsanto, *The EFSA Journal* (2006) 431, 1-18.

alterations in composition, agronomy and phenotype compared with the control lines and reference lines. The GMO Panel therefore concludes that sugar beet H7-1 is compositionally and phenotypically equivalent to non-genetically modified sugar beet, except for the trait that has been introduced.

A 90-day sub-chronic rodent study with processed pulp from sugar beet H7-1 indicated that there are no adverse effects from the consumption of products produced from sugar beet H7-1.

A feeding study conducted on sheep with sugar beet H7-1 showed no adverse effects. The GMO Panel considers that the nutritional properties of products produced from this GM sugar beet would be no different from those of conventional sugar beet. The GMO Panel has, therefore, not identified any issue requiring post-market monitoring of sugar beet.

Since the scope only covers food produced from or containing ingredients produced from sugar beet H7-1 and feed produced from sugar beet H7-1, an environmental monitoring plan is not required.

In conclusion, the GMO Panel considers that the information available for sugar beet H7-1 addresses the outstanding questions raised by the Member States and considers that products produced from sugar beet H7-1 are unlikely to have any adverse effect on human and animal health or the environment in the context of its intended uses.

Key words: products produced from GMO, sugar beet, *Beta vulgaris*, H7-1, glyphosate-tolerant, CP4 EPSPS, food safety, feed safety, human health, import, Regulation (EC) 1829/2003.

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BACKGROUND

On 26 November 2004 EFSA received from the United Kingdom Competent Authority an application (reference EFSA-GMO-UK-2004-08) for authorisation of products produced from sugar beet H7-1 (Unique Identifier KM-ØØØH71-4), submitted jointly by KWS SAAT AG and Monsanto Company within the framework of Regulation (EC) No 1829/2003 on genetically modified food and feed (EC, 2003).

After receiving the application EFSA-GMO-UK-2004-08 and in accordance with Articles 5(2)(b) and 17(2)b of Regulation (EC) No 1829/2003, EFSA informed the Member States and the European Commission and made the summary of the dossier publicly available on the EFSA website[2]. EFSA initiated a formal review of the application to check compliance with the

[2] http://www.efsa.eu.int/science/gmo/gm_ff_applications/catindex_en.html

requirements laid down in Articles 5(3) and 17 (3) of Regulation (EC) No 1829/2003. On 29 March 2005, EFSA received additional information (requested on 11 March 2005) and declared the application as formally valid in accordance with Article 6(1) and 18(1) of Regulation (EC) No 1829/2003 on 20 May 2005.

EFSA made the valid application available to the Member States, the European Commission and nominated risk assessment bodies of the Member States, including the national Competent Authorities within the meaning of Directive 2001/18/EC. Although the product does not contain or consist of GMOs, EFSA, following its established procedures, consulted the Member States. In this context, the Member States risk assessment bodies, including national competent authorities under Directive 2001/18/EC, were given three months after the date of receipt of the valid application (until 20 August 2005) within which to make their opinion known.

On 24 October 2005 the GMO Panel asked for further clarification on the data provided in the compositional analysis. The applicant sent its response on 15 February 2006. The GMO Panel was not satisfied with the response and on 6 March 2006 asked for additional compositional data. The applicant responded on 13 September 2006. After receipt and evaluation of the response, the GMO Panel finalised its risk assessment.

The GMO Panel carried out a scientific assessment of the genetically modified sugar beet H7-1 with reference to its intended use, in accordance with Article 6(6) and 18(6) of Regulation (EC) No 1829/2003, taking into consideration the scientific comments of the Member States and the additional information provided by the applicant.

The scope of this application is for food produced from or containing ingredients produced from sugar beet H7-1 and feed produced from sugar beet H7-1. Thus the scope only includes products produced from sugar beet H7-1 which contain no viable plant parts. Therefore there are no requirements for scientific information on environmental risks associated with the adventitious release or cultivation of sugar beet H7-1.

In accordance with Article 6(1) and 18(1) of Regulation (EC) No 1829/2003 EFSA has, in giving its opinion to the European Commission, the Member States and the applicant, endeavoured to respect a time limit of six months as from the receipt of a valid application. As additional information was requested by the GMO Panel, the time-limit of 6 months was extended accordingly in line with Articles 6(1), 6(2), 18(1), and 18(2) of Regulation (EC) No 1829/2003.

According to Regulation (EC) No 1829/2003, the EFSA opinion shall include a report describing the assessment of the food and feed and stating the reasons for its opinion and the information on which its opinion is based. This scientific opinion is to be seen as the report requested under Articles 6(6) and 18(6) of the Regulation and will become part of the overall opinion in accordance with Articles 6(5) and 18(5).

TERMS OF REFERENCE

The GMO Panel was requested, in accordance with Articles 6(6) and 18(6) of Regulation (EC) No 1829/2003, to carry out a scientific assessment of products produced from the genetically modified sugar beet H7-1 for food and feed uses.

Where applicable, any conditions or restrictions which should be imposed on the placing on the market and/or specific conditions or restrictions for use and handling, including post-market monitoring requirements based on the outcome of the risk assessment should be indicated in accordance with Articles 6(5)(e) and 18(5)e of Regulation (EC) No 1829/2003.

The GMO Panel was not requested to give an opinion on information required under Annex II to the Cartagena Protocol or to consider proposals for labelling and methods of detection

(including sampling and the identification of the specific transformation event in the food/feed and/or food/feed produced from it), which are matters related to risk management.

ASSESSMENT

1. Introduction

The genetically modified (GM) sugar beet H7-1 is assessed with reference to its intended uses and the appropriate principles described in the Guidance document of the GMO Panel for the risk assessment of genetically modified plants and derived food and feed (EFSA, 2006). The scope of this application is for food produced from or containing ingredients produced from sugar beet H7-1 and feed produced from sugar beet H7-1. The assessment presented here is based on the information provided in the application as well as on additional information from the applicant in reply to EFSA questions.

2. Molecular characterisation

2.1. Issues raised by Member States

Issues were raised about (1) a mismatch in the *cp4epsps* coding region, (2) whether the bioinformatic analysis was a sufficient proof of absence of new ORFs, and (3) the cause of variation in the CP4 EPSPS content in some root samples.

2.2. Relevant background data

2.2.1. The transformation process and vector constructs

Sugar beet (*Beta vulgaris* subsp. *vulgaris*) cotyledons were transformed by using an *Agrobacterium* binary vector system. A regenerant from this transformation, named H7-1, was evaluated for safety in the application.

The disarmed vector PV-BVGT08 used in the transformation contained a *cp4 epsps* gene cassette (conferring tolerance to glyphosate) between left and right borders and a bacterial selectable marker gene *aad* (conferring resistance to spectinomycin/streptomycin) outside the borders. The *cp4 epsps* gene cassette contained a synthetic *epsps* coding sequence based on the original sequence from *Agrobacterium* sp. strain CP4 but modified to allow higher expression in plants. Expression of the *cp4 epsps* gene was driven by the 35S promoter obtained from a modified figwort mosaic virus gene. The transcriptional terminator sequence was obtained from the pea rubisco small subunit gene. The CP4 EPSPS protein was directed to chloroplasts by using a *ctp2* targeting sequence from *Arabidopsis thaliana*.

2.2.2. Transgenic constructs in the genetically modified plant

The inserted DNA constituted the sequences between the left and right borders of the *Agrobacterium* vector, the right border not being transferred. The number of insertion sites in the sugar beet genome, copy number, integrity of inserted promoter, coding sequence and poly-A region, as well as the absence of plasmid backbone were tested using Southern analysis which included the use of a number of appropriate restriction enzymes and probes. The sensitivity of the Southern analysis was tested with appropriate controls and found to be satisfactory. Southern blot data indicated the presence of an intact single copy insert with no plasmid backbone sequences present.

Inverse-PCR analysis and DNA sequencing were used to verify the organisation of the insert and to identify the flanking regions. Sequencing of the 5' and 3' junctions demonstrated that the insert contains only part of the left border and no right border sequences. The sequence inserted corresponds exactly to the sequence of the *cp4 epsps* gene cassette in the plasmid except for four mismatches, one of them in the *cp4 epsps* coding region. However, this alteration at the molecular level does not change the CP4 EPSPS amino acid sequence or the activity of the protein. The other three mismatches are outside the coding region.

Bioinformatic analysis was carried out to investigate the creation of potential fusion proteins. No significant sequence homologies were found to known allergens, toxins or pharmacologically active proteins. The GMO Panel considers that the information from the bioinformatic analysis indicates a low probability for an unintended expression of potential fusion proteins.

2.2.3. Information on the expression of the insert

The genetically modified sugar beet H7-1 contains a single functional protein, CP4 EPSPS, expressed from the inserted DNA. The expression of this protein in leaf (tops) and processed root (brei) tissues were analysed with a validated ELISA. The materials analysed were obtained from sugar beets harvested from European field studies at ten locations (two in the UK, seven in France and one in Belgium) in 1998 and six locations (UK, France, Spain, Italy, Germany and Belgium) in 1999. Both glyphosate-treated and non-treated sugar beets were analysed. Each sample was a composite of 30 sugar beets.

The CP4 EPSPS protein was identified in all sugar beet H7-1 samples and in both types of tissue studied. The expression levels were similar in glyphosate-treated and non-treated root samples, whereas expression levels were slightly lower in non-treated tops than in tops treated with glyphosate. However, this difference was not statistically significant. No expression was detected in the non-GM reference material (non CP4 EPSPS-expressing, non-transgenic segregants from sugar beet H7-1). Very similar average expression levels of the CP4 EPSPS protein in the tops were observed in 1998 and 1999, the levels being 0.172 and 0.161 μg/mg fresh weight, respectively. In the processed root tissue (the brei) the expression was 0.053 μg/mg fresh weight in 1998 and 0.181 μg/mg fresh weight in 1999. The expression varied between 0.102 and 0.307 μg/mg fresh weight in leaf material and between 0.033 and 0.233 μg/mg in root material in the respective years. The lower expression rate in roots in 1998 was observed in all analysed material. Since the protein is not known to be toxic or allergenic, the GMO Panel considers that this difference is of no particular concern.

2.2.4. Inheritance and Stability of inserted DNA

The presence of the insert in the nuclear genome was verified by Mendelian inheritance patterns. Stability of integration was tested using Southern analysis over three generations. The molecular analysis confirmed the stability of the inserted construct. Genetic stability was further confirmed by phenotype studies determining the segregation pattern of glyphosate tolerance over four years, as well as the stability of CP4 EPSPS expression over two years. The GMO Panel considers that the overall results provide sufficient proof of stability of the genetic modification.

2.3. Conclusion

The GMO Panel is of the opinion that the sugar beet H7-1 is sufficiently characterised at the molecular level and that there is no particular cause for concern. The glyphosate-tolerant sugar beet H7-1 contains a single copy insert with no plasmid backbone sequences present. The GMO Panel also considers that the sequenced insert and flanking regions, and subsequent bioinformatic analysis, provides sufficient proof of a low probability that any unintended, potential fusion protein resulting from the genetic modification would be formed. Since there is

no evidence that the newly expressed protein is toxic or allergenic, the variation in protein levels observed in field trials does not raise any concern. The genetic stability of the inserted DNA was demonstrated by Southern analysis, as well as by segregation data for the glyphosate-tolerant trait over several generations. The glyphosate tolerance segregated according to Mendelian genetics. The GMO Panel is therefore of the opinion that sufficient evidence has been provided concerning the genetic and phenotypic stability of the sugar beet H7-1.

3. Comparative analysis

3.1. Issues raised by Member States

Some Member States raised scientific comments whether (1) the comparator used in the comparative assessment was the most appropriate one, (2) whether the data on minerals and secondary metabolites are sufficient and (3) pointed out that significant differences in content of dry matter, specific amino acids and saponins were observed between sugar beet H7-1 and its comparator.

3.2. Evaluation of relevant scientific data

3.2.1. Choice of comparator and production of material for the compositional assessment

The composition of sugar beet H7-1 was compared with the composition of a near-isogenic control similar to sugar beet H7-1 and a set of conventional sugar beet varieties, grown in the same field trials. The number of conventional sugar beet used as comparators were thirteen in 1998 and 1999, and eight in 2003. Comparisons were also made to compositional data on sugar beet available in the literature.

In order to study the agricultural characteristics of the sugar beet H7-1 in relation to commercial non-transgenic sugar beets and to collect material for compositional comparisons, field studies were conducted at eleven separate geographical sites in Europe (two in the UK, seven in France and 2 in Belgium) during 1998, at five sites in Europe (UK, France, Belgium, Italy and Germany) during 1999, and at five sites in the United States (Idaho, Michigan, Nebraska, Minnesota, and North Dakota) during 2003. The sites of the field trials were representative for the sugar beet cultivation areas of Europe and the United States.

The field-testing program provided data on the agronomic characteristics and produced material for the comparative compositional analysis. Samples for analysis were collected from aerial (top) and root parts of sugar beet H7-1 (either under conventional herbicide regimen (=non-treated) or treated with glyphosate), control sugar beet (under conventional herbicide regime), and thirteen different commercial sugar beets (under conventional herbicide regime). The conventional sugar beet herbicide programs consist of a pre-emergence treatment (optional) followed by two to four post-emergence applications with a mixture of active ingredients (Dewar *et al*., 2000; May *et al*., 2003; Wevers *et al*., 2005). Each sample to be analysed was made up of around 30 sugar beets. In 1998, one combined sample was supplied from each trial site, while in 1999 three replicates, and in 2003 four replicates, were obtained from each trial site.

3.2.2. Compositional analysis

Leaf (top) and processed root samples (brei) of the sugar beet H7-1 and its comparators from in total sixteen field trials in Europe in 1998 and 1999, and brei samples from five field trials in the United States in 2003, were analysed for their composition. With exception of phosphorous and magnesium, which were not analysed, the set of compounds analysed corresponded to those later suggested by OECD (2002). In addition, several components not suggested by OECD

were analysed. Thus, both top and brei were analyzed for proximates (crude ash, crude fibre, crude protein, crude fat, and dry matter), carbohydrates (determined by calculation), 18 different amino acids, and saponins (oleanolic acid liberated on hydrolysis of the saponin glycosides).

The applicant also presented data on the content of sugar, invert sugar, sodium, potassium, α-amino nitrogen, and secondary metabolites (ferulic acid, *p*-coumeric acid, oxalic acid and malonic acid) in root material of GM sugar beet H7-1, its non-transgenic control sugar beet and eight non-GM commercial sugar beet varieties harvested in field trials at five sites in the United States during 2003.

The statistical analysis for sugar beet composition was for the material harvested in 1998 and 1999 carried out on analytical data from all locations of the European field trials combined, not on a per location basis. A per site analysis was not possible as replications at each site were not introduced in the field studies until 1999. Two hundred and twenty compositional comparisons were made. The statistical analysis compared the treated and non-treated sugar beet H7-1 with the control and identified twenty three significant differences. Of these, twelve were in leaf (top) material and eleven in processed root. The significant differences were inconsistent – occurring in only one of the years or in only one of the treatments (glyphosate-treated or treated with commercial herbicides) of the sugar beet H7-1 – and measured levels were within the range observed for the commercial sugar beet varieties in the field study. Chemical analysis of the naturally occurring sugar beet saponins, which are anti-nutrients in animals, revealed no significant differences in the levels of these constituents in leaf and root material between sugar beet H7-1 and the near-isogenic control across the two years of field studies. The only consistent difference in the leaf material was found in the mean levels of the three amino acids alanine, histidine and tyrosine. Alanine was increased from 6.38% of total amino acids to 6.63 % in 1998 and from 6.44 % to 6.67 % in 1999. Histidine was reduced from 2.34 % to 2.06 % in 1998 and from 2.46 % to 2.29 % in 1999. Tyrosine was reduced from 4.02 % to 3.86 % in 1998 and from 3.65 % to 3.46 % in 1999. The mean level and range of these amino acids in the eight commercial varieties were 6.38 % (5.44-6.92), 2.23 % (1.49-2.89), and 3.92 % (3.09-4.53) in 1998 and 6.53 % (5.98-6.97), 2.26 % (1.75-2.68), and 3.63 % (3.21-4.79) in 1999, respectively. In processed root, the only consistent difference was the mean level of the amino acid glutamic acid, which was reduced from 18.26 % to 16.51 % in 1998 and from 18.58 % to 16.87 % in 1999. The mean level of glutamic acid in the eight commercial sugar beet varieties was 20.93 % (14.38-31.45) in 1999 and 19.21 % (13.76-25.07) in 1998. Thus, none of the consistent differences in the leaf material was observed in the root material. Furthermore, the ranges observed for these amino acids overlapped and were very similar to the range obtained in conventional sugar beet varieties. The GMO Panel considered these differences not to be biologically relevant.

However, as the data from the field studies performed in 1998 and 1999 did not allow a within site variation to be estimated, the GMO Panel requested from the applicant additional compositional data, according to the recommendations of the Guidance document (EFSA, 2006), and a statistical evaluation of data from each individual trial site, as well as across the trial sites. As a response, the applicant delivered the result of field studies performed at five sites in the United States representative for the sugar beet growing area of this country. Of the 138 statistical comparisons performed on this material, 14 (10 %) were statistically significant. At one of the trial sites, none of the studied parameters differed between the test crop and its comparator. At the four other sites a few statistical differences in the quantity of the analysed compounds were observed for each site. In ten cases, the identified difference was observed only at one of the five sites, was small, and fell within the tolerance interval calculated from the level of these constituents found in the commercial sugar beet varieties. The alanine content was significantly increased in root material from two of the five field studies. This observation was not consistent across the sites, and no significant difference were noted in the across site comparisons. When analysed across sites isoleucine and aspartic acid levels were significantly increased in the GM sugar beet H7-1 as compared to the non-GM conventional sugar beet.

When studied separately for each individual trial site, there was no difference in the isoleucine content of the GM and the conventional sugar beets. Furthermore, the isoleucine content fell within the range of commercial sugar beet varieties. The aspartic acid content was increased at one of the five trial sites. Although the level of this amino acid was high both for sugar beet H7-1 and control sugar beets at this site, they fell within the tolerance interval of the commercial sugar beet varieties.

Some data from the US field trials were available already in the original application. These data showed that the level of ferulic, p-coumeric, and malonic acid in roots of the transgenic sugar beet H7-1 did not differ from the levels in non-GM control sugar beet and eight conventional reference sugar beet varieties. However, the level of oxalic acid was reduced in sugar beet H7-1 compared with control sugar beets at one of the five trial sites. The oxalic acid levels were reduced in sugar beet H7-1 also in the combined site comparisons. For all sites combined, the oxalic acid content of sugar beet H7-1 was 0.51 % of the dry weight, as compared to 0.55 % of the dry weight for the control. As the oxalic acid level in the GM sugar beet H7-1 was within the 99 % tolerance interval established for the conventional sugar beet varieties grown in the field trial, and also were within the levels reported in the literature, these differences were not considered to indicate that unintended effects had occurred in the sugar beet H7-1.

The GMO Panel considered the statistical differences observed between sugar beet H7-1 and its comparator in the light of the field trial design, the biological variation and the level of these compounds in commercial sugar beet varieties and came to the conclusion that sugar beet H7-1, with exception of the CP4 EPSPS protein expressed, is compositionally equivalent to conventional sugar beets.

3.2.3. Agronomic traits

Extensive biological and agronomic data were collected from green house studies in Germany and field trials (four locations in France in 1998 and two locations each in France and Germany in 1999). In these studies sugar beet H7-1 was compared not only to the non-GM control but also to several commercial varieties and conventional proprietary breeding lines of sugar beet. Although variations were observed in this large data set, it could be established that no biologically meaningful difference exists in morphological, developmental, inflorescence and agronomic characteristics between sugar beet H7-1 and the non-GM control. Furthermore, no difference in the occurrence of pests and diseases was observed between the sugar beet H7-1 and the non-GM control. The reduced seed weight and germination rate and increased pollen tube length in sugar beet H7-1, as observed in comparisons with seed lots of the parental control and other conventional breeding lines between 1992 and 1998, were suggested to be attributed to environmental variation in climate and soil conditions during seed development and ripening in the fields and green houses, respectively, as well as to differences in seed preparation to enhance germination. In conclusion, the reproduction, dissemination and survivability of sugar beet H7-1 does not differ from that of the comparators.

3.3. Conclusion

After considering the field trial design, the biological variation, and the level of investigated sugar beet constituents in commercial sugar beet varieties, and evaluating the nutrient and anti-nutrient composition of leaf (top) and root material of the sugar beet H7-1 and its non-GM comparator, including statistical analysis of the compositional data, the GMO Panel concludes that the composition of the genetically modified sugar beet H7-1 is comparable to a near-isogenic control and conventional sugar beet lines, with exception of the newly expressed CP4 EPSPS protein. Furthermore, the morphological, developmental, inflorescence and agronomic characteristics (including pest and disease sensitivity), as well as the reproduction, dissemination and survivability of sugar beet H7-1 does not differ from that of non-GM control sugar beet.

4. Food/feed safety assessment

4.1. Issues raised by Member States

An (1) extended testing regime for potential toxicity and allergenicity, including an additional oral toxicity 90-day feeding study in rats with unprocessed sugar beet roots was requested, as were (2) data on the potential occurrence of the CP4 EPSPS protein in sugar beet products and (3) a post-market monitoring plan.

4.2. Evaluation of relevant scientific data

4.2.1. Production description and intended use

The scope of this application is for food produced from or containing ingredients produced from sugar beet H7-1 and feed produced from sugar beet H7-1.

The main product for human consumption from sugar beet is refined sugar (99% sucrose). Sugar is used as a food or as a food ingredient. Sugar production is comparatively simple. Clean mature sugar beet roots are sliced and sugar is osmotically extracted in hot water. The process gives a sugar-rich raw juice. The raw juice is mixed with lime solution (from a lime kiln operation), carbon dioxide and later sulphur dioxide, and the produced stabilized juice is evaporated to remove excess water. The thickened juice is seeded with sucrose crystals to promote sugar crystallization. Crystals are separated from the syrup (beet molasses) by centrifugation, then dried, sized by screening and made ready for distribution.

In some regions of Europe a beet syrup (Rübenkraut) is produced for human consumption. In this case the press juice of sugar beets is thickened to syrup for use as sandwich spread, for sweetening sauces, desserts and muesli, and as baking ingredient.

The by-products of sugar beet processing are pulp (the root left-over) and molasses, most often used as animal feed. Molasses may also be used as raw material for fermentation by yeast, moulds, and bacteria in brewing, baking and distilling industry, for example producing ethanol, citric acid, and specific amino acids. Pulp is mainly used as a constituent in animal feed as it contains highly digestible fibre and energy. However, in some cases pulp is used to prepare fibre and enzymes used by bakery and food industry. In some areas of Europe, beet leaves and small pieces of roots derived from the root processing are fermented to produce silage for animal feed. The latter product is not included in the scope of the present application.

4.2.2. Stability during processing

When corrected for extraction efficiency, roots of sugar beet H7-1 contain around 73 ppm of the CP4 EPSPS protein characteristic for this genetically modified sugar beet. Studies on sugar produced from sugar beet H7-1 could not detect the CP4 EPSPS protein. Thus, if present in sugar, which is unlikely, the level has to be under the limit of detection (0.004 ppm). Similarly, no DNA has been detected in the sugar. Of other products, also molasses are free from DNA and protein (limit of detection 0.002 ppm). The CP4 EPSPS protein can, however, be found in pulp at levels around 500 ppm.

4.2.3. Toxicology

4.2.3.1. The CP4 EPSPS protein used for safety assessment

As a relatively large quantity of the CP4 EPSPS protein was needed for the safety studies of the newly expressed protein in sugar beet H7-1 and purification of CP4 EPSPS from the sugar beet would give only small quantities due to the low CP4 EPSPS expression, a CP4 EPSPS protein expressed at high levels in *Escherichia coli* was used in the experimental studies instead of the CP4 EPSPS isolated from the sugar beet. Structural and functional identity of the CP4 EPSPS protein produced in recombinant *Escherichia coli* and in leaf tissue of sugar beet H7-1 was shown by analyzing the amino acid sequence of the protein and its 3-dimensional structure, by studying the catalytic activity of the protein and the homology of the active site residues, the protein molecular weight and glycosylation and its immunological properties.

4.2.3.2. Toxicological assessment of the expressed novel protein in sugar beet H7-1

Humans and animals have a long history of dietary exposure to EPSPS proteins, which occurs in a wide range of plants, fungi and certain microorganisms. No adverse effects associated with this exposure have been identified. The sugar beet H7-1 has been transformed to express the modified CP4 EPSPS protein. Previous applications for glyphosate tolerant crops containing the CP4 EPSPS protein have been evaluated and found to be safe for human and/or animal consumption in previous opinions (ACNFP, 1994; SCP, 1998a, b; EFSA, 2003a, b). The GMO Panel is of the opinion that no new scientific data have emerged which would change earlier EFSA opinions.

Stability and safety studies of the CP4 EPSPS protein submitted by the applicant, and also assessed in previous opinions, included:

In vitro digestibility. *In vitro* studies showed that the CP4 EPSPS protein (from *E. coli*) is readily degraded in simulated gastric fluid (pH 1.2) containing pepsin. The degradation was demonstrated by immunological detection (>95 % degraded in 15 sec) and measurement of enzyme activity (>90 % loss of activity within 15 sec). These two methods of identification were also used to demonstrate degradation in simulated intestinal fluid (>50 % protein degraded within 10 min, and >91 % loss of enzymatic activity within 4.5 hour).

Homology testing of the CP4 EPSPS protein to known toxic proteins. The amino acid sequence of the CP4 EPSPS protein was compared with the amino acid sequences of known toxic proteins using a bioinformatic approach based on computer algorithms. No significant sequence homologies between the CP4 EPSPS protein and known toxic proteins were found.

Acute toxicity testing of the CP4 EPSPS protein in mice. An acute oral (gavage) toxicity study in male and female CD-1 mice given various doses of the CP4 EPSPS protein showed no adverse effects up to the highest dose administered (572 mg/kg body weight).

4.2.3.3. Toxicological assessment of new constituents other than proteins

Since no new constituents other than the CP4 EPSPS protein are expressed in sugar beet H7-1, and the level of the endogenous compounds in sugar beet is maintained, a toxicological assessment of new constituents is not applicable.

4.2.4. Toxicological assessment of the whole GM food/feed

4.2.4.1. Subchronic oral toxicity

A 90-day subchronic toxicity study was performed in Sprague Dawley Crl:CD (SD)IGS BR® rats fed *ad libitum* diets containing pulp processed from sugar beet H7-1, control sugar beets with background genetics representative of sugar beet H7-1, or four conventional sugar beet varieties with different genetic backgrounds. Whereas all rats received 5 % (w/w) of their diet as pulp material, two doses of the tested H7-1 pulp was used, 2 % (and 3 % near-equivalent control pulp) and 5%. Chemical analysis (key nutrients, potential pesticide residues and mycotoxin contaminants) confirmed acceptable quality of the added pulp, and ensured that unacceptable residue levels would not interfere with the study results. Diets were analysed to confirm nutritional specifications.

All animals survived until necropsy, except one female rat fed a diet with 5 % conventional sugar beet. This rat died due to a urinary tract obstruction. The sugar beet pulp had no relevant influence on clinical chemistry and urine parameters, feed consumption and body weight development.

Although haematology parameters in general were comparable between rats given sugar beet H7-1 pulp and rats given control pulp in the diet, statistically significant differences were observed in absolute white blood cell counts (10.8±2.46 (mean± SD) (5 % GM), 11.0±2.41 (2 % GM), and 8.0±0.99 (control) x10^3 cells/microliter), absolute lymphocyte counts (8.7±2.16 (5 % GM), 8.7±2.36 (2 % GM), and 5.8±1.07 (control) x10^3 cells/microliter), relative lymphocyte counts (80±3.3 % (5 % GM), 79±5.1 (2 % GM), and 72±7.5 (control)) and relative neutrophil counts (10±1.7 % (5 % GM), 13±3.6 % (2 % GM), and 17±4.4 % (control)) at both levels of sugar beet H7-1 pulp in the diet in males. The individual and average values of blood cell levels in these groups, however, fell within the range of values observed in rats from the same strain fed diets containing various non-GM commercial sugar beet varieties.

A statistically significant effect on organ weight was found for the absolute weight (0.89±0.124 g (GM) and 0.80±0.102 g (control)) and relative weight of spleens in relation to body weight (0.192±0.028 (GM) and 0.171±0.0147 (control)) and for brain weight (42.764±5.7357 (GM) and 37.671±4.2706 (control)) in males receiving 5% sugar beet H7-1 pulp in the diet. The individual and average values of these groups, however, fell within the historical background range of spleen weight values measured in rats from the same laboratory. The macroscopic observations of the rats at necropsy, and the microscopic studies of the various tissues revealed no test article-related findings, including any findings that could possibly be linked to the differences observed in haematology or spleen weights.

The GMO Panel considers that these changes observed in one sex only (males) are not toxicologically relevant since they do not appear to be dose related and the histopathological examinations of tissues did not reveal evidence for adverse effects.

4.2.5. Allergenicity

The strategies used when assessing the potential allergenic risk focus on characterisation of the source of the recombinant protein, the potential of the newly expressed protein to induce *de novo* sensitisation or to elicit allergic reactions in already sensitised persons, and whether the transformation may have altered the allergenic properties of the genetically modified food. A weight of evidence approach is recommended, taking into account all of the information obtained with various test methods, since no single experimental method yields decisive evidence for allergenicity (EFSA, 2006; CAC, 2003).

4.2.5.1. Assessment of allergenicity of the newly expressed proteins

For several reasons it is highly unlikely that a sugar beet expressing the CP4 EPSPS protein would constitute an allergic risk to the consumer. First of all, there is no indication that the CP4 EPSPS protein is allergenic. An allergy risk evaluation of the CP4 EPSPS protein has previously been completed for applications/notifications evaluated by the GMO Panel (EFSA, 2003a, b), earlier EC Scientific Committees and national competent authorities using the guidelines proposed by Metcalfe *et al.* (1996). These include the absence of known allergenicity of the source, absence of sequence homology with known allergens and rapid and extensive degradation by proteolytic enzymes. The GMO Panel is not aware of any new information on allergenicity of the CP4 EPSPS protein which requires a change of this opinion.

The applicant has provided bioinformatic analysis of similarity of the amino acid sequence of the CP4 EPSPS protein with amino acid sequences of allergenic, toxic or pharmacologically active proteins. By using the sequence alignment tool FASTA, it was shown that the CP4 EPSPS protein shared no structurally significant sequence similarity to sequences of proteins in databases of allergenic proteins and toxic or pharmacologically active proteins (AD4, TOXIN5 and public domain (ALLPEPTIDES) databases). Neither did a sequence of the CP4 EPSPS protein share eight linearly contiguous amino acids identities to any sequence of the allergens.

Although there is no evidence to suggest that DNA sequences at the 5' and 3' junctions of the inserted T-DNA in sugar beet event H7-1 are transcribed, the applicant has provided a bioinformatic analysis of potential allergenicity, as well as toxicity and pharmacological activity, of putative peptides encoded at the junctions. Sequences spanning the junction were translated from stop codon to stop codon in all frames and each frame compared to appropriate sequence databases including those for allergens and toxins. The data provided demonstrate that in the unlikely event that junction polypeptides were translated they would not share a sufficient degree of sequence similarity to known allergens, toxins or pharmacologically active proteins.

Additionally, exposure will be negligible as proteins and polypeptides are removed during sugar production. Studies on sugar produced from sugar beet H7-1 have shown that the detectable level of the CP4 EPSPS protein characteristic for this genetically modified sugar beet is below the detection limit (0.004 ppm). Also molasses, which in some areas of Europe are used for production of syrup for human consumption, are free of protein (limit of detection 0.002 ppm).

4.2.5.2. Assessment of allergenicity of the whole GM plant or crop

Another related issue is that allergenicity of the whole crop could be increased as an unintended effect of the random insertion of the transgene in the genome of the host, e.g. through qualitative or quantitative modifications of the pattern of expression of endogenous proteins. This issue does not appear relevant to the GMO Panel since sugar beet is not considered a major allergenic food and possible over-expression of any endogenous protein not known to be allergenic would be unlikely to alter the overall allergenicity of the whole plant.

4.2.6. Nutritional assessment of GM food/feed

Feeding trials in which nutrient availability is measured by conducting digestibility studies is an accepted methodology for evaluating the nutritional assessment of feeds. Hartnell *et al.* (2005) have reported studies comparing the nutrient digestibility in sheep fed diets containing Roundup Ready or conventional fodder beet, sugar beet and beet pulp. The first trial, which considered whole sugar beet, compared the nutrient digestibility of sugar beet H7-1 with five conventional varieties. A total of 42 sheep were used, with seven sheep per treatment. As sugar beet should not be fed as the sole feed to sheep, the diet offered contained 30 % hay, with a known digestibility value, and 70% chopped sugar beet. In addition all diets included a small supplement of urea and sodium sulphate to ensure an adequate level of dietary nitrogen and

sulphur. All sheep received for three weeks the same diet except for the sugar beet, which was either the sugar beet H7-1 or one of the five conventional varieties. As is standard practise in such trials, the diet was fed at a maintenance level of feeding and data collected, starting after a two-week dietary adaptation period. Prior to the start of the experiment the chemical compositions of the hay and the six sugar beet varieties were analysed. With the exception of ash, which was a reflection of soil contamination, the nutrient content (dry matter, nitrogen, crude ash, acid insoluble ash, crude fat, sugar, crude fibre, neural detergent fibre, acid detergent fibre and gross energy) of the six sugar beet varieties were similar.

When considering the whole diet (sugar beet and hay) there was, with the exception of ash, no significant difference between the digestibility values recorded for the diets containing the six sugar beet varieties. As the digestibility values of the hay were measured in an earlier study it was possible to estimate the nutrient digestibility values for the sugar beet. With the exception of ash, there were no significant differences between the digestibilities estimated for the six sugar beet varieties. With the exception of one sheep, which was removed from a treatment containing one of the conventional sugar beet varieties, all sheep on all diets remained healthy throughout the study. In addition to these data, a further trial comparing the digestibility of the sugar beet pulp obtained from sugar beet H7-1 variety with sugar beet pulp obtained from five European locations was reported. While there were significant differences between the dry matter, organic matter, crude protein, neutral detergent and acid detergent fibre digestibility values these were not unique to sugar beet H7-1 and were all within the expected range.

These data indicate that the nutritional value of sugar beet H7-1 and the sugar beet pulp derived from this variety was comparable with the conventional varieties used in the studies.

4.2.7. Post-market monitoring of GM food/feed

No risks to human and animal health were identified in studies of the CP4 EPSPS protein expressed in sugar beet H7-1, and in studies of the genetically modified sugar beet itself. Thus, foods and feeds produced from sugar beet H7-1 is as safe and as nutritious as foods and feeds derived from conventional sugar beets. Dietary intake of products from sugar beet is not expected to increase on introduction of the genetically modified sugar beet H7-1 on the market, as products from sugar beet H7-1 varieties will only replace a portion of the products produced from conventional sugar beet. The GMO Panel has, therefore, not identified any issue regarding food and feed safety that would require post-market monitoring of sugar beet H7-1.

4.3. Conclusion

Sugar and molasses have been shown to be free from DNA and protein. Thus, the human exposure to the transgene and its corresponding expressed protein is likely to be very low, if existing at all. However, animals fed with pulp from sugar beet H7-1 will be exposed to the CP4 EPSPS protein. The CP4 EPSPS protein has been evaluated and found to be safe for human and/or animal consumption in several earlier applications where the crops had been made glyphosate-tolerant.

The molecular characterization and the comparative compositional analysis did not indicate the occurrence of any unintended effects due to the genetic modification. In addition the applicant provided a 90-day rat feeding study which did not indicate any adverse effect.

The GMO Panel concluded that products from sugar beet H7-1 are safe as food and feed, and, that the nutritional value of the sugar beet H7-1 and the derived sugar beet products is comparable to that of analogous products from conventional sugar beet. The GMO Panel is also of the opinion that the risk of allergenicity is of no concern with this product.

The GMO Panel has not identified any issue regarding food and feed safety that would require post-market monitoring of sugar beet H7-1.

5. Environmental risk assessment and monitoring plan

Since the scope of the application does not cover GMO or food and feed containing or consisting of GMO the environmental risk assessment and an environmental monitoring plan mentioned in Articles 5(5) and 17(5) of Regulation (EC) No 1829/2003 are not required. However, the possible transfer of the inserted DNA by transformation and its possible impact have been assessed.

5.1. Issues raised by Member States

Some Member States requested a clarification whether seeds, sugar beets or sugar beet material (portions of roots and remnants of leaves) fall under the scope of the application.

5.2. Evaluation of relevant scientific data

The scope of this application is for food produced from or containing ingredients produced from sugar beet H7-1 and feed produced from sugar beet H7-1. Thus the scope only includes products produced from sugar beet H7-1 which contain no viable plant parts. Therefore there are no requirements for scientific information on environmental risks associated with the accidental release or cultivation of sugar beet H7-1.

Sugar beet processing has been shown to significantly deplete the DNA levels of sugar and molasses to the point that no DNA is present at detectable levels. However, it is most likely that intact DNA is present in the dried pulp. The dried pulp is used as feed for domesticated animals (ruminants), therefore microorganisms in the digestive tract of these animals may be exposed to genetically modified DNA. Based on present scientific knowledge, and elaborated in more detail elsewhere (EFSA, 2004), gene transfer from genetically modified plant material to microorganisms under natural conditions is extremely unlikely, and would occur primarily through homologous recombination in microorganisms. The inserted gene *cp4 epsps* is isolated from the soil bacterium *Agrobacterium sp*. CP4 which is a widespread microorganism in natural habitats. Taking into account the origin and nature of the *cp4 epsps* gene and the lack of selective pressure in the intestinal tract, the likelihood that horizontal gene transfer would result in increased fitness or other selective advantages of microorganisms is very small. For this reason it is very unlikely that the *cp4 epsps* gene from sugar beet H7-1 would become established in the genome of microorganisms present in the digestive tract of domesticated animals. In the very unlikely event that such a horizontal gene transfer would take place, no adverse effects on human and animal health and the environment are expected as no specifically new traits would be introduced to the microbial community.

5.3. Conclusion

The scope of the application only includes products produced from sugar beet H7-1 which contain no viable plant parts. An environmental monitoring plan for sugar beet H7-1 is not required.

CONCLUSIONS AND RECOMMENDATIONS

Sugar beet H7-1 has been developed to provide tolerance to glyphosate-containing herbicides by insertion of the *cp4 epsps* gene from *Agrobacterium* sp. CP4.

The GMO Panel has evaluated information provided on the molecular characteristics of the insert and characteristics of the protein expressed in order to assess the safety of sugar beet H7-1 and its derived products. Further evaluations were focused on agronomic and compositional characteristics, and on nutritional, allergenic and toxicological properties of sugar beet H7-1 and its derived products. The GMO Panel concluded that products from sugar beet H7-1 are safe as food and feed, and, that the nutritional value of the sugar beet H7-1 and the derived sugar beet products is comparable to that of analogous products from conventional sugar beet.

As the scope of this application is for food produced from or containing ingredients produced from sugar beet H7-1 and feed produced from sugar beet H7-1 the GMO Panel considers that there is no requirement for scientific information on environmental risk assessment associated with the accidental release or cultivation of sugar beet H7-1. An environmental monitoring plan for sugar beet H7-1 is not required.

The GMO Panel is of the opinion that based on the outcome of the risk assessment no specific conditions or restrictions for use and handling including post-market monitoring requirements should be imposed for placing on the market products produced from sugar beet H7-1 for food and feed use. Furthermore, there is no need for specific conditions for the protection of particular ecosystems/environment and/or geographical areas.

The GMO Panel concludes that placing on the market products produced from sugar beet H7-1 are unlikely to have any adverse effect on human and animal health or the environment in the context of its intended uses.

DOCUMENTATION PROVIDED TO EFSA

1. Letter from the UK Competent Authority (Food Standards Agency), dated 26 November 2004 concerning the submission to EFSA of an application for products produced from sugar beet H7-1 within the framework of Regulation (EC) No 1829/2003.

2. Letter from EFSA to applicant, dated 11 March 2005, requesting clarification regarding the scope of the application (Ref. SR/AC/jq/(2005) 300).

3. Letter from CRL (IHCP-JRC), dated 11 May 2005, concerning the completeness check of application EFSA-GMO-UK-2004-08 in accordance with Article 5(3)(i) and (j) and Article 17(3)(i) and (j) of Regulation (EC) 1829/2003 (JRC 106-BGMO/GVDE/SC.D (2005)(122)11183).

4. Letter from applicant to EFSA, dated 20 May 2005, providing clarification regarding the scope of the application.

5. Letter from EFSA to applicant, dated 20 May 2005, concerning the "Statement of Validity" for application EFSA-GMO-UK-2004-08 on sugar beet H7-1 submitted under Regulation (EC) No 1829/2003 (Ref. SR/KL/jq (2005) 584).

6. Submission of the application EFSA-GMO-UK-2004-08 by the applicant to EFSA, containing:

   Part I – Technical dossier
   Part II – Summary

Part III – Cartagena Protocol
Part IV – Labelling proposal
Part V – Samples and detection method
Part VI – Additional information for GMOs

7. Comments of the Member States, provided on 20 August 2005 (GMO EFSAnet).
8. Letter from EFSA to applicant, dated 24 October 2005, requesting additional information and stopping the clock for application EFSA-GMO-UK-2004-08 (Ref. SR/AC/jq (2005) 1270).
9. Letter from applicant to EFSA, dated 15 February 2006, providing response to the request for additional information sent on 24 October 2005.
10. Letter from EFSA to applicant, dated 6 March 2006, requesting additional information and keeping the clock stopped for application EFSA-GMO-UK-2004-08 (Ref. SR/AC/jq (2006) 1407428).
11. Letter from applicant to EFSA, dated 12 September 2006, providing response to the request for additional information sent on 6 March 2006.

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ACKNOWLEDGEMENT

The GMO Panel wishes to thank Gijs Kleter and Richard Phipps for their contributions to the opinion.