Opinion of the Scientific Panel on Genetically Modified Organisms on an application (Reference EFSA-GMO-UK-2005-14) for the placing on the market of genetically modified potato EH92-527-1 with altered starch composition, for production of starch and food/feed uses, under Regulation (EC) No 1829/2003 from BASF Plant Science[1]

(Question No EFSA-Q-2005-070)

Opinion adopted on 7 December 2005

SUMMARY

This document provides an opinion of the Scientific Panel on Genetically Modified Organisms (GMO Panel) of the European Food Safety Authority (EFSA) on genetically modified potato EH92-527-1 (Unique identifier BPS-25271-9), with an altered starch composition (higher amylopectin:amylose ratio). Amylopectin starch potatoes are mainly used for the production of starch for industrial purposes. The GM potato tubers are not intended for direct human consumption. The potatoes will be marketed within a closed loop (identity preservation) system.

In delivering its opinion the GMO Panel considered the application (ref. EFSA-GMO-UK-2005-14) under Regulation (EC) 1829/2003, additional information provided by the applicant and the specific comments submitted by the Member States. Further information from another application, *i.e.* application C/SE/96/3501 under Directive 2001/18/EC, for placing the potato EH92-527-1 on the market under current regulatory procedure were taken into account where appropriate, as were issues raised by the Member States. Although an overall single risk assessment for all uses of potato EH92-527-1 has been made, for regulatory reasons, opinions for the application under Regulation (EC) No 1829/2003 and the notification under Directive 2001/18/EC are issued separately.

The potato EH92-527-1 was assessed with reference to its intended uses employing the appropriate principles as 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 examination of the DNA inserted into potato EH92-527-1, the nature and safety of the modification in protein expression in the plants with respect to toxicology and allergenicity. Furthermore, a comparative analysis of agronomic traits and composition as well as the safety of the food/feed was evaluated. Both nutritional and environmental risk assessments, including monitoring plan, were undertaken.

The potato EH92-527-1 is derived from the cultivar Prevalent. Potato leaf discs were transformed by *Agrobacterium*-mediated gene transfer technology. The modification involves inhibition of the expression of granule bound starch synthase protein (GBSS) responsible for amylose biosynthesis. As a result, the starch produced has little or no amylose and consists of amylopectin (branched starch), which modifies the physical properties of the starch. A gene conferring kanamycin resistance (*npt*II) was used as a selectable marker.

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Molecular analysis shows that potato EH92-527-1 contains two partial copies of the DNA fragment, *i.e.* the insert, including the flanking region, was duplicated in reverse orientation and joined tail-to-tail. This is present at a single locus in the nuclear genome of the GM plant. The complete DNA sequence of the insert was provided. The GMO Panel is of the opinion that bioinformatic analysis of the DNA insert and flanking regions indicates no cause for concern, and that sufficient evidence for the stability of the insert structure was provided.

The potato EH92-527-1 has been developed for amylopectin production. The amylopectin will mainly be used in technical non-food products such as paper. Compositional analysis shows that the potato EH92-527-1 falls within expected patterns of variation for potato, except for the change in starch composition due to the genetic modification. By-products of the starch extraction process (*e.g.* pulp) are used for other purposes including animal feed. The risk assessment includes an analysis of data from appropriate animal feeding trials. These data indicate that after starch extraction, the by-products of the GM potato are as safe as those from the non-GM parental line.

The intended use of potato EH92-527-1 is in the starch production industry with the pulp used for animal feed. However the applicant has concluded that it cannot be excluded that the GM potato and some products of the starch processing may be used as, or be present in food. The application EFSA-GMO-UK-2005-14 includes a scientific risk assessment of potato EH92-527-1 and by-products of the starch processing for food and feed uses. The GMO Panel was requested to conduct a scientific assessment of the potato EH92-527-1 and derived products for food and feed uses.

The EH92-527-1 potato tubers are not intended for human or animal consumption as a whole. Potential impact of the cultivation of the potato EH92-527-1 on the environment was addressed in the assessment of notification C/SE/96/3501 under Directive 2001/18/EC.

In conclusion, the GMO Panel considers that the information available for the potato EH92-527-1 addresses the outstanding questions raised by the Member States and considers that the potato EH92-527-1 is unlikely to have an adverse effect on human and animal health or the environment in the context of its proposed uses.

Key words: GMO, potato, *Solanum tuberosum*, EH92-527-1, starch, amylopectin, amylose, kanamycin, food/feed safety, human health, environment, Regulation (EC) 1829/2003, Directive 90/220/EEC, Directive 2001/18/EC.

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BACKGROUND

On 25 April 2005 EFSA received from the Competent Authority of United Kingdom an application (Reference EFSA-GMO-UK-2005-14) submitted by BASF Plant Science within the framework of Regulation (EC) No 1829/2003 on genetically modified food and feed (EC, 2003). The application was originally submitted to the Competent Authority of the United Kingdom under Articles 5 and 17 of Regulation (EC) No 1829/2003.

EFSA initiated a formal review of the application immediately, to check compliance of the dossier with the requirements laid down in Articles 5(3) and 17(3) of Regulation (EC) No 1829/2003. On 12 July 2005 EFSA declared the application as valid and started the clock in accordance with Articles 6(1) and 18(1) of Regulation (EC) No 1829/2003.

As initial steps in the administrative procedures and risk assessment, EFSA made the valid application available to the Member States and the Commission and consulted risk assessment bodies of the Member States, including the national Competent Authorities within the meaning of Directive 2001/18/EC (EC, 2001) following the requirements of Articles 6(4) and 18(4) of Regulation (EC) No 1829/2003, to request their comments on the safety assessment of the genetically modified food/feed. The Member State bodies had three months after the date of receipt of the request (until 12 October 2005) within which to make their opinion known. All comments were evaluated by the GMO Panel and taken into consideration in further risk assessment. During the assessment period by the GMO Panel, EFSA requested further clarification from the applicant. Comments on risk management issues, such as co-existence of different agronomic systems, were excluded from further considerations.

In delivering its opinion the GMO Panel considered the application, additional information provided by the applicant and the specific comments raised by the Member States. Further information from another application (Reference notification C/SE/96/3501) for the placing on the market of the potato EH92-527-1 under Directive 2001/18/EC was taken into account where appropriate, as were comments from the Member States. Although an overall single risk assessment for all uses of potato EH92-527-1 has been made, for regulatory reasons, opinions for the application under Regulation (EC) No 1829/2003 and the notification under Directive 2001/18/EC (EFSA, 2006) are issued separately.

In accordance with Articles 6(1) and 18(1) of Regulation (EC) No 1829/2003 EFSA shall, in giving its opinion to the Commission, the Member States and the applicant, endeavour to respect a time limit of six months as from the receipt of a valid application. Apart from the requirements listed in Articles 6(5) and 18(5) of Regulation (EC) No 1829/2003, the EFSA opinion shall include a report describing the assessment of the food and feed uses and stating the reasons for its opinion and the information on which its opinion is based. This document is

to be seen as the report requested under Articles 6(6) and 18(6) of Regulation (EC) No 1829/2003 and thus will be part of the overall opinion as required by Regulation (EC) No 1829/2003.

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 the genetically modified potato EH92-527-1 for food/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 and, in the case of GMOs or food/feed containing or consisting of GMOs, conditions for the protection of particular ecosystems/environment and/or geographical areas 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 Carthagena Protocol. Neither did the GMO Panel consider proposals for labelling and methods of detection as these are matters related to risk management. The latter would include information on sampling and the identification of the specific transformation event in the food/feed and/or foods/feeds produced from it.

ASSESSMENT

1. Introduction

Genetically modified (GM) potato EH92-527-1 (Unique identifier BPS-25271-9) was assessed with reference to its intended uses and the appropriate 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' (EFSA, 2004a). In its evaluation the GMO Panel also considered the issues that were raised by the Member States during the initial assessment of the notification introduced under Directive 2001/18/EC as well as during the 3-month consultation period as required by Regulation (EC) No 1829/2003. Although an overall single risk assessment for all uses of potato EH92-527-1 has been made, for regulatory reasons, opinions for the application under Regulation (EC) No 1829/2003 (Reference EFSA-GMO-UK-2005-14) and the notification under Directive 2001/18/EC (Reference C/SE/96/3501) are issued separately.

The GM potato EH92-527-1 has been developed for amylopectin (branched starch) production. The amylopectin will mainly be used in technical non-food products such as paper. By-products of the starch extraction process are used for other purposes including animal feed (*e.g.* pulp) or for other conventional non-food purposes (*e.g.* potato juice used as soil fertilizer). The GM potato tubers are not intended for direct human consumption.

Whereas the scope of notification C/SE/96/3501 includes the cultivation of potato EH92-527-1 for industrial starch production, the scope of application EFSA-GMO-UK-2005-14, as defined by the applicant, includes the potato EH92-527-1 and derived products for food and feed uses, since it cannot be excluded that the GMO potato and derived products may be used as or may be present in food. The GMO Panel was therefore requested to carry out a comprehensive scientific risk assessment of the GM potato for all uses.

2. Molecular characterisation

2.1. Issues raised by Member States

Questions were raised regarding (1) the difference in one amino acid of NPTII protein encoded by the vector and the insert, (2) the re-analysis of DNA sequence of the insert in order to check the presence of ORFs, and (3) the stability of the insert.

2.2. Evaluation of relevant scientific data

Having considered the information provided in the applications and the Member State comments, the GMO Panel requested from the applicant further data on the stability of the insert over several generations as well as on the bioinformatic analysis.

2.2.1. Transformation process and vector constructs

Potato EH92-527-1 was developed from the cultivar Prevalent by *Agrobacterium*-mediated gene transfer technology. The notification does not include any progeny derived from crosses between the GM potato EH92-527-1 and any other potato varieties.

The T-DNA, from plasmid pHoxwG, derived from pBIN19, was delivered to leaf discs of potato cultivar Prevalent using a binary vector system. The T-DNA contains *npt*II under the control of the nopaline synthase (nos) promoter and terminator and a potato genomic *gbss* fragment in antisense orientation under the control of its own promoter and the *nos* terminator. The potato *gbss* gene codes for Granule Bound Starch Synthase (GBSS) which is responsible for amylose biosynthesis. RNA expression from the antisense construct leads to reduction of natural levels of GBSS and of the amount amylose accordingly. Reduction of amylose content results consequently in a higher amylopectin:amylose ratio.

2.2.2. Transgenic constructs in the genetically modified plant

During the integration process, DNA sequences towards the left border region of the T-DNA were deleted and the entire T-DNA insert, including the flanking region, was duplicated in reverse orientation prior to integration. The insert comprises the 5' untranslated region of the nopaline synthase gene (*Pnos*); *npt*II coding sequence; 3' untranslated part of nopaline synthase gene; potato *gbss* promoter fragment; a truncated *gbss* coding region in antisense orientation without the terminator. The insert, including the potato flanking region, was duplicated in a tail-to-tail arrangement with two right border regions as junctions to the potato chromosomal DNA. Southern blot analyses indicated that no vector backbone sequences are inserted into potato EH92-527-1. This includes the absence of the *npt*III gene which could encode for resistance to amikacin, an aminoglycoside antibiotic.

The T-DNA and its flanking potato regions have been sequenced. Bioinformatic analysis has been carried out. Eighteen ORFs have been identified in the insert sequence of the potato EH92-527-1, eleven of which have no sequence homology with known coding regions. Moreover bioinformatic analysis showed that for all ORFs identified there are no homologies with known toxins or allergens. The only ORF having a complete coding region for a known protein is the *npt*II gene. While the original sequencing data suggested that there was one amino acid change in the NPTII protein in the GM plant, repeated re-sequencing showed that this was not the case. Bioinformatic analysis predicts that ORF4 could be transcribed due to its association with ORF 1 (*npt*II). The hypothetical ORF4 protein showed a high degree of similarity with two proteins that

are not known to be toxic or allergenic (see also Section 4.2.3.2(c)). Extensive studies indicated that, although ORF4 transcript is detectable in the GM potato, there is no corresponding translation into a protein, confirming expectations from the molecular characterisation of ORF4 and its association with ORF1. No new ORFs were found in the bioinformatic analysis repeated and reported in June 2005 in the light of new sequence information obtained for the insert in potato EH92-527-1. Thus there are no new safety concerns.

2.2.3. Information on the expression of the insert

The GM potato EH92-527-1 differs from its parental non-GM cultivar in two respects: it has reduced amount of endogenous GBSS protein (resulting in altered starch composition) and it expresses the NPTII protein (conferring resistance to kanamycin). Reduction of the GBSS protein as well as of the amylose content of tuber starch was demonstrated with conventional analytical methods.

Kanamycin resistance was used as the selectable marker in the genetic modification process. The amount of NPTII protein has been analysed from the leaves during plant development as well as from tubers, pulp and starch. Overall, NPTII levels were very low, 0.00082% of the soluble protein in pulp (8.2 ng/mg total protein; 55 ng/g fresh weight) and 0.0006% in tubers (6.82 ng/mg protein; 31 ng/g fresh weight). The amount of NPTII was much lower in the leaves and is undetectable in starch.

2.2.4. Inheritance and stability of inserted DNA

Stability of the inserted DNA in the potato EH92-527-1 was determined over several cycles of vegetative propagation. The composition of EH92-527-1 tuber starch was analysed for three consecutive years and the high amylopectin phenotype remained stable. Moreover, the applicant provided a comparative Southern analysis indicating that genomic DNA isolated in 1998 and 2005 had similar hybridization patterns with four different restriction enzyme combinations. These are considered as sufficient evidence to demonstrate the stability of the insert structure in potato EH92-527-1.

2.3. Conclusion

GM potato EH92-527-1 was generated through *Agrobacterium*-mediated transformation of the potato cultivar Prevalent. Two intended changes have been introduced into the potato: a reduction in the amount of endogenous GBSS protein (resulting in altered starch composition) and expression of NPTII protein (conferring kanamycin resistance). The GMO Panel is of the opinion that bioinformatic analysis of the DNA insert and flanking regions indicates no cause for concern, and that sufficient evidence for the stability of the insert structure was provided.

3. Comparative analysis

3.1. Issues raised by Member States

Questions were raised regarding the need for additional data (1) on agronomic characteristics (flowering), (2) on the compositional analysis of supplementary compounds, (3) on the metabolic pathways that might have been affected by the modification and (4) additional field trials in other countries than Sweden, such as in Southern Europe, were recommended.

3.2. Evaluation of relevant scientific data

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

In the field trials analysing agronomic and compositional characteristics, the GM potato EH92-527-1 was compared with its parent cultivar Prevalent, which is commercially cultivated for starch production and which is not genetically modified. These field trials have been carried out during various seasons in multiple locations in Sweden. Data on agronomic characteristics have been obtained from field trials carried out during 1994-1996 and variety trials during 1996-1997, while those on compositional analysis of potato tubers were from trials performed during 1996-1998.

Cultivation of starch potatoes within the European Union occurs in a selected group of Member States to which quotas for cultivation are assigned (EC, 1994). These member states currently include Austria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Latvia, Lithuania, Netherlands, Poland, Slovakia, Spain, and Sweden. The applicant intends to cultivate the GM potato close to industrial starch processing plants which supply the paper pulping industry. These are mostly located in Northern Europe.

3.2.2. Compositional analysis

The potato EH92-527-1 has been genetically modified to have a high and qualitatively altered starch production in tubers. The physicochemical characteristics of the starch derived from the GM potato were studied with various analytical methods. Compared with conventional starch, the characteristics of starch derived from the transgenic potato had been altered to produce a starch with little or no amylose.

Tubers obtained from the field trials performed during 1996-1998 were analysed for composition. These trials were carried out in multiple locations with replicated plots. The compounds analysed are in agreement with the recommendations put forward in the OECD consensus document on key compositional parameters for novel varieties of potato (OECD, 2002). The analysed compounds included dry matter, protein, fat, ash, carbohydrates, fibre, digestible fibre, fructose, glucose, sucrose, starch, chlorogenic acid, solanine, chaconine, nitrate, vitamin C, and minerals (Na, K, Ca, Mg, P, Fe, Zn, Cu, Mn, Cd).

In addition to the intended alterations in starch composition of the GM potato, some statistically significant differences between the GM potato and its control were observed each year, including a decrease in yield and dry matter and an increase in sucrose content (1.7g/100g in the GM potato versus 1.2g/100g in parental cultivar) and vitamin C content (67 mg/100g in the GM potato versus 49 mg/100g in parental cultivar). With regard to yield, additional data on potato EH92-527-1 tested during starch production trials in 1998-2000 shows similar values for yield compared with equivalent potato cultivars. Other differences were also noted during single years, but not consistently throughout the three years, such as decreases in glycoalkaloid levels of solanine and chaconine in potato EH92-527-1 during two years. The changes in vitamin C and glycoalkaloids were still within the background ranges reported in literature. The GMO Panel considered that the change in sucrose content was related to the intended altered starch biosynthesis. The GMO Panel concludes that the observed differences are unlikely to cause adverse health effects.

Furthermore analysis of the gross and mineral compounds of pulp and juice derived from transgenic potato EH92-527-1 and non-transgenic cultivar Prevalent showed that their compositions were similar.

3.2.3. Agronomic traits and GM phenotype

From field trials, the comparison between the transgenic potato EH92-527-1 and its parental cultivar Prevalent revealed no differences in plant morphology (including flowering characteristics) and susceptibility to herbicide, late blight fungal disease, and frost. In addition, the GM potato did not show altered susceptibility to insects, bacteria, other fungi, nematodes and plant viruses.

3.3. Conclusion

In addition to the intended alteration in starch composition of the GM potato, the analysis of agronomic and compositional characteristics showed some differences between the transgenic potato EH92-527-1 and its parental line Prevalent, including altered levels of vitamin C and sucrose. Given that the genetic modification alters starch composition, the GMO Panel considers the observed changes not unusual given the altered carbohydrate metabolism. In addition, the levels of vitamin C and glycoalkaloids were within the background range. The GMO Panel concludes that the observed differences do not raise safety concerns.

4. Food/feed safety assessment

4.1. Issues raised by Member States

Questions were raised regarding (1) the need for toxicological studies on the whole food/feed (*e.g.* 90-day subchronic oral toxicity studies in rodents exposed to whole crop or potato pulp) and the putative ORF4 protein in order to provide additional reassurance about the safety aspects of any eventual unintended effects of the genetic modification, (2) the need for additional feeding studies, including an appropriate experimental design, with other animal species, (3) the proposal for feed-testing of protein purified from potato juice on domestic animals, (4) the recommendation for extended animal feeding studies as well as genotoxicity assays, (5) the expression of the *npt*II gene, (6) the potential glycemic effects due to accidental human consumption of potato EH92-527-1 by diabetics and (7) the apparent increase in the number of thyroid cysts in male rats fed the GM potato) as noted in the results of microscopic examinations.

4.2. Evaluation of relevant scientific data

Having considered the information provided in the applications and the Member State comments, the GMO Panel requested from the applicant further data on the 90-day rat feeding study.

4.2.1. Product description and intended use

The intended use of potato EH92-527-1 is in the starch production industry with the pulp used for animal feed. However the applicant has concluded that it cannot be excluded that the GM potato and some products of the starch processing may be used as, or be present in food. The application EFSA-GMO-UK-2005-14 includes a scientific risk assessment of potato EH92-527-1 and by-products of the starch processing for food and feed uses. Although the GM potato tubers are not intended for direct human consumption. The aspects of cultivation, import and processing of GM potato EH92-527-1 are covered by another application (Ref C/SE/96/3501) submitted under Directive 2001/18/EC.

4.2.2. Stability during processing

Based on the data of the compositional analysis of the raw agricultural commodities of potato EH92-527-1 and its non-GM parent Prevalent, the GMO Panel is of the opinion that the stability of the processed products derived from this potato is equal to the non-GM processed products, except for the characteristics related to the altered starch (higher amylopectin:amylose ratio).

A study was carried out on the presence of NPTII as detected by ELISA in boiled tubers, pulp, and starch. The results showed that while NPTII could be detected in pulp, none of it was detected in boiled tubers and starch.

4.2.3. Toxicology

4.2.3.1. NPTII protein used for safety assessment

In the safety assessment of the transgenic NPTII protein, purified preparations of recombinant NPTII generated by the genetically modified bacterium *Escherichia coli* have been used for the acute oral toxicity study (Fuchs *et al.*, 1993b). Given that the low expression levels of NPTII in the transgenic potato make purification of this protein difficult, the GMO Panel considers it acceptable to use purified preparations of the same transgenic protein produced by alternative host organisms, provided the equivalence with the protein expressed in transgenic plants is established. The final data provided on the inserted DNA indicate that the amino acid sequence of the translated NPTII in potato EH92-527-1 has not been changed compared with that encoded by the vector sequence. In addition, the authors of the study on acute oral toxicity and degradation in simulated gastric fluid also studied the equivalence of the NPTII protein produced by *E. coli* with NPTII produced in genetically modified cotton, potato, and tomato (Fuchs *et al.*, 1993a,b). Equivalence was established in assays involving N-terminal sequencing, Western blotting, and enzymatic activity measurement. In addition, the NPTII proteins produced by *E. coli*- and by plants showed lack of glycosylation (Fuchs *et al*., 1993a). Whereas this study did not include the potato EH92-527-1, the evidence presented indicates that NPTII expressed in *E. coli* retains the same characteristics as NPTII introduced by genetic modification into various plants, including potato.

4.2.3.2. Toxicological assessment of expressed novel protein in potato EH92-527-1

The introduced *gbss* antisense gene fragment results in reduced amounts of the GBSS protein, but no new protein. The transgenic NPTII protein has been the subject of previous safety assessments of NPTII-expressing genetically modified crops, including MON863 maize (EFSA, 2004c,d). Its role in antibiotic resistance was assessed in an opinion of the GMO Panel on the safety of antibiotic resistance markers used in genetic modification of crops (EFSA, 2004b). The *npt*II gene is considered to belong to a class of antibiotic resistance genes that is acceptable for commercial releases.

(a) Acute oral toxicity

A study on the acute oral toxicity of NPTII in mice is reported in scientific literature (Fuchs *et al*., 1993b). Mice that had received an oral dose of 100, 1000, or 5000 mg NPTII/kg bodyweight were subsequently monitored for adverse effects over the following seven days. The authors concluded that no treatment-related adverse health effects had occurred. The GMO Panel accepts the authors' conclusion.

(b) Degradation in simulated digestive fluids

Ruminants such as cows are important target animals for pulp derived from potatoes. Degradation of proteins contained within ingested crops may occur in the rumen of these animals. The degradation of a commercially obtained preparation of purified NPTII was studied after addition to *in vitro* samples of ruminal fluid obtained from fistulated sheep. The levels of NPTII in the incubations were equal to, or exceeded, the estimated levels of intake of this protein in livestock. The transgenic NPTII protein was found to be degraded to low or non-detectable levels within hours.

Data in the scientific literature show that the NPTII protein is degraded rapidly both in simulated human gastric fluid (*i.e.* within 10 seconds) and in simulated human intestinal fluid (*i.e.* within 15 minutes) (Fuchs *et al*., 1993b).

(c) Bioinformatic studies

With regard to the hypothetical ORF4 protein, bioinformatic studies showed that it shared a high degree of similarity with parts of the bleomycin-resistance protein from *E. coli* transposon Tn5 and ornithine cyclodeaminase from *A. tumefaciens*, which relates to the genetic construct that has been used for genetic modification. These proteins are not known to be toxic or allergenic. In addition, the sequence showing resemblance to the bleomycin resistance protein only constitutes a fragment of the latter and a functional bleomycin resistance protein is not produced, as evidenced by lack of bleomycin- and zeocin-resistance after artificial cloning of ORF4 into *E. coli* (see also Section 2.2.2.).

4.2.3.3. Toxicological assessment of new constituents other than proteins

As previously described for the compositional analysis (see Section 3.2.2.), differences have been observed in the levels of several compounds between the transgenic potato EH92-527-1 and its parent cultivar Prevalent, in addition to the intended alteration in starch composition of the GM potato. These differences included increases in vitamin C and sucrose and a decrease in glycoalkaloids. The GMO Panel does not anticipate adverse health effects to occur resulting from these differences.

4.2.4. Toxicological assessment of the whole GM food/feed

Subchronic oral toxicity

A subchronic animal toxicity study with the whole GM potato was performed in rats. Three groups consisting of ten animals each, five female and five male, received a standard laboratory diet for 90 days, or a diet containing five percent of freeze-dried potato, either from the parental line Prevalent or from the transgenic line EH92-527-1. The animals were checked daily for appearance and mortality and weekly for body weight, feed consumption, appearance and behaviour. At the end of the experimental period, animals were checked for appearance, behaviour, sensory and motor reflexes, and motor activity. In addition, samples of urine and blood were taken for urinalysis, clinical chemistry, and haematology. After termination of the feeding experiment, pathology examination of the animals was undertaken, examining them for gross lesions. Organs were removed and selected organs were further weighed, and examined microscopically. The results for animals fed either one of both potato-containing diets were compared statistically and also with data obtained from animals fed the standard laboratory diet.

In female animals, statistically significant differences in white blood cells and spleen weight were noted between animals that were fed the transgenic potato and those given a diet containing the parental cultivar. However, these differences fell within the range of values observed in animals fed the standard rodent laboratory diet. Moreover, these changes were not accompanied by any changes in other lymphoid organs besides the spleen.

In addition, the findings of cysts in thyroids checked by microscopy were slightly increased in male animals fed diets containing the transgenic potato compared with animals fed the standard laboratory rodent diet. No cysts were observed in the thyroids of female animals fed either diet. Thyroid cysts occur commonly in rats, while their frequency varies during ageing (*e.g.* Takaoka *et al*., 1995). No findings were reported that could be related to any possible thyroid malfunction. Therefore, the GMO Panel considers that the slightly increased incidence of thyroid cysts in males fed transgenic potato is likely to be due to natural variability and does not trigger a further safety assessment.

4.2.5. Allergenicity

In assessing the allergenic risk, the strategy concentrated on characterisation of the source of the recombinant protein, the potential of the newly expressed protein to induce sensitisation or to elicit allergic reactions in persons who are already sensitised and whether the transformation may have altered the allergenic properties of the 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 definitive evidence for allergenicity (EFSA, 2004a; CAC, 2003).

4.2.5.1. Assessment of allergenicity of the newly expressed protein

The NPTII protein has been previously evaluated for its safety within the framework of other applications for the placing of GM crops on the market that express NPTII (EFSA, 2004c,d).

The degradation of NPTII in simulated digestive fluids, which is also relevant for the assessment of potential allergenicity, has been discussed in Section 4.2.3.2(b).

As stated under Section 4.2.3.2(c), the hypothetical ORF4 protein showed a high degree of similarity with two proteins that are not known to be toxic or allergenic. In addition, if screened against a database of sequences of allergenic proteins, the ORF4 protein does not show any similarities, which in the opinion of the GMO Panel could be relevant and raise concerns about potential allergenic risk.

4.2.5.2. Assessment of allergenicity of the whole GM crop

Allergenicity of the whole crop could be increased as an unintended effect of the random insertion of the transgene in the genome of the recipient, for example through qualitative or quantitative modifications of the pattern of expression of endogenous proteins. This issue does not appear relevant to the GMO Panel since potato is not considered a major allergenic food and possible over-expression of any endogenous protein that is not known to be allergenic would be unlikely to alter the overall allergenicity of the whole plant. The same considerations also apply for exposure by inhalation during processing.

4.2.6. Nutritional assessment of GM food/feed

As stated under Section 3.2.2., ruminants are a target group to be fed potato pulp, an animal feed product originating as a by-product from the GM potato starch extraction and shown to be similar in composition to pulp of the non GM comparator Prevalent. A feeding study was performed in which heifers received pulp derived from potato EH92-527-1 or from conventional pulp at 30% dry weight of the total diet during 8 weeks. No differences were observed in feed consumption and body weight increases between animals fed the pulp derived from transgenic potatoes or those derived from conventional potatoes. Neither were any adverse effects noted of pulp feeding on health and intestinal function of the animals. The GMO Panel recognised the limitations of the feeding study but is of the opinion that the results obtained support the conclusions of the compositional comparison between the GM potato pulp and the control pulp, which stated that these feed products are compositionally similar and therefore nutritionally equivalent. In the view of the GMO Panel, no additional nutritional feeding studies are considered necessary.

The starch composition of the GM potato has shifted to a higher amylopectin:amylose ratio. In general, amylose is considered to be less glycemic than amylopectin. However, boiled, baked, and fried potatoes are considered highly glycemic due to gelatinisation of most of the starch during heating, which increases the availability of the starch for digestion (*e.g.* Garcia Alonso and Goni, 2000). The reported increase in the content of sucrose in the GM potato is considered by the GMO Panel to be minor as compared to the consumed quantities of carbohydrate that are known to cause physiological effects in humans (15-50 g glucose orally administered), such as an increase in insulin response (*e.g.* Gannon *et al.*, 1989). The GMO Panel therefore considers that consumption of the GM potato by diabetics is unlikely to pose a significantly altered glycemic risk over the consumption of conventional potatoes.

4.2.7. Post-market monitoring of GM food/feed

From a nutritional point of view the GM potato pulp is considered as equivalent to pulp processed from conventional potatoes. The risk assessment concluded that no data have emerged to indicate that GM potato EH92-527-1 is any less safe than its non-GM comparators. The opinion of the applicant that a post-market monitoring of the GM food/feed is not necessary is in line with the guidance document of the GMO Panel for the risk assessment of genetically modified plants and derived food and feed and is shared by the GMO Panel.

4.3. Conclusion

No toxicity of the NPTII protein has been observed and in simulated digestive fluids this protein is rapidly degraded. The hypothetical ORF4 protein, which has not been detected in potato EH92-527-1, shows no sequence similarities to known allergens or toxins. In addition, the subchronic 90-day feeding study in rats with freeze dried potatoes derived from potato EH92-527-1 and its parental line does not reveal any effects that in the opinion of the GMO Panel would raise concerns about the safety of the transgenic potato. An eight-week nutritional animal feeding study with pulp derived from transgenic potato EH92-527-1 and conventional pulp fed to heifers provided evidence of nutritional equivalence and showed no detrimental effects on animal health.

In summary, the safety of the transgenic protein NPTII and the hypothetical protein encoded by ORF4 and of the whole transgenic potato, as well as the composition and nutritional characteristics of animal feed containing transgenic potato pulp, have been considered. The

data considered indicated that there were no outstanding safety issues and therefore no further studies are required.

The GMO Panel is of the opinion that the weight of evidence from these studies, taken together, indicates that potato EH92-527-1 and derived products are no more likely to cause adverse effects on human and animal health than conventional potato, in the context of the proposed uses.

5. Environmental risk assessment

5.1 Issues raised by Member States

Questions were raised regarding (1) the absence of data from field trials in Southern Europe, (2) the need for more information on the effects on plant-associated organisms, (3) the horizontal gene flow of *npt*II gene and (4) the degradability of the whole plant in respect to biogeochemical cycles of the GM potato compared to the parental cultivar.

5.2. Evaluation of relevant scientific data

Having considered the information provided in the application (Ref C/SE/96/3501) and the Member State comments, the GMO Panel requested further data from the applicant on the cultivation areas of this potato in Europe and information on the impact on plant-associated organisms (e.g. invertebrates).

5.2.1. Potential unintended effects on plant fitness due to the genetic modification

Potato competes poorly outside the cultivated environment but can survive mild winter temperatures as tubers in soil. The experimental data indicated that potato EH92-527-1 does not differ from its non GM comparator with respect to frost tolerance, sensitivity to chemical treatment and susceptibility to diseases and pests (see 3.2.3.). These studies showed no evidence of enhanced competitiveness or over winter survival to indicate increased weediness or invasiveness of potato EH92-527-1.

5.2.2. Potential for gene transfer

(a) Plant to bacteria gene transfer

The modified potato contains an *npt*II gene for kanamycin resistance with the potential for transfer from plant material to microbes in the soil. However, considering the likelihood of degradation of cell DNA during autolysis in any plant material left in the soil and the natural occurrence of kanamycin resistance in soil bacteria, any additional contribution from potential transfer to soil microbes is considered to be insignificant.

The GMO Panel recently formulated an Opinion (EFSA, 2004b) on the use of antibiotic resistance genes in GM plants and concluded that the use of *npt*II as a selection marker did not pose a risk to the environment or to human and animal health. This conclusion was based on the limited use of kanamycin and neomycin in human and veterinary medicine, the already widespread presence of this gene in bacterial populations and the low risk of gene transfer from plants to bacteria (reviewed by Bennett *et al*., 2004). *Npt*II is a well-established selection marker with a history of safe use (Nap *et al*., 1992; Redenbaugh *et al*., 1994). This conclusion is

consistent with earlier safety evaluations of *npt*II (SCP, 2002). In addition, gene transfer of the antisense *gbss* construct was not considered to pose an environmental risk by the Member States or the GMO Panel.

In the very unlikely event that a plant to bacteria gene transfer would take place, no adverse effects on human and animal health and the environment are expected as no essentially new traits would be introduced into microbial communities.

(b) Plant to plant gene transfer

The natural exchange of genetic material is only possible with other varieties of potato, *Solanum tuberosum.* No natural genetic exchange has been detected with the potato's wild relatives in Europe, *Solanum nigrum* and *Solanum dulcamara.* Very low frequency exchange has been found with *Solanum nigrum* under artificial and forced hybridisation. Therefore the chances of successful hybridisation between transformed potatoes and other *Solanum* species under field conditions is considered to be very unlikely. Any genetic spread is assessed as limited to cross-pollination with other potatoes. Since the chance of any successful transfer is considered to be remote and would convey no selective advantage to any hybrid, the potential risk is considered to be extremely low. Therefore the GMO Panel concludes that plant to plant gene transfer of the *npt*II and the antisense *gbss* genes are unlikely to be of environmental concern.

5.2.3. Interactions between the GM plant and target organisms

There are no specific "target organisms" for the potato EH92-527-1 and consequently this was not considered to be an environmental issue by the Member States and by the GMO Panel.

5.2.4. Interactions of the GM plant with non-target organisms

The GMO Panel requested additional data from field records of plant-associated organisms. From the field studies carried out in Sweden, Germany and The Netherlands, the applicant provided data on the impact of the modified crops on plant-associated organisms. The results of field studies suggest neither greater susceptibility nor greater resistance to pests (*e.g.* aphids, leafhoppers, potato cyst nematodes (sp *Globodera*)) and diseases (*e.g.* late blight (*Phytophthora infestans*), potato early blight (*Alternaria solani*), Erwinia rots) than non-GM potato lines. There was no evidence of changes in sensitivity to the plant-associated viruses PVY, PLRV, PMTV, and TRV. In view of this and the equivalent composition of the GM potato plant, it is considered that no adverse effects on plant-associated organisms would be expected from cultivation of the potato EH92-527-1.

The GMO Panel is of the opinion that the field data originated in Northern Europe, contained in the environmental risk assessment provided by the applicant, are representative for most of the starch potato growing areas in Europe. Moreover, according to the system of cultivation quotas adopted in the EU (EC, 1994), the majority of quotas are allocated to Member States located in Northern Europe (see Section 3.2.1.). The applicant intends to cultivate the potato EH92-527-1 close to industrial starch processing plants supplying the paper pulping industry and mostly located in Northern Europe. Furthermore the potatoes will be marketed within a closed loop system (see Section 5.2.6.).

Although some different interactions with plant-associated organisms may occur in Southern regions, on the basis of the additional studies provided to the GMO Panel and considering the nature of the new trait, there is no indication that plant-associated organisms would be adversely affected.

Unanticipated effects of growing the potato EH92-527-1 in all regions will be covered by general surveillance.

5.2.5. Potential interaction with the abiotic environment and potential effects on biogeochemical processes

It is considered that no adverse effects on the abiotic environment would be likely from cultivation of this GM potato, due to the nature of the modified trait and to the equivalence of the agronomic traits of the GM potato with respect to the non GM parental lines. Although GM tubers have a different starch composition and therefore may be decomposed by a changed microbial community, overall effects on biogeochemical cycles are unlikely. A similar conclusion can be reached for the potato juice used as fertilizer. The GMO Panel considers that no further tests on degradability of the potato EH92-527-1 are needed and the GMO Panel agrees with the applicant and lead member state risk assessments that no adverse effects on the abiotic environment and biogeochemical processes are likely.

5.2.6. Potential impacts of the specific cultivation, management and harvesting techniques

The potatoes will be marketed within a closed loop system: they will be cultivated under contracts with the applicant who will then supply them directly to the processors for starch extraction. The cultivation and handling of potato EH92-527-1 will be governed under an Identity Preservation system, controlled and supervised through manuals, instructions, checklists and report forms at all the levels of the production. The purpose of the Identity Preservation System is to ensure the quality of EH92-527-1 by keeping other potato cultivars separated from EH92-527-1. This management system will facilitate general surveillance of EH92-527-1 (see 6.2.4).

The GMO Panel agrees with the applicant that no specific cultivation management will be needed for the potato EH92-527-1.

5.3. Conclusion

The environmental risk assessment from the applicant is in line with the intended cultivation of this GM potato. From the information supplied by the applicant, and from studies of relevant literature, there are no indications that this potato will cause adverse environmental impacts in the EU. Unanticipated effects of growing the potato EH92-527-1 will be covered by general surveillance.

6. Post market environmental monitoring plan

6.1. Issues raised by Member States

Questions were raised regarding (1) the need for additional information to comply with requirements of Annex VII of Dir 2001/18/EC as well as (2) the role of the Identity Preservation System in defining concrete actions, including monitoring and labelling to guarantee traceability.

6.2. Evaluation of relevant scientific data

The GMO Panel considered these issues and also critically examined the environmental monitoring plan initially submitted by the applicant. The GMO Panel requested additional

information on the farm questionnaires and how the Identity Preservation System can be used for general surveillance.

Notification C/SE/96/3501 for potato EH92-527-1 is for cultivation, and thus a monitoring plan is required that considers the environmental impact of full commercial scale, cultivation and production.

6.2.1. General aspects of monitoring

The objectives of a post market environmental monitoring plan according to Annex VII of Directive 2001/18/EC (EC, 2001) are to confirm that any assumption regarding the occurrence and impact of potential adverse effects of the GMO, or its use, in the environmental risk assessment are correct and to identify the occurrence of adverse effects of the GMO, or its use, on human health or the environment that were not anticipated in the environmental risk assessment (EFSA, 2004a).

The GMO Panel is of the opinion that the structure of the environmental monitoring plan provided by the applicant complies with the requirements defined in the Directive 2001/18/EC, the Guidance Notes to Annex VII (EC, 2002b) and the Guidance document provided by EFSA (EFSA, 2004a). The monitoring plan describes objectives, responsibilities and tasks, flow of information and monitoring methods.

6.2.2. Interplay between environmental risk assessment and monitoring

The GMO Panel agrees with the applicant that the environmental risk assessment did not identify risk that required case-specific monitoring.

6.2.3. Case-specific monitoring of potato EH92-527-1

The GMO Panel agrees that no case-specific monitoring is needed. However, the GMO Panel welcomes the proposals by the applicant to monitor the stability of the inserts and phenotypic expression during cultivation of the potato EH92-527-1.

6.2.4. General surveillance of the impact of potato EH92-527-1

The objective of general surveillance is to identify unforeseen adverse effects of the GM plant or its use on human health and the environment which were not predicted in the risk assessment. The methods and approaches should be appropriate, proportional and cost-effective to allow for the detection of GMO effects. Potential data sources and related networks should be identified.

The GMO Panel gives its opinion on the scientific quality of the general surveillance as part of the environmental monitoring plan provided by the applicant.

The applicant currently proposes using a comprehensive programme of farm surveys directly under their own supervision. The applicant also considers the use of additional appropriate surveillance networks already present in areas where this potato will be cultivated. The GMO Panel considers the format of the questionnaires provided by the applicant as comprehensive. In addition the GMO Panel welcomes the approach of the applicant to use the Identity Preservation System (IPS) as a basis for developing farm questionnaires and a reporting system for general surveillance

6.2.5. Reporting the results of monitoring

The GMO Panel recommends the adoption of the proposals for annual reporting made in the EFSA guidance document (EFSA 2004a,b). The GMO Panel also recommends that effective reporting procedures are established with the Competent Authorities of the countries where this GM potato is grown and with the Commission as required under Directive 2001/18/EC and Regulation 1829/2003/EC.

6.3. Conclusion

The GMO Panel agrees with the general methods and approaches of the environmental monitoring plan.

CONCLUSIONS AND RECOMMENDATIONS

The GMO Panel was asked to consider whether there is any reason to believe that the placing on the market of the potato EH92-527-1, intended for starch production and for uses in food/feed, is likely to cause adverse effects on human and animal health or the environment.

The GM potato tubers have an altered starch composition (higher amylopectin:amylose ratio) due to the reduced amount of granule bound starch synthase. The GMO Panel has evaluated the molecular analysis of the transgenic line and recognised that only the intended DNA fragment has been integrated at a single locus. From the sequence data provided by the applicant there is no reason to assume that the DNA regions transferred code for toxic and/or allergenic products. Furthermore, in the unlikely event that horizontal transfer of gene sequences would occur between the GM potato and bacteria, the bacteria would not pose any additional risk to human health or the environment. Compositional analysis has shown that the GM potato falls within expected variation for potato, except for the change in starch composition due to the genetic modification. The risk assessment included an analysis of data from appropriate animal feeding studies. These data indicate that after starch extraction the by-products of the GM potato are as safe as those from the non-GM parental cultivar.

The GMO Panel is of the opinion that the weight of evidence indicates that potato EH92-527-1 and derived products are no more likely to cause adverse effects on human and animal health or the environment than conventional potato, in the context of the proposed uses.

DOCUMENTATION PROVIDED TO EFSA

1. Letter from the British Competent Authority (Food Standards Agency), dated 22 April 2005 concerning the submission to EFSA of application EH92-527-1 potato within the framework of Regulation (EC) 1829/2003 (ref. NFU577).

2. Letter from EFSA to applicant with request for clarification/additional information (ref. SR/AC/jq (2005) 509, 11 May 2005).

3. Letter from EFSA to applicant, dated 12 July 2005, concerning the 'Statement of Validity' for application EFSA-GMO-UK-2005-14, GM potato EH92-527-1 submitted under Regulation (EC) 1829/2003 (ref. SR/SM/jq (2005) 917).

4. Submission of the application EFSA-GMO-UK-2005-14 by BASF Plant Science to EFSA, containing:
   - Part I – technical dossier
   - Part II – summary
   - Part III – Carthagena Protocol
   - Part IV – labelling proposal
   - Part V – samples and detection method
   - Part VI – additional information for GMOs

5. The notification C/SE/96/3501 concerning GM potato EH92-527-1 submitted under Directive 2001/18/EC, including the initial assessment report, the respective Member States comments/objections and additional information submitted by BASF Plant Science were considered where appropriate.

6. Letter from EFSA to applicant with request for clarification/additional information (ref. SR/AC/sp (2005) 650, 2 June 2005).

7. Additional information submitted by BASF Plant Science on 16 June 2005 in response to EFSAs request for further information.

8. Letter from EFSA to applicant with request for clarification/additional information (ref. SR/SM/sp (2005), 22 September 2005).

9. Additional information submitted by BASF Plant Science on 7 October 2005 in response to EFSAs request for further information.

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