European Food Safety Authority

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Opinion of the Scientific Panel on Genetically Modified Organisms on application (reference EFSA-GMO-NL-2006-36) for the placing on the market of the glyphosate-tolerant genetically modified soybean MON89788, for food and feed uses, import and processing under Regulation (EC) No 1829/2003 from Monsanto[1]

(Question No EFSA-Q-2006-182)

Adopted on 2 July 2008

PANEL MEMBERS

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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 soybean MON89788 (Unique Identifier MON-89788-1) developed to provide tolerance to glyphosate by expressing the CP4 EPSPS protein.

In delivering its scientific opinion, the GMO Panel considered the new application EFSA-GMO-NL-2006-36, additional information provided by the applicant (Monsanto) and the scientific comments submitted by the Member States. The scope of application EFSA-GMO-NL-2006-36 is for food and feed uses, import and processing of soybean MON89788 and all derived products, but excluding cultivation in the EU.

The GMO Panel assessed soybean MON89788 with reference to the intended uses and the appropriate principles described in the Guidance Document of the Scientific Panel on Genetically Modified Organisms

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[*] This opinion is not shared by 0 members of the Panel. / (conflict of interest) 0 members of the Panel did not participate in (part of) the discussion on the subject referred to above.

for the risk assessment of genetically modified plants and derived food and feed (EFSA, 2006). The scientific assessment included molecular characterization of the inserted DNA and expression of the new protein. A comparative analysis of agronomic traits and composition was undertaken and the safety of the newly expressed protein and the whole food/feed was evaluated with respect to potential toxicity, allergenicity and nutritional quality. An assessment of environmental impacts and the post-market environmental monitoring plan were undertaken.

Soybean MON89788 was transformed by *Agrobacterium tumefaciens*-mediated gene transfer technology. Soybean MON89788 expresses the codon-optimized *epsps* from *Agrobacterium sp.* strain CP4 encoding CP4 EPSPS that confers glyphosate tolerance to the plant.

The molecular characterisation data established that a single insert with one copy of the intact *cp4 epsps* expression cassette is integrated in the soybean genomic DNA. Appropriate analyses of the integration site including sequence determination of the inserted DNA and flanking regions and bioinformatics analysis have been performed. Bioinformatics analysis of junction regions demonstrated the absence of any potential new ORFs coding for known toxins or allergens. The expression of the genes introduced by genetic modification has been sufficiently analysed and the stability of the genetic modification has been demonstrated over several generations. The GMO Panel is of the opinion that the molecular characterisation of the DNA insert and flanking regions of soybean MON89788 does not raise any safety concern, and that sufficient evidence for the stability of the genetic modification was provided.

The GMO Panel compared the composition and agronomic characteristics of soybean MON89788 and its non-GM counterpart, assessed all statistical differences identified, and came to the conclusion that soybean MON89788 is compositionally equivalent to conventional soybean lines, except for the introduced transgenic trait. The risk assessment included an analysis of data from analytical studies, bioinformatics, and *in vitro* and *in vivo* studies. The GMO Panel concluded that the soybean MON89788 is as safe as its non GM counterpart and that the overall allergenicity of the whole plant is not changed.

The application for soybean MON89788 concerns food and feed uses, import and processing of soybean MON89788 and all derived products, but excluding cultivation in the EU. There is therefore no requirement for scientific assessment of possible environmental effects associated with the cultivation of soybean MON89788. Considering the scope of the application, not for cultivation, the GMO Panel is of the opinion that the likelihood of the spread and establishment of soybean MON89788 is very low and that unintended environmental effects due to this soybean will be no different from that of conventional soybean varieties. The scope of the post-market environmental monitoring plan provided by the applicant is in line with the intended uses of soybean MON89788. The monitoring plan provided by the applicant is in line with the EFSA Guidance Document (EFSA, 2006) and the Opinion of the GMO Panel on post-market environmental monitoring (EFSA, 2006).

In conclusion, the GMO Panel considers that the information available for soybean MON89788 addresses the scientific comments raised by the Member States and that the GM soybean MON89788 is as safe as its non genetically modified counterpart with respect to potential effects on human and animal health or the environment. Therefore the GMO Panel concludes that soybean MON89788 is unlikely to have any adverse effect on human or animal health or on the environment in the context of its intended uses.

Key words: GMO, soybean, MON89788, glyphosate tolerance, EPSPS, MON-89788-1, human and animal health, environment, import, processing, food, feed, Regulation (EC) No 1829/2003.

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BACKGROUND

On 7 November 2006, EFSA received from the Competent Authority of The Netherlands an application (Reference EFSA-GMO-NL-2006-36), for authorisation of the glyphosate-tolerant genetically modified soybean MON89788 (Unique Identifier MON-89788-1), submitted by Monsanto within the framework of Regulation (EC) No 1829/2003 on genetically modified food and feed (EC, 2003) for food and feed uses, import and processing.

After receiving the application EFSA-GMO-NL-2006-36 and in accordance with Articles 5(2)(b) and 17(2)b of Regulation (EC) No 1829/2003, EFSA informed the Member States as well as the European Commission and made the summary of the dossier publicly available on the EFSA website. EFSA initiated a formal review of the application to check compliance with the requirements laid down in Articles 5(3) and 17(3) of Regulation (EC) No 1829/2003. On 19 April 2007 EFSA received additional information requested under completeness check (requested on 30 March 2007) and on 8 June 2007 EFSA declared the application as valid in accordance with Articles 6(1) and 18(1) of Regulation (EC) No 1829/2003.

EFSA made the valid application available to Member States and the European Commission and consulted nominated 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 scientific opinion. The Member State bodies had three months after the date of receipt of the valid application (until 8 September 2007) within which to make their opinion known.

The GMO Panel carried out a scientific assessment of genetically modified (GM) soybean MON89788 taking into account 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, 2006).

On 19 October 2007, 20 December 2007, 21 January 2007 and 18 March 2008, the GMO Panel asked for additional data on soybean MON89788. The applicant provided the requested information on 30 October 2007, 8 February 2008, 18 February 2008, 28 February 2008, 29 February 2008 and 5 May 2008. After receipt and assessment of the full data package, the GMO Panel finalized its risk assessment of soybean MON89788.

The GMO Panel carried out a scientific assessment of the GM soybean MON89788 for food and feed uses, import and processing in accordance with Articles 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.

In giving its opinion on GM soybean MON89788 to the European Commission, the Member States and the applicant, and in accordance with Articles 6(1) and 18(1) of Regulation (EC) No 1829/2003, EFSA has endeavoured to respect a time limit of six months from the receipt of the valid application. As additional information was requested by the EFSA 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 document is to be seen as the report requested under Articles 6(6) and 18(6) of that Regulation and thus will be part of the overall opinion in accordance with Articles 6(5) and 18(5).

TERMS OF REFERENCE

The GMO Panel was requested to carry out a scientific assessment of the genetically modified soybean MON89788 for food and feed uses and import and processing in accordance with Articles 6(6) and 18(6) of Regulation (EC) No 1829/2003. 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/environments 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 EFSA GMO Panel was not requested to give an opinion on information required under Annex II to the Cartagena Protocol, nor on the 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 GMO risk management.

ASSESSMENT

1. Introduction

The genetically modified (GM) soybean MON89788 (Unique Identifier MON-89788-1) was assessed with reference to its intended uses, taking account of 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, 2006). In its evaluation the GMO Panel also considered the scientific comments that were raised by Member States on application EFSA-GMO-NL-2006-36. The risk assessment presented here is based on the information provided in the application relating to soybean MON89788 submitted in the EU including additional information from the applicant.

2. Molecular characterisation

2.1. Issues raised by the Member States

Issues raised by Member States are addressed in Annex G of the EFSA overall opinion.

2.2. Evaluation of relevant scientific data

2.2.1 Transformation process and vector constructs

Meristem tissue excised from embryos of germinated A3244 elite soybean seeds was transformed with plasmid PV-GMGOX20 using *Agrobacterium*. The cells were induced to form shoots directly without a callus phase.

The plasmid PV-GMGOX20 contained T-DNA with a CP4 *epsps* expression cassette conferring tolerance to glyphosate. The cassette consists of the following elements between the right and left border regions of *Agrobacterium* T-DNA: 1) promoter from *Tsf1* gene of *Arabidopsis thaliana* that encodes constitutively expressed EF-1 alpha elongation factor, linked with sequences from the 35S promoter of the Figwort Mosaic Virus that provides enhanced expression; 2) 5'-nontranslated leader sequence and intron from *Tsf1* for enhanced expression; 3) *A. thaliana* sequences encoding chloroplast transit peptide of the 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) for transfer of the protein to chloroplast (the site of aromatic amino acid synthesis); 4) codon-optimized *AroA* (*epsps*) from *Agrobacterium sp.* strain CP4 encoding CP4 EPSPS that confers glyphosate-tolerance to the plant; 5) sequences that direct transcriptional termination and polyadenylation from *RbcS2* gene of pea encoding the small subunit of RuBisCO.

2.2.2. Transgenic constructs in the genetically modified plant

Southern analyses of genomic DNA from the genetically modified soybean MON89788 and its non-transgenic counterpart A3244 digested with four restriction endonucleases were performed using ten overlapping probes that cover the whole plasmid. This analysis demonstrated that the genetically modified soybean MON89788 contains a single insert with one copy of the intact CP4 *epsps* expression cassette. No elements from the vector backbone were detected.

The nucleotide sequence of the insert as well as *ca.* 1 kb of both 5' and 3' flanking regions was determined from the genetically modified soybean MON89788. This confirmed the conclusions drawn from the Southern analysis. Sequencing of the parental soybean line showed that a 40 bp segment was deleted from the insertion site of the parental soybean and short novel DNA stretches (10 bp, 6 bp) were introduced during the insertion. There is no indication that any soybean gene was interrupted by the insertion.

2.2.3. Information on the expression of the insert

2.2.3.1. Expression of the introduced gene

CP4 EPSPS is expressed throughout the plant. Protein levels were analysed by ELISA from replicated field trials across five locations in Argentina (2004-2005) and five locations in the US (2005), and were (µg/g fresh weight): 27-163 for over-season leaves, 98-228 for seeds, 13-43 for roots and 41-94 for forage.

2.2.3.2. Putative cryptic open reading frames in MON89788

Bioinformatic analyses were performed to assess the potential for allergenicity, toxicity, or bioactivity of putative (poly)peptides encoded by the 5' and 3' inserted DNA-soybean genomic DNA junctions. Sequences spanning the 5' soybean genomic DNA-inserted DNA junction and the 3' inserted DNA-soybean genomic DNA junction were translated from stop codon to stop codon in all six reading frames. Putative (poly)peptides from each reading frame were compared to databases that contained (poly)peptides, including allergens and toxins, using bioinformatic tools (FASTA). In addition to each putative polypeptide, an eight amino acid sliding window search was performed within the allergen database. No similarities to known allergens, toxins or other bioactive proteins were found that would raise a safety concern for human or animal health.

2.2.4. Inheritance and stability of inserted DNA

To assess the stability of inserted DNA, Southern analysis was conducted on four generations of MON89788 soybean (R_4 to R_7) using three overlapping DNA probes covering the whole insert and the 5' and 3' flanking regions. The Southern data confirmed the stability of the insert and its copy number. Phenotypic segregation data confirmed the stability of the glyphosate tolerance trait and followed a Mendelian segregation pattern.

2.3. Conclusion

The molecular characterisation data establish that the genetically modified soybean MON89788 contains one copy of an intact CP4 *epsps* expression cassette. No other parts of the plasmid used for transformation are present in the transformed plant. Bioinformatic analysis of the 5' and 3' flanking regions did not reveal any putative peptides that would cause safety concerns. The stability of the inserted DNA and the herbicide tolerance trait were confirmed over several generations and a Mendelian inheritance pattern demonstrated.

3. Comparative analysis

3.1 Issues raised by Member States

Questions were raised regarding the herbicide treatment in the field trials and the validity of some reported data in the application. A question concerning the spectrum of conventional soybean varieties chosen to assess the natural range of variation was also raised.

3.2 Evaluation of relevant scientific data

Having considered the information provided in the application and the Member States comments, the GMO Panel requested from the applicant further information with respect to the analysis of data on the agronomic and phenotypic characteristics, in particular separation of data on soybean varieties containing the GM event 40-3-2 from data of conventional soybean varieties describing the natural variation in the respective plant characteristics. The Panel also requested a compositional comparison of soybeans MON89788 to its appropriate control, both materials being treated with the same set of herbicides. Accordingly, the applicant provided the requested analysis on separated background data, and additional compositional data on seeds of soybean MON89788, unsprayed and sprayed with glyphosate herbicides, from field trials in the USA in 2006 and 2007.

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

In the compositional studies, the GM soybean MON89788 was compared to the non-transgenic Asgrow variety A3244, which is a conventional soybean variety with background genetics similar to MON89788. In addition to the comparator, 2-3 conventional soybean varieties were included in the field trial at each site, in total 12 different conventional soybean varieties being used. At each trial site each treatment was replicated three times. Soybean MON89788 was treated with glyphosate herbicides at the recommended dose for commercial use, and the comparator A3244 and the 12 conventional soybean varieties with other commercial herbicides. The field trials were in the season 2004-2005 carried out in Argentina and in year 2005 in USA, each season/year at five different geographical sites. As the comparison of the level of various key constituents in soybeans MON89788 and A3244 did not reveal any statistically significant differences (see section 3.2.2.) for any of the constituents for which a food safety concern could be foreseen, the GMO Panel noted that the field trial sites in 2004 and 2005 were not the same. However, as the applicant had not originally supplied compositional data comparing the GM plant and its most appropriate control grown in the same field under comparable conditions, the Panel requested data where the GM and non-GM soybean had been treated in the same way and therefore comparable. The applicant supplied data where soybean MON89788 sprayed with glyphosate herbicides were compared with unsprayed MON89788. As no non-GM controls were available in these additional field trials from USA in 2006 (8 sites) and 2007 (2 sites), the experimental design was unbalanced, was not optimal and was inconsistent with the Guidance Document (EFSA, 2006a). However, the Panel identified no compositional differences requiring further considerations and in this specific case accepted that the total set of field trials, including the GM soybean MON89788, its control soybean and conventional soybean varieties, contained sufficient data to be able to assess the composition of soybean MON89788. The conventional soybean varieties included in the original field trials were used as reference material to determine the naturally occurring variability in composition expected for various analytes in commercial soybeans.

3.2.2. Compositional analysis

Soybean seeds were analysed for proximates, including fiber fractions, as well as for amino acids, fatty acids, the micro-nutrient vitamin E, anti-nutrients (i.e. phytic acid, trypsin inhibitor, lectins, stachyose and raffinose) and other secondary metabolites (isoflavones). Forage was analysed for proximates, including fiber fractions. In total 63 different compounds were analysed, essentially those recommended by OECD

(2001). The analytes vitamin E, raffinose and stachyose were not analysed in samples from the field trial of season 2004-2005. The data on each analyte were statistically analysed for potential differences in their levels in soybean MON89788 and soybean A3244 within-site and across-sites (data from all sites combined). Several of the fatty acids analysed were rare and occurred at levels below the limit of quantification. When this occurred in more than 50% of the samples, the analyte was omitted from the statistical analysis.

Thirty-five of the 475 comparisons (7.4%) performed within sites showed statistically significant differences in the level of the measured analyte between soybeans MON89788 and soybean A3244. In twenty-nine of the thirty-five cases the significant difference occurred only at a single site. For three compounds (forage moisture, seed linolenic acid, and seed raffinose) it occurred at two of five sites. Thus, no consistent alteration in the level of the studied components was found between sites and between growing seasons. Furthermore, the differences were generally small and fell within the interval of natural variation calculated from the occurrence of these constituents in conventional soybean varieties.

A statistical difference across sites was observed for four constituents in one of the two seasons. These constituents were moisture in forage, and the level of daidzein, glycitein and vitamin E in seeds. Differences relative to the control were small (-1.6%, -7.4%, -10.6% and 7.4%, respectively), and were well within the natural variation calculated from the occurrence of these constituents in the 12 conventional soybean varieties. They also fell within the natural variation of these constituents of soybean described in the USDA-ISO (2006) isoflavone database. When statistically analysed per site, the level of the first three of these four constituents were significantly altered at only one of the five trial sites, whereas for the fourth, vitamin E, the level was not significantly altered at a single site.

As the soybean MON89788 and its near-isogenic control had not been treated in the same way (given the same pesticide treatments), the applicant supplied additional compositional data from materials collected in field trials in the USA to show that there was no difference in composition between soybean MON89788 sprayed with glyphosate and unsprayed MON89788. The additional data was obtained from seeds collected at eight field trial sites in 2006 and two field trial sites in 2007. No non-GM controls were included in these field trials. Analysis of the combined-site data set from 2006 indicated statistically significant differences between unsprayed and sprayed soybean MON89788 for tryptophan, 17:0 heptadecanoic acid, and stachyose. Soybean MON89788 sprayed with glyphosate herbicides showed 2.1%, 10.9%, and 5.9% higher levels of these constituents than unsprayed soybean, respectively. Analysis of the combined-site data set from 2007 indicated statistically significant differences between unsprayed and sprayed soybean MON89788 for carbohydrates, stachyose, and trypsin inhibitor. Plants sprayed with glyphosate herbicides showed 2.1% increase, 6.2% reduction, and 11.0% increase in the level of these constituents as compared to the unsprayed plants, respectively. The only soybean constituent, which level was statistically different between unsprayed and sprayed soybean MON89788 both years of these field trials was stachyose. However, sprayed plants contained higher levels in 2006, and reduced levels in 2007. Taken together, these data show that differences were not consistent, were small and fell within the normal variation of soybean constituents demonstrated by the ILSI database. The applicant statistically analysed the additional and original data sets from field studies 2004-2007 to ensure their comparability. The result of this analysis is consistent with the conclusion that the composition of unsprayed and sprayed soybean MON89788 and the near-isogenic control are similar regardless of treatment with glyphosate.

The GMO Panel considered the total compositional data supplied and the observed compositional differences between soybean MON89788 and its comparator in the light of the field trial design, measured biological variation and the level of the studied compounds in conventional soybean varieties, and concludes that soybean MON89788 is compositionally equivalent to the non-GM counterparts soybean A3244 and other conventional soybean varieties, except for the introduced trait.

3.2.3. Agronomic traits and GM phenotype

The applicant provided information on agronomic performance, phenotypic characteristics and ecological interaction of soybean MON89788 and soybean A3244 (control) from 17 field trials performed in the USA in 2005. These studies also gave information on reproduction, dissemination and survivability of these soybeans, as well as three to four commercial soybean varieties for each trial site (in total 23 varieties for all trial sites). The phenotypic characteristics evaluated were early stand count, seedling vigour, days to 50% flowering, flower colour, plant height, lodging, pod shattering, final stand count, seed moisture, seed test weight, yield and growth stage monitoring. Of the 181 comparisons statistically evaluated within sites, 7.7% of the parameters showed a significant difference between soybean MON89788 and its control. These were distributed over seven of the phenotypic characteristics studied and were usually found only at a single or a few trial sites. The Panel concluded that several of these most likely appeared by chance alone, and are unlikely to be of biological importance. The only difference that was confirmed in the analysis over all trial sites were plant height, which was reduced in soybean MON89788 as compared to the control (77.9 vs 82.0 cm). The reduction in plant height was noted at four of the seven sites, but was always within the variation of the commercial soybean varieties (48.8 to 108.2 cm). As the magnitude of the difference was small (around 5.3%), the plant height fell within the normal variation and no ecological risks could be linked to the reduction in height, the panel found this difference to be of no biological importance. No difference in pollen morphology and viability was observed.

Of the 12 insect categories, 18 disease categories and 10 abiotic stressors evaluated in the studies of ecological interactions, only one difference between soybean MON89788 and its comparator was noted – a reduced severity of symptoms caused by leafhopper in MON89788 plots as compared to control plots at a single trial site and a single point in time. The leafhopper susceptibility of the plant fell within the range observed among commercial soybean varieties. In addition, quantitative data were collected on the abundance of specific pests and beneficial insects, and the prevalence of plant damage. Three out of the 66 comparisons performed were statistically significant different for insect abundance (pests and beneficial insects), which was more or less the number of statistical differences expected due to random variation in the samples taken. These three organisms occurred at low quantities. The corn earworm (*Helicoverpa zea*) (0.7 vs 0.0), southern corn rootworm (*Diabrotica undecimpunctata howardi*) (2.0 vs. 0.0) and tarnished plant bug (*Lygus lineolaris*) (0.3 vs. 0.0) were more common in soybean MON89788 than in the control but only at a single point in time and at a single site. At other times and at other plots no difference was noted. No difference was noted between soybean MON89788 and the control with respect to plant damage. The GMO Panel is of the opinion that these observations are of no biological relevance.

The GMO Panel assessed the provided data and considers soybean MON89788 to be agronomically equivalent to the currently grown non-GM soybean A3244, with the exception of the newly introduced trait. The small reduction in plant height was considered to have no agronomic consequence.

3.3 Conclusion

Analyses carried out on materials from field trials with soybean MON89788 and its closely genetically related comparator indicated that these soybeans are compositionally and agronomically equivalent except for the introduced transgenic trait. The comparative analysis of soybean MON89788 to the non-GM variety A3244 and other conventional soybean varieties provided no indication for unintended effects resulting from the genetic modification.

4. Food/Feed safety assessment

4.1. Issues raised by Member States

Member States requested an extended bioinformatics study on the similarity of all hypothetical polypeptides present in the inserted T-DNA border regions with known allergens and raised issues regarding the potential similarity of CP4 EPSPS to allergenic proteins, and the finding that no IgE-binding of serum from one patient allergic to soybeans was reported for the extract of the control non-GM soybean variety A3244.

4.2. Evaluation of relevant scientific data

4.2.1. Product description and intended use

The scope of application EFSA-GMO-NL-2006-36 is for food and feed uses, import and processing of soybean MON89788 and its derived products. The main product for human use is soybean oil. Also around 10% of the defatted soybean meal goes to production of human soybean products, including flours, soybean protein concentrates and various textured products simulating meats, seafoods and cheeses. The rest of the defatted soybean meal goes to feed, in the European Union mainly to poultry (46%), pig (32%) and cattle (9%) (OECD, 2001). Whole soybeans are used to produce soy sprouts, baked soybeans, and roasted soybeans. There is also a limited direct use of soybeans as animal feeds.

The genetic modification of soybean MON89788 results in the expression of the CP4 EPSPS enzyme, which is less sensitive to glyphosate (which normally inhibits the synthesis of aromatic amino acids) than the endogenous plant EPSPS enzyme and, therefore, allow soybean MON89788 to produce aromatic amino acids and grow normally also in the presence of glyphosate herbicides. Thus, the genetic modification is intended to improve agronomic performance only and is not intended to influence the nutritional aspects, the processing characteristics and overall use of soybean as a crop.

4.2.2. Stability during processing

Since soybean MON89788 is compositionally equivalent to the control soybean and conventional soybean varieties, except for the newly expressed trait (see Section 3.2.2), the stability of soybean MON89788 constituents during processing is not expected to be different from conventional soybean varieties.

4.2.3. Toxicology

4.2.3.1. CP4 EPSPS protein used for safety assessment

Due to the low expression level of the CP4 EPSPS protein in soybean MON89788 and the very difficult task to isolate a sufficient quantity of purified protein from the genetically modified soybean, the safety studies with the newly expressed protein were conducted with a CP4 EPSPS protein encoded by the *cp4 epsps* gene from *Agrobacterium* sp. strain CP4 and expressed in *Escherichia coli*. The structural similarity and physicochemical and functional equivalence of the CP4 EPSPS protein produced by *E. coli* to that produced

in soybean MON89788 was shown by N-terminal sequencing (Edman degradation), Western analysis, mobility in SDS-PAGE, MALDI-TOF mass spectrometry, glycosylation analysis and CP4 EPSPS enzymatic activity. All these methods confirmed the equivalence of the bacterial and the plant CP4 EPSPS proteins. Based on the identified similarity in structure and equivalence in physicochemistry and function between these proteins, the GMO Panel accepts the use of CP4 EPSPS test material derived from *E. coli* for the degradation studies and safety testing of the CP4 EPSPS protein present in soybean MON89788 and as a reference standard in the ELISA to estimate CP4 EPSPS expression levels in various tissues of soybean MON89788.

4.2.3.2. Toxicological assessment of expressed novel protein

The newly introduced gene in soybean MON89788 is derived from *Agrobacterium* species strain CP4. The gene codes for a protein, CP4 EPSPS, unknown to be pathogenic to humans and animals, and also not known to be a common allergen. Humans and animals have a history of safe consumption of the endogenous plant protein EPSPS, and the CP4 EPSPS protein is structurally and functionally similar to the EPSPS. Furthermore, CP4 EPSPS expressing crops have now been consumed as food and feed over ten years without any adverse effects being linked to the consumption. For example, around 60% of all soybeans consumed during the last years are estimated to contain this protein.

(a) Acute toxicity testing

The applicant provided a single dose toxicity study with 10 male and 10 female DC-1 mice per treatment group. The animals were gavaged with 0, 49, 154 or 572 mg of the CP4 EPSPS protein produced in *Escherichia coli*, which previously had been demonstrated to be structurally and functionally equivalent to the CP4 EPSPS protein expressed in soybean MON89788 (see section 4.2.3.1). Animals were observed for 15 days after dosing and macroscopic examination of internal organs was carried out at necropsy. All animals survived and there were no indications of adverse effects up to the highest dose tested.

(b) Degradation in simulated digestive fluids

Digestion of the CP4 EPSPS protein in simulated gastric fluid was studied *in vitro* by following the CP4 EPSPS enzymatic activity, and by identifying peptide fragments using SDS-PAGE colloidal blue gel staining and Western blot analysis methods. The SDS-PAGE colloidal blue gel staining demonstrated that at least 98% of the CP4 EPSPS protein produced in *E. coli* was fully degraded by pepsin-containing simulated gastric fluid of pH 2 within 15 seconds. In agreement with this finding, Western blotting showed that most of the CP4 EPSPS protein was digested in simulated gastric fluid within the same time frame. Similarly, studies on the function of CP4 EPSPS exposed to simulated gastric fluid revealed that the enzymatic activity was reduced by more than 90% within 15 seconds.

(c) Bioinformatic studies

Searches for amino acid sequence homology of the CP4 EPSPS protein expressed in soybean MON89788 with amino acid sequences of toxic and general proteins stored in data bases indicated significant homology only with other EPSPS- and related- proteins. No sequence homology with known toxic proteins was found.

4.2.3.3. Toxicological assessment of new constituents other than proteins

No new constituent other than the CP4 EPSPS protein is expressed in soybean MON89788 and no relevant changes in the composition of soybean MON89788 were detected by the compositional analysis.

4.2.4. Toxicological assessment of the whole GM food/feed

The applicant provided a sub-chronic 90-days feeding study in which three groups of 20 rats of each sex of the Sprague-Dawley strain Crl:CD® (SD) were given a diet containing 15% processed soybean meal (w/w), as this is the concentration of soybean meal in the Certified Rodent LabDiet. One of the groups received 15% soybean meal from the control A3244, one group 15% of soybean MON89788 (high dose group), and the third group approximately 10% A3244 and 5% MON89788 (low dose group). Diets were formulated to be comparable to the Certified Rodent Labdiet. The composition of the diet and its quality, including herbicide residues, were controlled by analysis. Whereas soybean MON89788 had been sprayed with glyphosate, the soybean control (A3244) had been sprayed with various conventional herbicides. In parallel with the 13-week toxicity study with a diet containing 15% meal of soybean MON89788, the applicant also performed a similar feeding study with six different diets containing 15% meal of reference soybean varieties produced by conventional breeding. The data obtained from this study was used when assessing the toxicological significances of statistically significant differences observed in the rat feeding study with soybean MON89788. Also data from historical controls (fed diets with 15% processed soybean meal) were used when assessing the relevance of statistically significant differences observed. The feed and water was presented *ad libitum*.

All animals survived the treatments. Inclusion of soybean MON89788 in the diet had no influence on feed intake, body weights, and behaviour of the animals. There were also no haematological changes noted, and in relation to serum chemistry the only statistically significant alteration in males was increased mean triglyceride levels (88 vs 63 mg/dL) in rats receiving the diet with 5% soybean MON89788. The triglyceride level was unchanged both in the 15% dose group in males and in both dose groups in females. The increased triglyceride level in the male rats was due to higher levels than normal in four rats. In the absence of a dose-response, and noting that increased levels were sometimes observed also in rats fed any of the six different reference soybean varieties and were within the ranges of the historical control (11-170 mg/dL), the GMO panel concluded that this observation is of no relevance for food and feed safety of soybean MON89788. In female rats, the only influence on serum chemistry was a slightly reduced calcium level (10.9 vs 10.6 mg/dL) in rats receiving 15% soybean MON89788. As the reduction was small (<3%), and the calcium level fell within the range of calcium values for the rats given the six reference soybean varieties and were within the historical control range (7.7-14.3 mg/dL), the Panel also found this observation of no toxicological concern. Urinalysis parameters were comparable in treated and control rats. At necropsy, there were no macroscopic findings related to the treatment. The only observation on organs was a significantly reduced relative brain weight to final body weight in males receiving 5% meal of soybean MON89788. There was no influence on this parameter in the high-dose group and in females. The significance was probably due to dividing a slightly non-significantly reduced (2.8%) mean absolute brain weight with a slightly non-significantly increased (4.0) mean body weight. Furthermore, the values fell within the values obtained in rats given the reference soybean diets and the historical rat controls. Microscopic studies revealed no alterations related to the tested soybean. The GMO-panel concludes that the 13-week feeding study in rats gave no indication other than soybean MON89788 being as safe as soybean A3244 and other conventional soybean varieties.

4.2.5. Allergenicity

The strategies used when assessing the potential allergenic risk focus on the characterisation of the source of the recombinant protein, the potential of the newly expressed protein to induce sensitisation or to elicit allergic reactions in already sensitised persons 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 decisive evidence for allergenicity (CAC, 2003; EFSA, 2006a).

4.2.5.1. Assessment of allergenicity of the newly expressed proteins

The *cp4 epsps* gene originates from *Agrobacterium sp.* strain CP4, a soil-borne and plant-interacting micro-organism that is not known to be allergenic. A bioinformatics-supported comparison of the amino acid sequence of the CP4 EPSPS protein with the sequences of known allergens, gliadins, and glutenins has been performed. This analysis included both overall sequence alignments using the FASTA algorithm and searches for short identical stretches of at least eight contiguous amino acids and no identity higher than 35% was found between CP4 EPSPS and allergens. As described above, CP4 EPSPS is rapidly degraded under simulated gastric conditions.

Based on these results, the GMO Panel considers that the newly expressed CP4 EPSPS protein is unlikely to be allergenic.

4.2.5.2. Assessment of allergenicity of the whole GM plant

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. However, given that equivalence (with the exception of the introduced trait) to the conventional comparator was demonstrated on the basis of extensive compositional and agronomic analysis, no increased allergenicity is anticipated for soybean MON89788. Because the soybean is a recognised allergenic food, the applicant performed extensive *in vitro* allergenicity studies with extracts of soybeans MON89788, A3244 (a conventional soybean variety with background genetics similar to soybean MON89788), and 24 different commercial varieties (both non-GM and GM varieties). The IgE-binding of soybean proteins to sera from 16 patients allergic to soybean, and 5 non-allergic individuals was quantified with a validated ELISA method in order to demonstrate that the allergenicity potential of soybean MON89788 is not altered in comparison to conventional soybean varieties. Upon request from the Panel the applicant also presented the analysis of data from non-GM commercial soybean extracts. Whereas none of the soybean varieties showed IgE-binding to sera from non-allergic patients, all but one serum from allergic patients had similar reactivity to extracts from soybeans MON89788 and A3244. Furthermore, the reactivity was within the tolerance interval defined by the reactivity to the 14 commercial non-GM soybean varieties. The deviating serum had an IgE-binding to A3244 that did not fulfil the acceptance criteria of the ELISA method (variability within each triplicate sample $\leq$25 %), and, therefore, was removed from the analysis. The presence of this deviating data led the Panel to ask the applicant more information. In addition the Panel asked the applicant to provide detailed information on any modification of the qualitative and quantitative pattern of expression of endogenous allergens in soybean MON89788 as compared to the non-GM soybean control. The applicant provided two studies. One was a Western blot analysis that showed that the binding pattern of IgE antibody samples from soybean-allergic patients (pooled sera, 1-D PAGE) to soy-bean extracts from MON89788 did not differ to that from extracts of control soybean A3244 and the commercial soybean variety Hensel. The other study demonstrated that there was no meaningful qualitative and quantitative differences observed in the IgE-

binding patterns between MON89788 and A3244 soybean extracts when probed individually with sera from six soybean allergic patients (2-D PAGE). These *in vitro* studies indicate that no new allergenic protein is expressed as a consequence of the genetic modification.

Based on the extensive information provided, the GMO Panel concludes that the overall allergenicity of the whole GM soybean MON89788 is unlikely to be different from that of conventional soybeans.

4.2.6. Nutritional assessment of GM food/feed

The applicant has provided a 42-day broiler chicken feeding study (Ross × Ross 308) performed according to generally accepted guidelines (ILSI, 2003), and consisting of eight treatments groups. One group received soybean MON89788, another soybean A3244 (a non-GM soybean with comparable background genetics to MON89788), and the other six groups different conventional non-GM soybean varieties.

Each treatment consisted of 50 male and 50 female broilers (in pens of 10 birds/pen and pens in a randomised complete block design) fed diets containing approximately 33% (w/w) of soybean meal in the starter diet and 30% soybean meal in the grower/finisher diet. The diets contained meal from soybean MON89788 sprayed with glyphosate, and meal from soybean A3244 and conventional varieties sprayed with conventional herbicides, diets were quality controlled and formulated based on nutrient and pesticide analyses performed before diet formulation.

Mortality was comparable in all treatments of the study, being around 4% in the group receiving soybean MON89788, which is close to rates commonly reported for broiler chickens in feeding studies. There were no effects observed on body weight, feed conversion and carcass yield in this study.

Thus, the broiler feeding study supported the results of the comparative compositional analysis that showed that soybean MON89788 is compositionally and, therefore, nutritionally equivalent to soybeans of the non-GM comparator and commercial soybean varieties.

4.2.7. Post-market monitoring of GM food/feed

The risk assessment concluded that no data have emerged to indicate that soybean MON89788 is any less safe than its non-GM comparator. In addition, soybean MON89788 is, from a nutritional point of view, equivalent to conventional soybean. Therefore, and in line with the Guidance document (EFSA, 2006a), the GMO Panel is of the opinion that post-market monitoring of the GM food/feed is not necessary.

4.3. Conclusion

No toxicity of the CP4 EPSPS protein was observed in an acute toxicity study in mice where the protein was administered orally. The CP4 EPSPS is quickly degraded in simulated gastric fluid without leaving stable peptide fragments. Bioinformatics studies demonstrated that the CP4 EPSPS protein show no homology to known toxic and allergenic proteins. Moreover, the CP4 EPSPS protein has also been introduced into various other GM crops that have already been extensively assessed for their safety. A comparative analysis of compositional, agronomic, and phenotypic characteristics showed that soybean MON89788 is equivalent to conventional non-GM soybean varieties except for the introduced trait. A 90-day toxicity study in rats fed diets with up to 15% processed soybean meal indicated no toxicity. Whole-product testing with sera from

soy-allergic patients showed that the overall allergenicity of the whole plant had not been changed. A 42-day feeding study on broiler chickens showed that soybean MON89788 is not nutritionally different from its genetically closely related non-GM soybean or commercial soybean varieties included in the study. The GMO Panel is of the opinion that soybean MON89788 is as safe as conventional soy, and considers that no additional animal safety or nutritional wholesomeness study is needed.

5. Environmental risk assessment and monitoring plan

5.1. Issues raised by the Member States

Comments were provided regarding the environmental monitoring plan, in particular a more detailed general surveillance plan.

5.2. Evaluation of relevant scientific data

5.2.2. Environmental risk assessment

The scope of this application EFSA-GMO-NL-2006-36 is for food and feed uses, import and processing and excludes cultivation. Therefore, the environmental risk assessment is limited to accidental release into the environment of GM soybean seeds during transportation and processing for food and feed uses.

As this application is not for cultivation, concerns regarding the use of glyphosate herbicides on soybean MON89788 apply only to imported and processed soybean that may have been treated with these glyphosate herbicides in the countries of origin. However, the regulation and risk assessment of glyphosate is within the scope of Directive 91/414/EEC concerning the placing on the market of plant protection products (EC, 1991).

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

Cultivated soybean *(Glycine max (L.) Merr.)* belongs to the subgenus *Soja* of the genus *Glycine*. The species originated from eastern Asia and is a highly domesticated crop (Lu, 2005). The major worldwide soybean producers are the United States, Brazil, Argentina and China. In Europe, soybean is mainly cultivated in Italy, France and Romania (FAOSTAT, 2005). Weedy soybean has not been reported growing naturally outside its centre of origin in other parts of the world such as the Americas and Europe where only the cultivated soybean is commercially grown (Lu, 2005).

Seed and pollen are potential sources of gene dispersal. Soybean (*Glycine max*) is an annual almost completely self-pollinating crop in the field which has a percentage of cross-pollination usually lower than 1% (Weber and Hanson, 1961; Caviness, 1966; Lu, 2005).

Dispersal of soybean seeds by animals is not expected due to the characteristics of the seed, but accidental release into the environment of seeds may occur during transportation and processing for food, feed and industrial uses. However, cultivated soybean seeds rarely display any dormancy characteristics and only under certain environmental conditions grow as a volunteer in the year following cultivation (OECD, 2000). Even in the agroecosystem soybean seeds usually do not survive due to predation, rotting, germination resulting in death during the winter, or due to management practices prior to planting the subsequent crop (Owen, 2005).

In the event of an accidental release and establishment of soybean MON89788 in the environment, the GM soybean plants will only be fitter when cultivated in the presence of glyphosate herbicides which are not currently used on cultivated soybean or in most areas where the GM soybean might be spilled.

The data presented in the application indicate that, in the field studies carried out in United States and Argentina during the years 2004 (5 sites) and 2004-2005 (5 sites) respectively, soybean MON89788 has no altered survival, multiplication or dissemination characteristics compared to its conventional counterparts except in the presence of glyphosate. In addition to the data presented by the applicant, the GMO Panel is not aware of any scientific report of increased spread and establishment of soybean MON89788 and any change in survival capacity, including overwintering. Furthermore there is no evidence that the glyphosate tolerant trait introduced by genetic modification results in increased invasiveness of any crop species, except in the presence of the glyphosate herbicides. The accidental release of soybean MON89788 seeds would not result in the establishment of plants exhibiting dissemination capabilities different from existing conventional soybean varieties and would not create additional agronomic or environmental impacts.

Therefore the GMO Panel is of the opinion that the likelihood of unintended environmental effects of the soybean MON89788 in Europe will not be different to that of conventional soybean varieties.

5.2.1.2. Potential for gene transfer

A prerequisite for any gene transfer is the availability of pathways for the transfer of genetic material, either through horizontal gene transfer of DNA, or vertical gene flow via seed dispersal and cross-pollination.

(a) Plant to bacteria gene transfer

Based on current scientific knowledge and elaborated in more detail elsewhere (EFSA, 2004; EFSA, 2007), gene transfer from GM plants to microorganisms under natural conditions is extremely unlikely.

Food and feed products derived from the soybean MON89788 are likely to contain transgenic DNA. Therefore microorganisms in the digestive tract of humans and animals may be exposed to transgenic DNA.

The CP4 *epsps* gene is under the control of the promoter from *Tsf1* gene of *Arabidopsis thaliana* (see section 2.2 of the scientific opinion). Taking into account the origin and nature of the CP4 *epsps* gene, its natural occurring related genes and the lack of selective pressure in the intestinal tract and the environment, the likelihood that horizontal gene transfer of the CP4 *epsps* gene would result in increased fitness of microorganisms is very limited. It is very unlikely that the CP4 *epsps* gene from soybean MON89788 would become transferred and established in the genome of microorganisms in the environment (including plant-associated microorganisms *e.g.* rhizobia) or human and animal digestive tract. In the very unlikely event that such a horizontal gene transfer occurs, no adverse effects on human and animal health and the environment are expected as no new traits would be expressed in microbial communities.

(b) Plant to plant gene transfer

Considering the scope of the application and the physical characteristics of soybean seeds (see section 5.2.1.1), a possible pathway of dispersal is from seed spillage and pollen from the occasional soybean plant originating from accidental seed dispersal during transportation and processing.

The genus *Glycine* is divided into two distinct subgenera: G*lycine* Willd. and *Soja*. Soybean (*Glycine max*) is in the subgenus *Soja*. The subgenus *Glycine* contains 16 perennial species, especially indigenous to Australia, and the subgenus *Soja* contains three annual species, *G. max*, *G. soja*, and *G. gracilis* originally from eastern Asia (Hymowitz and Singh, 1987; Hymowitz *et al.*, 1998;). Weedy soybean has not been reported in other parts of the world such as the Americas and Europe where only the cultivated soybean is grown (Lu, 2005). Therefore, the plant to plant gene transfer from this soybean is restricted to cultivated and the occasional soybean plants resulting from seed spillage.

Seed and pollen are potential sources of gene dispersal. Soybean (*Glycine max*) is an annual almost completely self-pollinating crop in the field which has a percentage of cross-pollination usually lower than 1% (Weber and Hanson, 1961; Caviness, 1966; Lu, 2005). Soybean pollen dispersal is limited because the anthers mature in bud and directly pollinate the stigma of the same flower (OECD, 2000). However, Ahrent and Caviness (1994) as well as Gumisiriza and Rubaihayo (1978) observed natural cross-pollination rates as high as 2.5 and 4.5%, respectively. Ray *et al.* (2003) recorded natural cross-pollination rates ranging from 0.7 to 6.3%, suggesting the potential of some within-crop gene flow in soybean. These results indicate that natural cross-pollination rates can fluctuate significantly among different soybean varieties under particular environmental conditions such as favourable climate for pollination and abundance of pollinators (Lu, 2005).

The GMO Panel takes into account that this application does not include cultivation of the soybean within the EU so that the likelihood of cross-pollination between cultivated soybean crops and the occasional soybean plants resulting from seed spillage is considered to be extremely low. Even if transgene flow occurred to cultivated soybean plants, a selective advantage would only occur if the complementary glyphosate herbicides were applied.

5.2.1.3. Potential interactions of the GM plant with target organisms

This point was not considered an issue by the Member States or by the GMO Panel considering the intended uses of soybean MON89788, excluding cultivation and the absence of target organisms.

5.2.1.4 Potential interactions of the GM plant with non-target organisms

This point was not considered an issue by the Member States or by the GMO Panel.

5.2.1.5. Potential interaction with the abiotic environment and biogeochemical cycles

This point was not considered an issue by the Member States or by the GMO Panel considering the intended uses of soybean MON89788, excluding cultivation and the low level of environmental exposure.

5.2.2. Monitoring

The objectives of a monitoring plan according to Annex VII of Directive 2001/18/EC 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 which were not anticipated in the environmental risk assessment.

Monitoring is related to risk management, and thus a final adoption of the monitoring plan falls outside the mandate of EFSA. However, the GMO Panel gives its opinion on the scientific quality of the monitoring plan provided by the applicant (EFSA, 2006a). Exposure to the environment of soybean MON89788 would be related to accidental release of GM seeds during transportation and processing.

Since the environmental risk assessment identified no potential adverse environmental effects, case-specific monitoring is not considered necessary.

The general surveillance plan proposed by the applicant includes i) the description of an approach involving operators, reporting to the applicant, via a centralised system, any observed adverse effect of soybean MON89788 on human health and the environment, ii) a coordinating system newly established by EuropaBio for the collection of the information recorded by the various operators, iii) the use of networks of existing surveillance systems. The applicant will submit a general surveillance report on annual basis and a final report at the end of the consent. In case of confirmed adverse effects, the applicant will immediately inform the European Commission and the Member States.

The GMO Panel is of the opinion that the general approaches and measures of the monitoring plan proposed by the applicant are in line with the EFSA opinion on post-market environmental monitoring (EFSA, 2006b) as well as with the intended uses of soybean MON89788. Since the environmental risk assessment identifies no potential adverse environmental effects, no case-specific monitoring is necessary. The GMO Panel agrees with the proposal made by the applicant on the reporting intervals of the general surveillance plan.

5.3. CONCLUSION

The scope of application EFSA-GMO-NL-2006-36 is for food and feed uses, import and processing of soybean MON89788 and excludes cultivation. Considering the proposed uses of soybean MON89788, there is no requirement for scientific information on potential environmental effects associated with cultivation. The GMO Panel considered the environmental comments raised by Member States in the above sections. The GMO Panel takes into account that this application does not include cultivation of the soybean so that the likelihood of cross-pollination between cultivated soybean crops and the occasional soybean plants which might occur from accidental release is considered to be extremely low.

If accidental release and subsequent establishment into the environment of soybean MON89788 plants were to occur, soybean MON89788 plants would only be fitter in the presence of glyphosate herbicides which are not currently used on cultivated soybean or in most areas where the soybean might be spilled. Therefore the GMO Panel is of the opinion that the likelihood of the spread and establishment of soybean MON89788 is very low and that unintended environmental effects due to this soybean will be no different from that of conventional soybean varieties. The scope of the monitoring plan provided by the applicant and the reporting intervals are in line with the intended uses of soybean MON89788.

CONCLUSIONS AND RECOMMENDATIONS

The GMO Panel was requested to carry out a scientific risk assessment of the soybean MON89788 for food and feed uses, import and processing of soybean MON89788 and all derived products.

The GMO Panel is of the opinion that the molecular characterisation provided for the transformation event MON89788 is sufficient for the safety assessment. The bioinformatic analysis of the inserted DNA and flanking regions does not raise any safety concern. The expression of the genes introduced by genetic modification has been sufficiently analysed and the stability of the genetic modification has been demonstrated over several generations. The GMO panel considers that the molecular characterization does not indicate any safety concern.

Comparative analysis has shown that soybean MON89788 is compositionally and agronomically equivalent to conventional soybean, except for the introduced transgenic traits. The risk assessment included an analysis of data from analytical studies, bioinformatics, and *in vitro* and *in vivo* studies. The GMO Panel concluded that the soybean MON89788 is as safe as its non GM counterpart and that the overall allergenicity of the whole plant is not changed.

The application EFSA-GMO-NL-2006-36 concerns food and feed uses, import and processing. There is therefore no requirement for scientific assessment on possible environmental effects associated with the cultivation of soybean MON89788 in the EU. Considering the scope of the application, not for cultivation, the GMO Panel is of the opinion that the likelihood of the spread and establishment of soybean MON89788 is very low and that unintended environmental effects due to this soybean will be no different from that of conventional soybean varieties. The scope of the monitoring plan provided by the applicant and the reporting intervals are in line with the intended uses of soybean MON89788.

In conclusion, the GMO Panel considers that information available for soybean MON89788 addresses the comments raised by the Member States and considers that it is unlikely that soybean MON89788 will have any adverse effect on human and animal health or on the environment in the context of its proposed uses.

DOCUMENTATION PROVIDED TO EFSA

1. Letter from the Competent Authority of The Netherlands (VROM), received 7 November 2006, concerning a request for placing on the market of soybean MON89788 in accordance with Regulation (EC) No 1829/2003.

2. Acknowledgement letter, dated 10 November 2006, from EFSA to the Competent Authority of The Netherlands (Ref. SR/KL/jq (2006) 1827639).

3. Letter from EFSA to applicant, dated 30 March 2007, with request for clarifications under completeness check (Ref. SR/KL/shv (2007) 2064007).

4. Letter from applicant, dated 19 April 2007, providing EFSA with an updated version of the application EFSA-GMO-NL-2006-36 submitted by Monsanto Europe S.A. under Regulation (EC) No 1829/2003:

   Part I – Technical dossier

   Part II – Summary

Part III – Cartagena Protocol

Part IV – Labelling and Unique Identifier

Part V – Samples and Detection

Part VI – Additional information for GMOs

5. Letter from EFSA to applicant, dated 8 June 2007, delivering the 'Statement of Validity' for application EFSA-GMO-NL-2006-36, soybean MON89788 submitted by Monsanto Europe S.A. under Regulation (EC) No 1829/2003 (Ref. SR/KL/shv (2007) 2166968).

6. Letter from EFSA to applicant, dated 17 July 2007, with request for clarifications (ref. SR/KL/shv (2007) 2260849).

7. Letter from applicant to EFSA, dated 19 July 2007, responding to request for clarifications.

8. Letter from applicant to EFSA, dated 10 September 2007, sending complementary information spontaneously.

9. Letter from EFSA to applicant, dated 29 September 2007, acknowledging the receipt of the complementary information sent spontaneously (Ref. SR/KL/shv (2007) 2406888).

10. Letter from EFSA to applicant, dated 15 October 2007, with request for additional information (Ref. SR/KL/shv (2007) 2438649).

11. Letter from EFSA to applicant, dated 19 October 2007, *corrigendum* the request for additional information sent on 15 October 2007 (Ref. SR/KL/shv (2007) 2456916).

12. Letter from EFSA to applicant, dated 19 October 2007, requesting an additional paper copy of the dossier (Ref. KL/shv (2007) 2455877).

13. Letter from applicant to EFSA, dated 26 October 2007, sending the additional copy requested.

14. Letter from applicant to EFSA, dated 30 October 2007, responding to request for additional information.

15. Letter from EFSA to applicant, dated 20 December 2007, with request for additional information (Ref. SR/KL/shv (2007) 2588529).

16. Letter from EFSA to applicant, dated 21 January 2008, with request for additional information (Ref. SR/KL/shv (2007) 2634551).

17. Letter from applicant to EFSA, dated 08 February 2008, responding to request for additional information.

18. Letter from applicant to EFSA, dated 18 February 2008, responding to request for additional information (Ref. SR/KL/shv (2008) 2871913).

19. Letter from applicant to EFSA, dated 28 February 2008, providing an updated monitoring plan.

20. Letter from applicant to EFSA, dated 29 February 2008, providing corrigendum figure 1.

21. Letter from EFSA to applicant, dated 18 March 2008, with request for additional information (SR/KL/shv (2008) 2871913.

22. Letter from applicant to EFSA, dated 05 May 2008, responding to request for additional information.

23. Letter from EFSA to applicant, dated 10 June 2008, re start the clock (SR/KL/shv (2008) 3080732).

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