Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Advice of the Belgian Biosafety Advisory Council on application EFSA-GMO-NL-2015-126 (genetically modified soybean MON 87705 x MON 87708 x MON 89788) from Bayer CropScience N.V. under Regulation (EC) No. 1829/2003

18 December 2024
Ref. SC/1510/BAC/2024_1571

Context

Application EFSA-GMO-NL-2015-126 was submitted by Bayer CropScience N.V. for the marketing of genetically modified (GM) soybean MON 87705 x MON 87708 x MON 89788 (Unique Identifier MON-877Ø5-6 X MON-877Ø8-9 X MON-89788-1), for food and feed uses, import and processing (excluding cultivation) within the European Union, within the framework of Regulation (EC) No. 1829/2003[1].

The three-event stack soybean MON 87705 x MON 87708 x MON 89788 was obtained by conventional crossing (no new genetic modification involved) of the corresponding single events:
- MON 87705, producing dsRNAs downregulating endogenous FAD2 and FATB enzymes, and expressing the CP4 EPSPS protein, conferring an altered fatty acid profile (increased oleic acid content) and tolerance to glyphosate-based herbicides;
- MON 87708, expressing DMO, conferring tolerance to herbicides containing dicamba;
- MON 89788, expressing CP4 EPSPS, conferring tolerance to glyphosate-based herbicides.

The application was validated by EFSA on 16 February 2016. A formal three-month consultation period of the Member States was started, lasting until 17 May 2016, in accordance with Articles 6.4 and 18.4 of Regulation (EC) No. 1829/2003 (consultation of national Competent Authorities within the meaning of Directive 2001/18/EC designated by each Member State in the case of genetically modified organisms being part of the products).

Within the framework of this consultation, the Belgian Biosafety Advisory Council (BAC), under the supervision of a coordinator and with the assistance of its Secretariat, contacted experts to evaluate the dossier, chosen from the common list of experts drawn up by the BAC and the Service Biosafety and Biotechnology (SBB). Eight experts answered positively to this request, and formulated a number of comments to the dossier. See Annex I for an overview of all the comments and the comments forwarded to EFSA on 13 May 2016.

The opinion of the EFSA Scientific Panel on GMOs was published on 18 May 2020 (EFSA Journal 2020;18(5):6111[2]), together with the responses from the EFSA GMO Panel to comments submitted by the Member States during the three-month consultation period. Due to the applicant not providing a 90-day study on MON 87705 soybean in line with the applicable legal requirements in the context of this three-event stack soybean application (i.e. no treatment with the intended herbicide was applied to MON 87705 soybean used to produce the test material), and not providing a proposal for a post-market monitoring (PMM) (considering the altered fatty acid profile of the GM soybean), the GMO Panel was in 2020 not in the position to finalise the risk assessment of soybean MON 87705 x MON 87708 x MON 89788 under the current regulatory frame.

[1] Regulation (EC) No 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed (OJ L 268, 18.10.2003, p.1).
[2] https://www.efsa.europa.eu/en/efsajournal/pub/6111

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In 2024 the applicant provided additional information consisting of the results of a 90-day feeding study on soybean MON 87705 and a proposal for PMM. Upon assessment of this information, the EFSA Scientific Panel on GMOs published on 28 October 2024 a statement complementing its scientific opinion from 2020 (EFSA Journal 2024;22:e9061[3]).

In delivering the present advice the BAC considered in particular the following information:
- The comments formulated by the experts on application EFSA-GMO-NL-2015-126 and the answers or feedback provided by the EFSA GMO Panel;
- The opinion and complementing statement of EFSA;
- The advices already adopted by the BAC on the single events. The conclusions of the BAC for the most recent applications for the single events and the lower-order stacks[4] were as follows:

Event	Application number	BAC advice	Conclusions
MON 87705	EFSA-GMO-NL-2010-78	BAC/2012/1009 (7/12/2012) and BAC/2014/0366 (05/06/2014)	Unlikely to pose any risk to human and animal health. No risk identified for the European environment.
MON 87708	EFSA-GMO-NL-2011-93	BAC/2014/0325 (21/05/2014)	No conclusion on food safety. No risk identified for the European environment.
MON 89788	EFSA-GMO-RX-011	BAC/2018/1090 (11/12/2018)	Unlikely to pose any risk to human and animal health. No risk identified for the European environment.
MON 87705 x MON 89788	EFSA-GMO-NL-2011-100	BAC/2015/0598 (08/09/2015)	Unlikely to pose any risk to human and animal health. No risk identified for the European environment.
MON 87708 x MON 89788	EFSA-GMO-NL-2012-108	BAC/2015/0811 (08/12/2015)	No conclusion on food safety. No risk identified for the European environment.

[3] https://www.efsa.europa.eu/en/efsajournal/pub/9061
[4] This list is not exhaustive at the level of lower-order stacks already assessed, but covers all the applications covering lower-order stacks and for which the BAC issued an advice. For an exhaustive list of all the lower-order stacks already assessed, we refer to the EFSA opinion.

Scientific evaluation

1. Molecular characterisation

With regard to the molecular characterisation, the Biosafety Advisory Council is of the opinion that the information provided is sufficient and does not raise safety concerns.

2. Assessment of food/feed safety and nutritional value

2.1. Assessment of compositional analysis

Taking into account the previous assessment of the single events and the new data on compositional analysis provided by the applicant for the three-stacked event, the Biosafety Advisory Council agrees with the GMO panel of EFSA that the compositional data of GM soybean MON 87705 x MON 87708 x MON 89788, in comparison with its conventional counterpart, do not raise safety concerns.

2.2. Assessment of toxicity

The Biosafety Advisory Council has evaluated the safety of the newly expressed CP4 EPSPS protein in the context of previous applications, and no concerns regarding toxicity were identified. In its advice on the single event MON 87708, expressing the DMO protein, the Council had expressed some concerns regarding the results of the sub-chronic 90-day rat feeding study with the whole GM soybean: some significant differences in clinical pathology parameters were observed between male rats fed diets containing soybean MON 87708 and control animals. The Council concluded that without further investigation it was not convinced that these differences were incidental. Since no new information has been provided in the current application in relation with the toxicological assessment of the whole food derived from GM soybean MON 87708 or MON 87705 x MON 87708 x MON 89788, the concerns expressed above are still valid. As a consequence, the Biosafety Advisory Council is unable to determine whether GM soybean MON 87705 x MON 87708 x MON 89788 is as safe as conventional soybean from a toxicological perspective.

2.3. Assessment of allergenicity

The Biosafety Advisory Council has evaluated the safety of the newly expressed DMO and CP4 EPSPS proteins in the context of previous applications, and no allergenicity concerns were identified. Since no new information on allergenicity of these proteins has become available, the Council is of the opinion that its previous conclusions remain valid.
The Biosafety Advisory Council is also of the opinion that the combined presence of the newly expressed proteins in the stacked event does not raise concerns regarding the allergenicity.

2.4. Nutritional value

The Biosafety Advisory Council is of the opinion that the information provided is sufficient to conclude that the nutritional characteristics of soybean MON 87705 x MON 87708 x MON 89788-derived food and feed do not raise safety concerns from a nutritional point of view.

3. Environmental risk assessment

The Biosafety Advisory Council is of the opinion that it is unlikely that the accidental release of soybean MON 87705 x MON 87708 x MON 89788 (i.e. during transport and/or processing) into the European environment[5] will lead to environmental harm.

[5] As the application doesn't imply cultivation of the GM crop in the EU, a full environmental assessment, as in the case of a cultivation dossier, is not warranted.

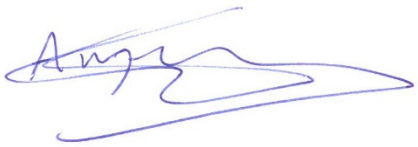
4. Monitoring

With regard to monitoring, the Biosafety Advisory Council is of the opinion that the information provided is sufficient.

Conclusion

Based on the whole set of data on soybean MON 87705 x MON 87708 x MON 89788 provided by the applicant, the scientific assessment of the dossier done by the Belgian experts, the opinion and complementing statement of EFSA, the answers of the EFSA GMO panel to the questions raised by the BAC, and the advices already adopted by the BAC on the three single events and two lower-order stacks, the Biosafety Advisory Council is of the opinion that as a result of remaining uncertainties concerning the toxicity of the whole food derived from the GM plant, it is not possible to draw a final conclusion on the food safety of soybean MON 87705 x MON 87708 x MON 89788.

Given the scope of the application of the GM soybean (no cultivation in the EU) and the fact that the establishment of volunteer plants would be unlikely (soybean does not survive without human assistance, nor as a weed in Europe), the potential environmental release of soybean MON 87705 x MON 87708 x MON 89788 is unlikely to pose any threat to the European environment.



Dr. ir. Geert Angenon
President of the Belgian Biosafety Advisory Council

Annex : Outcome of the assessment of the application and comments sent to EFSA

Annex : Outcome of the assessment of application EFSA-GMO-NL-2015-126 by the Biosafety Advisory Council during the formal consultation of the Member States (3-month commenting period in accordance with Articles 6.4 and 18.4 of Regulation (EC) No 1829/2003) and feedback from the EFSA GMO Panel

Coordinator: René Custers
Experts: Eddy Decuypere (KUL), Patrick du Jardin (ULg), Leo Fiems (ILVO), Johan Grooten (UGent), André Huyghebaert (UGent), Peter Smet (Consultant), Jan Van Doorsselaere (KATO), Michel Van Koninckxloo (HEP Hainaut-Condorcet)
SBB: Fanny Coppens

Application: EFSA-GMO-NL-2015-126
Applicant: Monsanto (Bayer CropScience)
GMO: soybean MON87705 x MON87708 x MON89788
Validation of dossier by EFSA: 16 February 2016

Scope of the application:
☒ GM plants for food use
☒ Food containing or consisting of GM plants
☒ Food produced from GM plants or containing ingredients produced from GM plants
☒ GM plants for feed use
☒ Feed produced from GM plants
☒ Import and processing (Part C of Directive 2001/18/EC)
☐ Seeds and plant propagating material for cultivation in European Union (Part C of Directive 2001/18/EC)

Given the characteristics of the GMO and its intended uses, experts were consulted to cover the following areas of expertise:
☒ Molecular characterization
☒ Environmental aspects
☒ Allergenicity
☒ Toxicology
☒ Food and Feed aspects

The experts were asked to evaluate whether the information provided in the application is sufficient in order to state that the marketing of the genetically modified plant for its intended uses, will not raise any problems for the environment or human or animal health. If information is lacking, the expert was asked to indicate which information should be provided and what the scientifically reasoning is behind this demand.

Comments sent to EFSA are highlighted in grey, with the answers from the GMO Panel from EFSA provided underneath.

List of comments/questions received from the experts

GENERAL COMMENTS

Comment 1
No questions.

Comment 2
Because of the purpose of MON87705 × MON87708 × MON89788 soybean, developed to contain more unsaturated fatty acids and to be resistant to glyphosate and dicamba herbicides, I have evaluated the 3-stacked event MON87705 × MON87708 × MON89788 soybean as a whole. This means that I have taken into account the possible repercussions of a genetically modified glyphosate-resistant soybean, not only because of the presence of new proteins, but also because it may have implications for human and animal health by the presence of residues of the herbicide itself or its metabolites.
Single events dealing with FAD, DMO and CP4 EPSPS proteins have already been assessed and EFSA concluded that they are safe for human and animal health. It is assumed that there is no plausible or testable hypothesis for an interaction of the newly-inserted proteins. Consequently, the genetic modification of MON87705 × MON87708 × MON89788 soybean is no reason to prohibit its import and processing in the EU.
Although there is no direct effect of the genetic modification of MON87705 × MON87708 × MON89788 soybean, an indirect effect cannot be excluded due to an increased use of the herbicides glyphosate and dicamba. Some health concerns about glyphosate have been reported. MON87705 × MON87708 × MON89788 soybean is not intended for cultivation in the EU. The introduction of the MON87705 × MON87708 × MON89788 soybean elsewhere in the world may increase the use of these herbicides. As a consequence, imported soybean, destined for food and feed use, may contain residues of these herbicides and their metabolites.
It is advised that the EU should delay the approval of the import of MON87705 × MON87708 × MON89788 soybean until new epidemiological and toxicology studies clearly demonstrate the safety of glyphosate and its metabolites for human and animal health and the environment.

Comment from the coordinator:
This again is a stacked GM event that combines different herbicide tolerances. As this dossier concerns only import and processing, and not cultivation, any possible indirect impact of the application of the herbicides does not have to be assessed. Only residues and metabolites of the herbicides can be imported. And any levels of residues should fulfil European requirements concerning maximum residu levels. This is a matter for the pesticide authorities. In certain GM herbicide tolerant crops the herbicides may be differently metabolized than in non-GM crops. It is important that any changed degradation of the herbicide is taken into account, when setting the MRL levels of herbicides for which GM herbicide tolerant crops exist in which the degradation differs from the normal situation.

Feedback from the EFSA GMO Panel:
The GMO Panel thanks Belgium for the comment. It is highlighted that the assessment of herbicide residues is not under the remit of the GMO Panel.

Comment 3
The information provided in the application is sufficient.

Comment 4
None.

A. HAZARD IDENTIFICATION AND CHARACTERISATION

A.1. INFORMATION RELATED TO THE RECIPIENT OR (WHERE APPROPRIATE) THE PARENTAL PLANT

Comment 1
Urease, trypsin inhibitors, lectins: the heat of steam on the spent flakes in order to remove hexane does inactivate these 3 proteins, thereby increasing digestibility and nutritional value of SBM; no questions.

Comment 2
The information provided in the application is sufficient.

Comment 3
None.

A.2. MOLECULAR CHARACTERISATION

A.2.1. INFORMATION RELATING TO THE GENETIC MODIFICATION including:

- Description of the methods used for the genetic modification
- Source and characterization of nucleic acid used for transformation
- Nature and source of vector(s) used

Comment 1
MON87705 x MON87708 x MON89788 is produced by conventional crossing soybean containing MON88705 (suppression of FATB and FAD2 genes), MON87708 (dicamba tolerance conferred by DMO-protein), and MON89788 (glyphosate tolerance conferred by CP4-EPSPS protein).
No further questions; expression of the inserts is same for stacked event as for the single events (tables 5 and 6).
Horizontal gene transfer is extremely unlikely in regard of the barriers (gastric acid, pancreatic nucleases, intestinal epithelium, vascular endothelium, blood nucleases and cellular barriers such as endosomal sequestration and lysosomal degradation), and has not been observed.
No interactions of the inserts have been observed by EFSA in several applications either separately or in combination.

Comment 2
No comments.
The dossier describes the stacking of single events by traditional breeding methods. The single events have been approved by EFSA. The stability of the single events in the stacked line is demonstrated and the genes are expressed.

Comment 3
The information provided in the application is sufficient.

Comment 4

Section 1.2.1.3 (c) page 26 of Main text: when performing the bioinformatics search for similarity of the newly expressed proteins DMO and CP4 EPSPS with toxins and allergens, the applicant concluded on the lack of such similarities and refers to the CI annexes (Basu and Silvanovich 2015b) and (Silvanovich and Kessenich, 2015b). However I could only find annexes named "Alignments_Basu and Silvanovich 2015b" and "Alignments_Silvanovich and Kessenich, 2015b" and these annexes only contain the raw data with the alignments. I consider that the dossier should contain a description and commentary of the best hits (with E-scores) and explain why the applicant considers they are not relevant. Maybe this information is in missing annexes Basu & Sivanovich (2015b) and Silvanich and Kessenich (2015b)?
On the same line, the annex Base & Silvanovich (2015a) indicates "*A complete description of the EST_2015, NT_2015, and NR_2015 databases can be found in Basu and Silvanovich (2015b).*" This confirms that this document is missing in the dossier, as the alignments dossiers do not describe the databanks.

Comment from the SBB:
The SBB has checked and confirms that the two above-mentioned references are missing.

Feedback from the EFSA GMO Panel:
The applicant provided updated bioinformatic analyses (information received: 6/10/2017 and 4/07/2019) which was in line with the requirements laid in the applicable EFSA GMO Panel guidelines and legislative documents.

A.2.2. INFORMATION RELATING TO THE GM PLANT including:

- Description of the trait(s) and characteristics which have been introduced or modified
- Information on the sequences actually inserted or deleted
- Information on the expression of the insert
- Genetic stability of the inserted/modified sequence and phenotypic stability of the GM plant

Comment 1
No questions.

Comment 2
The applicant stated that there is no scientific basis to support the notion that sequences would be intrinsically more unstable when combined together by traditional breeding (Technical Dossier, p.47). In the case of MON87705 × MON87708 × MON89788 soybean no detectable rearrangements of these inserts occurred. However, Ali et al. (2014) assumed that stacked events, such as those using MON810 maize, tended to be more instable than single events, so that some alertness is desirable.

Comment from the coordinator:
The data in the "Ali et al." publication do not point to higher instability in stacked events when compared to single events. The only thing they found is in 2 out of 100 samples of the stacked event a mutation in the 3' region of the modification.

Comment 3
None.

A.3. COMPARATIVE ASSESSMENT

A.3.1. CRITERIA FOR THE SELECTION OF COMPARATOR(S)

Comment 1
A3525 as isogenic control (cfr fig. 4 from breeding tree) and 18 conventional reference lines: no further questions.

Comment 2
MON 87705 x MON 87708 x MON 89788 is obtained by traditional breeding methods from parental lines.
It is expected that no significant changes in nutrients will be found for MON 87705 x MON 87708 x MON 89788 in comparison with the parental lines.
MON 87705 x MON 87708 x MON 89788 is compared with conventional soybean counterparts with similar background and with commercially available varieties.

Comment 3
The information provided in the application is sufficient.

Comment 4
None.

A.3.2. FIELD TRIALS: EXPERIMENTAL DESIGN AND STATISTICAL ANALYSIS

Comment 1
No questions.

Comment 2
No remarks.

Comment 3
The information provided in the application is sufficient.

Comment 4
Page 52 of Main Text: the applicant indicates that the 8 field trials for the comparative assessment correspond to a "*variety of agronomic practices, soils and climatic factors*" and refers to Figure 5 for the field locations. However, this figure seems to indicate a very limited spread of the fiel trial across the territory of Argentina, hence it is not clear from the text and map whether a variety of agroclimatic contexts is indeed covered. Could the applicant substantiate the representativeness of the field locations and agronomic conditions? The detailed report in Carringer et al. 2015a (CI) does not comment further on these points and it is difficult to conclude on the representativeness of the field trials on the sole basis of the tables 3 and 4 of this report.

Feedback from the EFSA GMO Panel:
The GMO Panel thanks Belgium for the question. To improve the representativeness of the selected field trials, the GMO Panel published a guidance document on the agronomic and phenotypic characterisation of genetically modified plants (EFSA GMO Panel, 2015). Application EFSA-GMO-NL-2015-126 was submitted during the transitional period of the GMO Panel guidance. Therefore, the requirements of the guidance document were not fully applicable for this application. The selected field

trial sites were located in the major commercial soybean-growing regions of Argentina, covering a limited geographical range. The GMO Panel requested further justification on the selected sites. Based on the additional information provided by the applicant on 8/8/2016, the GMO Panel concluded that the geographical locations, soil characteristics, meteorological conditions of the field trial sites and the management practices applied are typical of the receiving environments where the test materials could be grown.

A.3.3. COMPOSITIONAL ANALYSIS

Comment 1

Expected changes are observed in saturated and unsaturated fatty acids because of FATB and FED2 in both treated and untreated MON88705 x MON88708 x MON89788.

Trypsin inhibitor was significantly higher in the stacked event than in the conventional control but not meaningful in vue of the larger range in conventional counterpart and the overlap of all values with the range of conventional counterpart.

I agree with the conclusion of compositional similarity between MON88705 x MON88708 x MON89788 and the conventional soybean counterpart except for the fatty acid composition that was intentionally changed and as expected had decreased levels of saturated fats (16:0 and 18:0) and increased levels of unsaturated fatty acids (18:1 and 18:2).

Comment 2

Several composition parameters analysed in MON87705 × MON87708 × MON89788 soybean were different from non-GM soybean. However, mean values were within the range of soybean references and the absolute differences between them were minor, so that differences are not of biological relevance.

The concentration of glyphosate is not discussed in this section. As part of MON87705 × MON87708 × MON89788 soybean was treated with dicamba and glyphosate (Technical Dossier, p.57), it is highly desirable to report the concentrations of glyphosate and its metabolites.

Comment 3

As it is usually the case the OECD guidelines, 2012, were followed for the selection of compounds.

Nutrients assessed in the beans included:

- proximates: protein, fats, ash, moisture => no comment
- amino acids => important indispensible amino acids are included
- fatty acids => the whole range of fatty acids is covered
- carbohydrates by calculation => no information on the specific carbohydrates
- fibre => the detergent method is applied; no information on soluble and insoluble fibre
- minerals: calcium, phosphorous => no comment
- vitamins: α – tocopherol, phylloquinone (K1) => no information on other vitamins, other tocopherols and tocotrienols
- anti-nutrients: lectin, phytic acid, raffinose, stachyose and trypsin inhibitors => no comment
- other components: isoflavones => in previous applications mentioned under anti-nutrients; important in the discussion about the relationship between soybeans and human health
- identified allergens => although allergenicity is usually covered in a separate chapter in aa application, identified allergens are included for the first time in the comparative analysis; due to the growing concern about food allergenicity; this is a significant positive step
- further comment: although a significant number of analyses is performed, the information obtained is not adequate to label product according to the EU labelling system, as mentioned before.

Nutrients in forage are limited to proximates => no comment
Statistical analysis: Results are discussed in detail. No statistical difference was found for most of the compounds, of course with the exception of the fatty acid composition. In case differences were observed it was concluded of being of no compositional relevance.
I agree with this overall conclusion.

Comment 4
The information provided in the application is sufficient.

A.3.4. AGRONOMIC AND PHENOTYPIC CHARACTERISTICS

Comment 1
No questions.

Comment 2
No remarks.

Comment 3
The information provided in the application is sufficient.

Comment 4
None.

A.3.5. EFFECTS OF PROCESSING

Comment 1
No questions.

Comment 2
Taking into account the results of the comparative analysis no major effects on processing of MON87705 × MON87708 × MON89788 are to be expected with the exception of the intended traits such as the modified fatty acid composition.

Comment 3
The information provided in the application is sufficient.

A.4. TOXICOLOGICAL ASSESSMENT

A.4.1. METHODOLOGY USED FOR TOXICITY TESTS

Comment 1
No questions.

A.4.2. ASSESSMENT OF NEWLY EXPRESSED PROTEINS including:

- Molecular and biochemical characterisation of the newly expressed proteins
- Up-to-date bioinformatic search for homology
- Information on the stability of the protein under the relevant processing and storage conditions for the food and feed derived from the GM plant
- Data concerning the resistance of the newly expressed protein to proteolytic enzymes
- Repeated dose toxicity studies using laboratory animals

Comment 1
The only novel proteins are DMO and CP4-EPSPS, and:
- They have been demonstrated to be safe already;
- No structural similarity to known toxins as well (see 1st paragraph of p.101; EFSA-GMO-NL-2010-78 and EFSA-GMO-NL-2011-100);
- No toxic effects on mammals; and I should also add “and birds”, because soybean meal is for 50% consumed by poultry (p.17);
- Rapid digestibility in simulated digestive fluids;
- Heat treatment is destroying their functional activity.
No testable hypothesis to justify 28-day oral toxicity studies for the combined DMO and CP4-EPSPS proteins.

Comment 2
It is unlikely that the new proteins of MON87705 × MON87708 × MON89788 soybean will pose serious risks for toxicity. It is assumed that there is no biological pathway in which the newly-inserted genes would directly or indirectly interact safety (Kok et al., 2014; Zdziarski et al., 2014). There is no plausible or testable hypothesis for the interaction of DMO and CP4 EPSPS proteins in MON87705 × MON87708 × MON89788 soybean (Steiner et al., 2013).

Comment 3
None.

Comment 4
The amounts of the proteins in the stacked event are comparable to those in the single event control.
Although significant differences are seen for some of the antinutrients and secondary metabolites, none of these seem to be of biological relevance.
Safety assessment with the newly expressed proteins was conducted earlier.
The bioinformatic evaluation of the protein sequence indicates no structurally relevant sequence similarity to toxins or other biologically active proteins that could be harmful to human or animal health.

A.4.3. ASSESSMENT OF NEW CONSTITUENTS OTHER THAN PROTEINS

Comment 1
No questions.

A.4.4. ASSESSMENT OF ALTERED LEVELS OF FOOD AND FEED CONSTITUENTS

Comment 1
No questions.

Comment 2
The information provided in the application is sufficient.

A.4.5. ASSESSMENT OF THE WHOLE FOOD AND/OR FEED DERIVED FROM GM PLANTS

Comment 1
No additional 90-day feeding study with whole feed in rodents, or other animal studies, is scientifically justified or needed to assess the safety of MON88705 x MON87708 x MON89788.

Comment 2
The information provided in the application is sufficient.

Comment 3
90-day rat feeding study: In dossier 93, I raised the following concerns:
- The number of eosinophils is elevated only in male rats, both compared to the control and the references. What about the amount of formaldehyde in the SBM? Can this excert an effect on granulocytes? Why only in male subjects? This has to be further investigated.
- The alanine aminotransferase (ALT) activities are higher compared to the control as well as the references and statistically significant for the 30% feeding group. The values are outside the historical range. As for the eosinophil count, only male rats are affected. Further investigation is needed.

The comment from EFSA:
The EFSA GMO Panel assessed the 90-day toxicity study and concluded that the outcome of the study in rats with diets containing toasted defatted soybean meal from soybean MON87708, its conventional counterpart or any of two non-GM soybean varieties did not raise safety concerns.

Comment from the SBB:
These comments were already forwarded to EFSA for dossier 93. The EFSA opinion was as follows:
"*Statistically significant differences in clinical pathology and urinalysis parameters between rats fed diets containing soybean MON87708 and control animals (i.e. lower mean absolute monocytes counts in females fed the 15% MON87708 diet; higher mean percent eosinophils, higher alanine aminotransferase activity and serum chloride levels in male rats fed 30% MON87708; changes in urinary specific gravity, pH and volume in females fed 15% test diet; and lower spleen weight in female rats given diets containing 15% soybean MON87708) were considered incidental and not relevant because the differences were minimal, were not associated with changes in related parameters or in histopathology, and were within the range of reference dietary groups and/or historical control data. At macroscopic or microscopic examination (histopathology on rats given 30% inclusion rate diets) no MON87708-diet related findings were observed, and all the detected changes were consistent with the background pathology of rats of this strain and age.*"
This issue has been discussed extensively in the Council in the frame of the evaluation of applications 93 (MON87708) and 108 (MON87708 x MON89788).
For application 93 (advice BAC_2014_0325), the Council concluded that "as a result of the absence of a sound explication of observed clinical differences between male rats sub-chronically fed with herbicide treated soybean MON87708 and the reference group, it is not possible to draw a final conclusion on the food safety of the event." Three members considered that in that case a negative advice should be issued and formulated a minority opinion.

For application 108 (advice BAC_2015_0811), in the absence of new information, the Council concluded that “as a result of remaining uncertainties concerning the toxicity of the whole food derived from the GM plant, it is not possible to draw a final conclusion on the food safety of soybean MON87708 x MON89788.”. Two members considered that in that case a negative advice should be issued and formulated a minority opinion.
For application 126, no new information related to the assessment of the whole food/feed derived from the GMO has been provided.

Feedback from the EFSA GMO Panel:
In line with Reg. (EU) No. 503/2013 and applicable EFSA guidance documents, animal studies on food/feed derived from the three-event stack soybean are not necessary. This is based on the outcome of the molecular characterisation assessment, comparative analysis and toxicological assessment, that did not identify indication of findings relevant to food/feed safety related to the stability and expression of the inserts or to interaction between the transformation events, and no modifications of toxicological concern in the composition of the soybean (see Sections 3.6.2.4 of the scientific opinion for further details). With regards to the comment on the 90-day on MON87708: the outcome of the study was assessed in the context of AP93, as stated by Belgium. With regards to clinical pathology and urinalysis the GMO Panel concluded: “Statistically significant differences in clinical pathology and urinalysis parameters between rats fed diets containing soybean MON 87708 and control animals (i.e. lower mean absolute monocytes counts in females fed the 15 % MON 87708 diet; higher mean percent eosinophils, higher alanine aminotransferase activity and serum chloride levels in male rats fed 30 % MON 87708; changes in urinary specific gravity, pH and volume in females fed 15 % test diet; and lower spleen weight in female rats given diets containing 15 % soybean MON 87708) were considered incidental and not relevant because the differences were minimal, were not associated with changes in related parameters or in histopathology, and were within the range of reference dietary groups and/or historical control data. At macroscopic or microscopic examination (histopathology on rats given 30 % inclusion rate diets) no MON 87708-diet related findings were observed, and all the detected changes were consistent with the background pathology of rats of this strain and age” and that “The result of a 90-day feeding study in rats did not raise safety concerns”. In the context f the current application, in order to fulfil the requirements of Regulation (EU) No 503/2013 for the three-event stack soybean, the GMO Panel asked the applicant to provide additional information on this study. This allowed to conclude that this is in line with the legal requirements and that there are no indications of adverse effects related to the 90-day administration to rats of a diet including defatted toasted meal from soybean MON 87708 (see Sections 3.6.2.4 of the scientific opinion for further details).

SBB comment on EFSA’s answer:
The additional information on the 90-day feeding study for MON 87708, mentioned at the end of EFSA’s answer, was part of application EFSA-GMO-NL-2016-135 (soybean MON 87708 x MON 89788 x A5547-127), for which the Council gave an inconclusive advice regarding food safety.

A.5. ALLERGENICITY ASSESSMENT

A.5.1. ASSESSMENT OF ALLERGENICITY OF THE NEWLY EXPRESSED PROTEIN including:

- Amino acid sequence homology comparison between the newly expressed protein and known allergens using a comprehensive database
- Specific serum screening
- Pepsin resistance and in vitro digestibility tests

- Additional tests

Comment 1
No questions.

Comment 2
Assessment of individual events
Based on the following:
- A weight of evidence analysis performed before for the individual newly expressed proteins concluded that the CP4 EPSPS (MON87705; MON89788) and DMO (MON87708) proteins are highly unlikely to be allergenic;
- The FAD2-1A/FATB1-A suppression cassette (MON87705) encodes for dsRNA, a non-allergenic biomolecule;
- The approved single GM events have been licensed for marketing in the EU and have been part of the food supply for some years without reported incident;
- An updated bioinformatics analysis using the AD_2015 database did not reveal sequence homologies with known allergens;
I agree with the applicant's conclusion that there is no new evidence indicating an increased risk for allergenicity of either inserted protein.

Assessment of stacked events
Based on the following:
- The single events behave as independent genetic loci, thus rendering unlikely mutual interactions at the genetic level, modulating gene expression and/or stability;
- The allergenic potential of MON87705 x MON89788 and MON87708 x MON89788 sub-stack combinations has been assessed before by EFSA;
- The present combination applied for differs from the already evaluated sub-stack combination MON87708 x MON89788 only by the insertion of a suppression cassette encoding dsRNA, a non-allergenic biomolecule.
I agree with the applicant's conclusion that it is highly unlikely that the co-expression of DMO and CP4 EPSPS proteins along with the expression of a dsRNA-encoding FAD2-1A/FATB1-A suppression cassette in MON87705 x MON87708 x MON89788 can cause an allergic reaction in humans or animals.

Comment 3
None.

A.5.2. ASSESSMENT OF ALLERGENICITY OF THE WHOLE GM PLANT

Comment 1
No questions.

Comment 2
Occupational allergies for handlers of raw soybeans were observed (Technical Dossier, p.69), although the responsible proteins are unknown. Therefore, a monitoring plan should be implemented and unanticipated adverse effects should be reported.

Comment 3

There are no indications that combining the individual traits of the separate GMO's will increase the allergenic potential of the hybrid soya plant.

A.5.3. ADJUVANTICITY

Comment 1
No questions.

Comment 2
No comments.

A.6. NUTRITIONAL ASSESSMENT

A.6.1. NUTRITIONAL ASSESSMENT OF FOOD DERIVED FROM GM PLANTS

Comment 1
Lack of nutritional concerns as applicable to MON87705 and MON88705 x MON89788 are also valid for MON88705 x MON87708 x MON89788, since no unintended effects of genetic modifications in the latter have been identified.

Comment 2
Based on the compositional equivalence and the fact that differences are not of biological relevance (see A.3.3), there is no reason to assume that the genetic modification has affected the nutritional value of food derived from MON87705 × MON87708 × MON89788 soybean.

Comment 3
The information provided in the application is sufficient.

A.6.2. NUTRITIONAL ASSESSMENT OF FEED DERIVED FROM GM PLANTS

Comment 1
Idem as for A.6.1.

Comment 2
Based on the compositional equivalence and the fact that differences are not of biological relevance (see A.3.3), there is no reason to assume that the genetic modification has affected the nutritional value of feed derived from MON87705 × MON87708 × MON89788 soybean.

Comment 3
The information provided in the application is sufficient.

B. EXPOSURE ASSESSMENT - ANTICIPATED INTAKE/EXTENT OF USE

Comment 1

No questions.

Comment 2

The MOEs for CP4 EPSPS and DMO based on consumption of whole soy-containing foods ranged from 4.4×10^2 to 2.6×10^2 (Technical Dossier, p.114). These values do not correspond to the values given in Table 20: 4.4×10^2 to 2.6×10^4. The applicant should verify the correctness of the values in the text and Table 20.

Feedback from the EFSA GMO Panel:

In the scientific opinion dietary exposure estimations were not linked to toxicological studies (risk characterization) when concluding on the safety of the proteins.

Comment 3

The information provided in the application is sufficient.

C. RISK CHARACTERISATION

Comment 1

No questions.

Comment 2

The information provided in the application is sufficient.

Comment 3

None.

D. POST MARKET MONITORING (PMM) OF FOOD AND FEED DERIVED FROM GM PLANTS

Comment 1

No questions.

Comment 2

The information provided in the application is sufficient.

E. ENVIRONMENTAL RISK ASSESSMENT

E.1. INTRODUCTION

Comment 1

No questions.

Comment 2

The information provided in the application is sufficient.

Comment 3

None.

E.2. General approach of the ERA

Comment 1
No questions.

Comment 2
The information provided in the application is sufficient.

Comment 3
None.

E.3. Specific areas of risk

As stated in the EFSA guidance on the environmental risk assessment of genetically modified plants (EFSA Journal 2010, 8(11):1879) the objective of the ERA is on a case-by-case basis to identify and evaluate potential adverse effects of the GM plant, direct and indirect, immediate or delayed (including cumulative long-term effects) on the receiving environment(s) where the GM plant will be released. For each specific risk the ERA consists of the six steps described in Directive 2001/18/EC:

1. Problem formulation including hazard identification,
2. Hazard characterisation,
3. Exposure characterisation,
4. Risk characterisation,
5. Risk management strategies,
6. Overall risk evaluation and conclusions.

E.3.1. Persistence and invasiveness including plant-to-plant gene flow

Comment 1
No questions; the numbering lay-out of the pages is a bit confusing since it refers to introduction, but also to specific areas of risk; this should be 5.3 etc…

Comment 2
The information provided in the application is sufficient.
Comment 3
None.

E.3.2. Plant to micro-organisms gene transfer

Comment 1
No questions.

Comment 2
The information provided in the application is sufficient.

Comment 3
None.

E.3.3. INTERACTION BETWEEN THE GM PLANT AND TARGET ORGANISMS

Comment 1
Not relevant.

Comment 2
None.

E.3.4. INTERACTION BETWEEN THE GM PLANT AND NON-TARGET ORGANISMS (NTOS)

Comment 1
Not relevant.

Comment 2
None.

E.3.5. IMPACTS OF SPECIFIC CULTIVATION AND MANAGEMENT AND HARVESTING TECHNIQUES

Comment 1
Not relevant.

Comment 2
MON87705 × MON87708 × MON89788 soybean is not intended for cultivation in the EU. Nevertheless, the introduction of glyphosate-tolerant crops may result in the accumulation in soils of glyphosate and its metabolites (aminomethylphosphonic acid) in regions where it is allowed, so that the sustainability of genetically modified glyphosate-tolerant crops is questionable (Mamy et al., 2010).
Herbicide use in the USA on soybean, corn and cotton declined slightly in the first years following introduction of herbicide resistant GM crops, but increased moderately in recent years (Fernandez-Cornejo et al., 2014), whereas Benbrook (2012) reported that herbicide-resistant crop technology has led to a 239 million kg increase in herbicide use in the USA between 1996 and 2011. Glyphosate use has risen almost 15-fold since genetically modified glyphosate-tolerant crops were introduced in 1996 (Benbrook, 2016).
MON87705 × MON87708 × MON89788 soybean is not intended for cultivation in the EU. Nevertheless, an indirect effect of the approval of MON87705 × MON87708 × MON89788 soybean is that it may have consequences in countries where its cultivation is allowed. The continued application of the same herbicide in subsequent rotations may lead to increased selection pressure for herbicide resistant weed populations. Furthermore, the continued application of same herbicides may result in an increased accumulation of residues of herbicides and metabolites in plant tissues (Reddy et al.,2008; Bøhn et al., 2014) and surface water (VMM, 2015). Health concerns with regard to the use of glyphosate (Guyton et al., 2015; Seneff et al., 2015) have been reported. Food and feed that compromise human and animal health is unacceptable.

The application of these herbicides in weed management should meet the restrictions specific to herbicide-treated crops. Herbicide mixing exposes weeds to multiple mechanisms of action, which may delay resistance evolution. However, herbicide mixtures are not a permanent solution to the problem of herbicide resistance, as they do not prevent it on the long run (Evans et al., 2015).

Comment from the coordinator:

The coordinator welcomes this comment. However this dossier is about import and processing, and not about cultivation in the EU.

Comment 3

Not relevant.

Comment 4

None.

E.3.6. EFFECTS ON BIOGEOCHEMICAL PROCESSES

Comment 1

No questions.

Comment 2

The information provided in the application is sufficient.

Comment 3

None.

E.3.7. EFFECTS ON HUMAN AND ANIMAL HEALTH

Comment 1

No further questions.

Comment 2

The new proteins in MON87705 × MON87708 × MON89788 soybean are unlikely to be detrimental for human and animal health. However, there is a side effect of the use of MON87705 × MON87708 × MON89788 soybean: glyphosate residues and its metabolites may be harmful for human and animal health.

Comment 3

The information provided in the application is sufficient.

Comment 4

None.

E.3.8. OVERALL RISK EVALUATION AND CONCLUSIONS

Comment 1

No questions.

Comment 2
Because of the controversy between the WHO (Guyton et al., 2015) and EFSA (EFSA, 2015) with regard to the safety of glyphosate, a new examination of glyphosate toxicity should be undertaken to adjust downward the acceptable daily intake for glyphosate, as proposed by Myers et al. (2016). In the meantime, the approval of MON87705 × MON87708 × MON89788 soybean for import and processing should be postponed.

Comment from the coordinator and the SBB:
The assessment of the safety of herbicides is not within the remits of the Biosafety Council.

Comment 3
The information provided in the application is sufficient.

Comment 4
None.

E.4. Post Market Environmental Monitoring plan

E.4.1. Interplay between environmental risk assessment and monitoring

Comment 1
No questions.

Comment 2
None.

E.4.2. Case-specific GM plant monitoring

Comment 1
No questions.

Comment 2
None.

E.4.3. General surveillance for unanticipated adverse effects

Comment 1
No questions.

Comment 2
None.

E.4.4. Reporting the results of monitoring

Comment 1
No questions.

Comment 2
None.

ADDENDUM FROM THE EXPERT-REVIEWER ON : "ADDITIONAL INFORMATION RELATED TO THE SAFETY OF THE GENETICALLY MODIFIED FOOD OR FEED" (PAGE 158 &SQ. OF MAIN TEXT)

Comment 1
I have no comments on this section.

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