Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Advice of the Belgian Biosafety Advisory Council on application EFSA-GMO-NL-2018-151 (genetically modified maize MON 89034 x 1507 x MIR162 x NK603 x DAS-40278-9) from Dow AgroSciences under Regulation (EC) No. 1829/2003

13 September 2022
Ref. SC/1510/BAC/2022_1053

Context

Application EFSA-GMO-NL-2018-151 was submitted by Dow AgroSciences for the marketing of genetically modified (GM) maize MON 89034 x 1507 x MIR162 x NK603 x DAS-40278-9 (Unique Identifier MON-89Ø34-3 x DAS-Ø15Ø7–1 x SYN-IR162-4 x MONØØ6Ø3–6 x DAS-4Ø278-9) for food and feed uses, import and processing (excluding cultivation) within the European Union, under the framework of Regulation (EC) No. 1829/2003[1].

The five-event stack, maize MON 89034 x 1507 x MIR162 x NK603 x DAS-40278-9, was obtained by conventional crossing (no new genetic modification involved) of the corresponding single events:

- MON 89034, expressing the Cry1A.105 and Cry2Ab2 proteins for resistance to lepidopteran insect pests;
- 1507, expressing the Cry1F protein conferring resistance to certain lepidopteran pests and the PAT protein conferring tolerance to herbicide products containing glufosinate ammonium;
- MIR162, expressing the Vip3Aa20 protein conferring resistance to certain lepidopteran insect pests, and the PMI protein, a selectable marker;
- NK603, expressing the CP4 EPSPS protein and its variant CP4 EPSPS L214P that confer tolerance to herbicide products containing glyphosate;
- DAS-40278-9, expressing the AAD-1 protein conferring tolerance to 2,4-D and AOPP-based herbicides.

The application was validated by EFSA on 15 October 2018. A formal three-month consultation period of the Member States was started, lasting until 26 January 2019, 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 chosen from the common list of experts drawn up by the BAC and the Service Biosafety and Biotechnology (SBB) to evaluate the molecular data of the five-stack event and the additional toxicity data provided for maize DAS-40278-9 in the dossier. Three experts answered positively to this request, and formulated a number of comments to the dossier (see Annex I).

[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).

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The opinion of the EFSA Scientific Panel on GMOs was published on 12 August 2022 (EFSA Journal 2022;20(8):7451[2]) together with the responses from the EFSA GMO Panel to comments submitted by the Member States during the three-month consultation period. Those documents were forwarded to the experts on 17 August 2022, with an invitation to react if needed.

In delivering the present advice the BAC considered in particular the following information:
- The comments formulated by the experts on application EFSA-GMO-NL-2018-151;
- The opinion of EFSA;
- The advices already adopted by the BAC on the single events and lower-order stacks containing these single events.

The conclusions of the BAC for the most recent applications for the single events and the lower-order stacks were as follows[3]:

Event(s)	Application number	BAC advice	Conclusions
MON89034	EFSA-GMO-RX-015	BAC/2019/1085	Unlikely to pose risks to human and animal health, and the European environment.
1507	EFSA-GMO-RX-001	BAC/2017/0186	Unlikely to pose risks to human and animal health, with minority declaration related to the lack of statistically convincing studies on toxicity. No risk identified for the European environment.
MIR162	EFSA-GMO-DE-2010-82	BAC/2012/0785	Unlikely to pose risks to animal health and the European environment; no conclusion on human health due to uncertainties on safety of the PMI protein. This protein has been positively assessed in subsequent applications.
NK603	EFSA-GMO-NL-2005-22 EFSA-GMO-RX-NK603	BAC/2009/1367	Unlikely to pose risks to human and animal health, and the European environment.
DAS-40278-9	EFSA-GMO-NL-2010-89	BAC/2017/0066	No conclusion about the food and feed safety of maize DAS-40278-9. No risk identified for the European environment.
MON 89034 x 1507	EFSA-GMO-NL-2017-139	BAC/2017/0742	Unlikely to pose risks to human and animal health, and the European environment.
MON 89034 x NK603	EFSA-GMO-NL-2016-131 EFSA-GMO-NL-2016-134 EFSA-GMO-NL-2017-144	BAC/2019/0745 BAC/2019/0746 BAC/2019/1083	Unlikely to pose risks to human and animal health, and the European environment.
1507 x NK603	EFSA-GMO-RX-008	BAC/2018/0705	Unlikely to pose risks to human and animal health, and the European environment.
1507 x MIR162	EFSA-GMO-DE-2011-103	BAC/2019/0393	Unlikely to pose risks to human and animal health, and the European environment.
NK603 x DAS-40278-9	EFSA-GMO-NL-2019-164	BAC/2022/0153	Unlikely to pose risks to human and animal health, and the European environment.
1507 x NK603 x MIR162	EFSA-GMO-NL-2015-127	BAC/2021/0068	Unlikely to pose risks to human and animal health, and the European environment.
MON 89034 x MIR162 x NK603	EFSA-GMO-NL-2016-131 EFSA-GMO-NL-2016-134	BAC/2019/0745 BAC/2019/0746	Unlikely to pose risks to human and animal health, and the European environment.
MON 89034 x 1507 x DAS-40278-9	EFSA-GMO-NL-2013-112 EFSA-GMO-NL-2013-113	BAC/2019/0248 BAC/2019/0101	Unlikely to pose risks to human and animal health, and the European environment.
MON 89034 x 1507 x NK603 x DAS-4027-9	EFSA-GMO-NL-2013-112	BAC/2019/0248	Unlikely to pose risks to human and animal health, and the European environment.

[2] See https://doi.org/10.2903/j.efsa.2022.7451

[3] 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 additional data on compositional analysis provided by the applicant for the five-stacked event, the Biosafety Advisory Council agrees with the GMO panel of EFSA that the compositional data of maize MON 89034 x 1507 x MIR162 x NK603 x DAS-40278-9, 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 Cry1A.105, Cry2Ab2, Cry1F, Vip3Aa20 proteins and PAT, CP4 EPSPS, CP4 EPSPS L214P and AAD-1 proteins in the context of previous applications, and no safety concerns were identified. Taking into account the updated information considered in the current application, the Council is of the opinion that its previous conclusions remain valid.

For the PMI protein, the Biosafety Advisory Council could previously not conclude on the toxicological safety for humans and animals, as the 28-day toxicity study was not fully compliant with the EFSA guidance recommendation (i.e. not sufficient animals were used for the haematological, clinical chemistry and coagulation examinations)[4]. Dossier EFSA/GMO/NL/2018/151 contains additional data on the potential toxicity of maize DAS-40278-9, namely a 90-day rat feeding study. The Biosafety Advisory Council is of the opinion that this study provides sufficient information to draw a positive conclusion on the toxicological safety of maize DAS-40278-9 and that it supports the safety of the PMI protein.

The Biosafety Advisory Council is also of the opinion that the combined expression of the newly expressed proteins in the stacked event does not raise toxicological concerns.

2.3. Assessment of allergenicity

The Biosafety Advisory Council has evaluated the safety of the newly expressed Cry1A.105, Cry2Ab2, Cry1F, Vip3Aa20 proteins and PAT, CP4 EPSPS, CP4 EPSPS L214P, AAD-1 and PMI proteins in the context of previous applications, and no 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 expression of the newly expressed proteins in the stacked event does not raise concerns regarding 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 maize MON 89034 x 1507 x MIR162 x NK603 x DAS-40278-9-derived food and feed are not expected to differ from those of conventional maize varieties.

[4] http://www.bio-council.be/sites/biocouncil.be/files/advices/BAC_2017_0066.pdf

3. Environmental risk assessment

Field observations indicate that maize grains can sometimes overwinter and germinate in certain regions of the EU (e.g. Palaudelmàs *et al*., 2009[5]; COGEM, 2011[6]; Pascher, 2016[7]). As a result, volunteer maize plants do sometimes occur in subsequent crops. There is also evidence of the rare occurrence of feral maize plants (e.g. Pascher, 2016; COGEM, 2018[8]). However, volunteer maize has been shown to grow weakly and is not considered an agricultural problem. The occurrence of feral maize plants has not resulted in the establishment of self-sustaining populations, mainly because maize is highly domesticated, has no weedy characteristics and is not tolerant to frost. Thus, the occurrence of volunteer and feral maize in the EU is currently limited and transient. In addition, maize has no sexual compatible wild relative in the EU. Therefore, the Biosafety Advisory Council is of the opinion that it is unlikely that the accidental release of maize MON 89034 x 1507 x MIR162 x NK603 x DAS-40278-9 (i.e. during transport and/or processing) into the European environment[9] will lead to environmental harm.

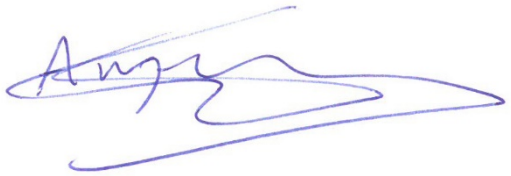
4. Monitoring

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 maize MON 89034 x 1507 x MIR162 x NK603 x DAS-40278-9 provided by the applicant, the scientific assessment of the dossier done by the Belgian experts, the opinion of EFSA and the advices already adopted by the BAC on the single and lower-order stacked events, the Biosafety Advisory Council:

1) Agrees with the GMO panel of EFSA that there is no reason to expect interactions between the newly expressed proteins that could impact on the food or feed safety;
2) Agrees with the GMO panel of EFSA that in the context of its proposed uses maize MON 89034 x 1507 x MIR162 x NK603 x DAS-40278-9 is unlikely to pose any risk to human and animal health;
3) Agrees with the GMO panel of EFSA that the spillage of maize MON 89034 x 1507 x MIR162 x NK603 x DAS-40278-9 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

[5] Palaudelmàs M., *et al*., 2009. Effect of volunteers on maize gene flow. Transgenic Res.18(4):583-594. doi:10.1007/s11248-009-9250-7

[6] COGEM, 2011. Research report "Crop volunteers and climate change. Effects of future climate change on the occurrence of maize, sugar beet and potato volunteers in the Netherlands". https://cogem.net/en/publication/crop-volunteers-and-climate-change-effects-of-future-climate-change-on-the-occurrence-of-maize-sugar-beet-and-potato-volunteers-in-the-netherlands/

[7] Pascher K., 2016. Spread of volunteer and feral maize plants in Central Europe: recent data from Austria. Environ. Sci Eur.28(1):30. doi:10.1186/s12302-016-0098-1

[8] COGEM, 2018. Research report "Are teosinte and feral maize present in the Netherlands?". https://cogem.net/en/publication/are-teosinte-and-feral-maize-present-in-the-netherlands/

[9] 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.

Minority declaration of P. Baret

On point 3 of this advice (Environmental risk assessment), the presence of feral populations of maize in Europe is mentioned but no proper assessment of the risk related to these populations is proposed. As the maize is resistant to insects and herbicides, the potential impact on biodiversity and on coexistence implies scientific data on fitness and survival. In absence of a comprehensive science based risk assessment, it is impossible to conclude that there is no environmental risk.

Annex : Outcome of the assessment of application EFSA/GMO/NL/2018/151 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)

Coordinator: René Custers
Experts: Frank Van Breusegem (VIB-UGent), Peter De Smet (Scientific Consultancy Smet & Pauwels)
SBB: Adinda De Schrijver

Application: **EFSA/GMO/NL/2018/151**
Applicant: **Syngenta**
GMO: **maize MON 89034 x1507 x MIR162 x NK603 x DAS-40278-9**
Date of validation by EFSA: **15 October 2018**

Scope of the application:
☒ Food containing or consisting of GM plants
☒ Food produced from GM plants or containing ingredients produced from GM plants
☒ Feed containing or consisting of GM plants
☒ Feed produced from GM plants
☒ Products other than food and feed containing or consisting of GM plants with the exception of cultivation
☒ 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

As this application concerns a stacked event, the Biosafety Advisory Council decided to evaluate only the specific risk assessment aspects linked to the stacked as mentioned in the Commission Implementing Regulation (EU) No 503/2013, i.e. stability of the traits, expression of the new proteins, and interactions between the newly expressed traits.

For maize DAS-40278-9 (dossier EFSA/GMONL/2010/89) the Biosafety Advisory Council could not conclude on the toxicological safety for humans and animals, as the 28-day toxicity study was not fully compliant with the EFSA guidance recommendation (i.e. not sufficient animals were used for the

haematological, clinical chemistry and coagulation examinations)[10]. Dossier EFSA/GMO/NL/2018/151 contains additional data on the potential toxicity of maize DAS-40278-9, namely a 90-day rat feeding study with maize DAS-40278-9. The experts were therefore invited to evaluate the 90-day rat feeding study and to consider whether this new information has an impact on the previous evaluation.

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 received are summarised below.

No comments were selected to be placed on the EFSAnet. EFSA will be informed that we do not have any comments and that we consider all the necessary information is present to conduct a robust risk assessment. It should be noted that all the comments received from the experts are considered in the evaluation of this dossier and in formulating the final advice of the Biosafety Advisory Council.

[10] http://www.bio-council.be/Advices/BAC_2017_0066.pdf

List of comments/questions received from the experts

PART I - GENERAL COMMENTS

No comments received

PART II - SCIENTIFIC INFORMATION

1. HAZARD IDENTIFICATION AND CHARACTERISATION

1.2. MOLECULAR CHARACTERISATION

1.2.1. Information relating to the genetic modification

Comment 1

I plead for a uniform (between the different single events) and accurate wording of the description of the results and the conclusions in 1.2.2.2 e) and f)

e) three different wordings are used to conclude on the integration site of the constructs and effects on maize genes: “there is no indication” + “the insert does not disrupt” + “it is unlikely that the insert disrupts.”. Why is the conclusion more firm in specific single events?

f) Except for event DAS-40278-9, the text on how the potential ORFs of junction regions forces the reader to make educated guesses on how exactly the analysis was done: threshold size ORF, translation of junction region not mentioned, etc… Please describe accurately (as in DAS case) and in a uniform way how exactly the bioinformatics analysis was performed.

Other comments:

- the word “Conversely” is wrongly used several times in the 1.2.2.2 f) section and in other parts of the text.
- what is meant with “no unexpected risks”. Such phrasing suggests that there are “expected risks”. I suggest to state “no risks”.

1.2.2. Information relating to the genetically modified plant

Have evaluated this section and consider the information adequate: 3 experts

1.2.3. Additional information relating to the genetically modified plant required for the environmental safety aspects

Comment 1

See above remarks in 1.2.1

1.2.4. Conclusions of the molecular characterisation

Have evaluated this section and consider the information adequate: 1 expert

Comment 1

Independent events in the stack are stable and protein expression is as in the single events

1.4. TOXICOLOGY

1.4.1. Testing of newly expressed proteins

Have evaluated this section and consider the information adequate: 1 expert

Comment 1
Appendix 170156 2017 (sequence homology cry1F) seems to be missing.

Note SBB: this appendix was uploaded on the extranet.

1.4.2. Testing of new constituents other than proteins

Have evaluated this section and consider the information adequate: 2 experts

1.4.3. Information on natural food and feed constituents

Have evaluated this section and consider the information adequate: 1 expert

Comment 1
Data for furfural seem to be missing.

Note SBB: The report 151077.H 2017, containing data for furfural, which were all under the LOQ, was uploaded on the extranet.

Note SBB and coordinator: There is no need to assess these data for a GM stacked event.

1.4.4. Testing of the whole genetically modified food or feed

Have evaluated this section and consider the information adequate: 1 expert

Comment 1
Additional information 141086 shows no effect on aad-1 protein in 90-day feeding study

1.4.5. Conclusion of the toxicological assessment

Have evaluated this section and consider the information adequate: 1 expert

3. RISK CHARACTERISATION

No comments received

4. POST-MARKET MONITORING ON THE GENETICALLY MODIFIED FOOD OR FEED

No comments received

7. ADDITIONAL INFORMATION RELATED TO THE SAFETY OF THE GENETICALLY MODIFIED FOOD OR FEED

No comments received