Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Advice of the Belgian Biosafety Advisory Council on application EFSA-GMO-RX-008 (maize 1507 x NK603) from Pioneer Hi-Bred International, Inc. and Dow AgroSciences LLC under Regulation (EC) No. 1829/2003

11 September 2018
Ref. SC/1510/BAC/2018_0705

Context

Application EFSA-GMO-RX-008 was submitted by Pioneer Hi-Bred International, Inc. and Dow AgroSciences LLC for the renewal of authorisation for the marketing of genetically modified (GM) maize 1507 x NK603 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 placing on the market of the insect-resistant and herbicide-tolerant maize 1507 x NK603 for food/feed uses, except cultivation, is currently authorised following a positive opinion of EFSA (EFSA Journal 2006;355, 1-23)[2].

The renewal application was validated by EFSA on 18 April 2017 and a formal three-month consultation period of the Member States was started, lasting until 1 August 2017, 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). Six 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. None of the comments were sent to EFSA.

The opinion of the EFSA Scientific Panel on GMOs was published on 25 July 2018 (EFSA Journal 2018;16(7):5347)[3], together with the responses from the EFSA GMO Panel to comments submitted by the Member States during the three-month consultation period.

The comments formulated by the experts on the renewal application together with the opinion of EFSA, as well as the previous advice of the BAC on maize 1507 x NK603 (BAC_2006_SC_392)[4] and its latest advices already adopted on the single events 1507 (BAC_2009_01368)[5] and NK603 (BAC_2009_01367)[6], form the basis of the advice of the Biosafety Advisory Council on application EFSA-GMO-RX-008 given below.

[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://doi.org/10.2903/j.efsa.2006.355
[3] https://www.efsa.europa.eu/en/efsajournal/pub/5347
[4] http://www.bio-council.be/Advices/BAC_2006_SC_392.pdf
[5] http://www.bio-council.be/Advices/BAC_2009_01368.pdf
[6] http://www.bio-council.be/Advices/BAC_2009_01367.pdf

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Scientific evaluation

The data for application EFSA-GMO-RX-008 provided by the applicant at the time of submission included the annual post-market environmental monitoring (PMEM) reports covering the years of import, two systematic literature searches covering the complete duration of the event's authorisation, an updated bioinformatic package including an analysis of the potential similarity of the newly expressed proteins and newly created open reading frames within the insert or spanning the junctions with genomic DNA to known toxins or allergens, and reports of additional studies performed by the applicant over the course of the authorisation period.

The Belgian experts and the members of the Biosafety Advisory Council did not identify any information elements in the renewal application EFSA-GMO-RX-008 that would raise a safety concern for human or animal health or the environment.

Conclusion

Based on the whole set of data on maize 1507 x NK603 provided by the applicant, the scientific assessment of the dossier done by the Belgian experts, the opinion of EFSA, the original advice of the the BAC on maize 1507 x NK603, and the BAC's latest advices on the single events 1507 and NK603, the Biosafety Advisory Council is of the opinion that in the context of its proposed uses, maize 1507 x NK603 is unlikely to pose any risk to human and animal health.

The Biosafety Advisory Council did not identify any risk that the import and processing of this GM maize could pose to the European environment.

In addition, the Biosafety Advisory Council recommends following up any unanticipated allergenicity aspects of the GM maize in the existing allergenicity monitoring systems.

Dr. Corinne Vander Wauven
President of the Belgian Biosafety Advisory Council

Annex I: Compilation of comments of experts in charge of evaluating the application EFSA/GMO/RX-008 (ref. BAC_2018_0685)

Bioveiligheidsraad
Conseil de Biosécurité

01/09/2017

Secretariaat
Secrétariat

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Compilation of comments of experts in charge of evaluating the application EFSA/GMO/RX-008

Mandate for the Group of Experts: Mandate of the Biosafety Advisory Council (BAC) of 20 June 2017.
Coordinator: Dr. Geert Angenon
Experts: Leo Fiems (ILVO), Johan Grooten (UGent), André Huyghebaert (UGent), Peter Smet (Consultant), Frank Van Breusegem (UGent), Jan Van Doorsselaere (KATO)
SBB: Didier Breyer, Fanny Coppens, Katia Pauwels.

♦ INTRODUCTION

Dossier **EFSA/GMO/RX-008** concerns an application for renewal submitted by the company **Dow AgroSciences** for authorisation to place on the market genetically modified **maize 1507 x NK603** in the European Union, according to Regulation (EC) No 1829/2003 on genetically modified food and feed.
The application has been officially acknowledged by EFSA on 12 May 2017.

The scope of the application is:
☒ 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)

Depending on their expertise, the experts were asked to evaluate the renewal submission, which should contain (1) a copy of the authorisation for placing the food/feed on the market, (2) a report on the results of the monitoring, if so specified in the authorisation (3) any other new information, which has become available, with regard to the evaluation of the safety of the food/feed and the risks of the food/feed to humans, animals or the environment, (4) where appropriate, a proposal for amending or complementing the conditions of the original authorisation, inter alia the conditions concerning future monitoring. Those aspects were evaluated with regards to their molecular, environmental, allergenicity, toxicity and/or food and feed aspects. If information was lacking, the expert was asked to indicate which information should be provided and what the scientifically reasoning is behind this demand.

The comments are structured as in the "Guidance for renewal applications of genetically modified food and feed authorised under Regulation (EC) 1829/2003" (EFSA Journal 2015;13(6):4129). Items are left blank when no comments have been received either because the expert(s) focused on other related aspects, or because for this dossier the panel of experts who accepted to evaluate the dossier didn't have the needed expertise to review this part of the dossier.
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. Comments placed on the EFSAnet are indicated in grey.

List of comments/questions received from the experts

A. GENERAL COMMENTS

Comment 1
The chance that the genetic modification of 1507 x NK603 maize is detrimental for animal and human health and the environment is negligible, so that the authorisation of 1507 x NK603 maize can be renewed.

Because the genetic modified 1507 x NK603 maize is intended to apply glyphosate for weed management, it is interesting that a maximum residue level of 1.0 mg/kg for glyphosate would be respected.
Although 1507 x NK603 maize is not intended for cultivation in the EU, the intensive use of other glyphosate-tolerant GM crops beside 1507 x NK603 maize around the world can result in a fast development of glyphosate-tolerant weeds, so that the sustainability of 1507 x NK603 maize is questionable.

SBB Comment:
The assessment of pesticide use is not within the remit of the Biosafety Advisory Council.

Comment 2
I have some issues with the literature and bioinformatics searches:

- It is not mentioned at all who performed the manual screening of the literature search hits. While this manual screening is crucial and the most prone to human bias, it is totally unclear whether this was performed by independent scientists or instead by staff from the applying companies. This lack of openness undermines in my view the reliability of the search.
- The bioinformatics searches were performed by a staff member from one of the applying companies (Dow). These analyses would be more trustworthy if an independent laboratory had performed them.

It is unclear to me whether EFSA rules require or not independent analyses but as far as I remember from previous dossiers, independent expert labs performed such analyses rather than the applicant.

Coordinator comment :
Literature searches as well as bioinformatics searches for similarities to toxins or allergens, characterization of flanking sequences of inserts etc. are typically done employees of the applying companies

Comment 3
Maize 1507 x NK603 will be further referred to as maize 008.

Comment 4
No comments

B. DATA REQUIREMENTS

B.1. COPY OF AUTHORISATION FOR PLACING THE FOOD/FEED ON THE MARKET

N/A

B.2. POST-MARKET MONITORING AND POST-MARKET ENVIRONMENTAL MONITORING REPORTS

Comment 1
No concerns regarding risk to human and animal health have emerged from the monitoring reports.

Comment 2
Monitoring reports from December 2008 to October 2016 are submitted. Information from importers, operators and processors is summarized.
The applicant concludes from this reports that no adverse effects on human and animal health and the environment have arisen from the import maize 008.
Maize imports in the EU are summarized in tables and commented.
The general surveillance system is described in detail and the role of importers/traders, silo operators and processors is further commented.

I agree with the overall conclusion about the absence of adverse effects.

I have a question about the presence of mycotoxins in maize.
Maize is known to be rather sensitive to the presence of a series of mycotoxins. It is a commodity of interest, included in monitoring plans on the level of member states of the EU.

I wonder how the potential presence of mycotoxins is reported. Food safety agencies of EU member states are in charge of the monitoring aspects. How is the link realized between the data of mycotoxin contamination on the member state level and the post-market monitoring aspects discussed in this report?

SBB Comment:
Post-market monitoring plan (PMM) regarding the use of GM food/feed for human/animal consumption is requested in cases where it is appropriate to verify that the conditions of use are properly applied and to monitor the consumption of the product.

B.3. NEW INFORMATION

B.3.1. SYSTEMATIC SEARCH AND EVALUATION OF LITERATURE:

- search for new scientific information in a comprehensive and structured manner.
- search in all available databases, since the date of authorisation of the event.
- relevant for the three main areas of risk assessment (molecular characterisation, food and feed safety, and the environment).

Comment 1
No comments.

Comment 2

A systematic search of studies published in the scientific literature has been performed on 21 September 2016.

New information has been published in the meantime (Mesnage et al., 2016), dealing with proteome profiles of NK603 maize kernels, and showing alterations in the levels of enzymes of glycolysis and TCA cycle pathways. These alterations may be reflective of an imbalance in energy metabolism, and show that NK603 and its isogenic control may not be substantially equivalent.

Coordinator comment :
EFSA [Broll et al., 2017. Relevance of a new scientific publication (Mesnage et al., 2016) on previous EFSA GMO Panel conclusions on the risk assessment of maize NK603. EFSA supporting publication 2017:EN-1249. doi:10.2903/sp.efsa.2017.EN-1249] has commented extensively on the publication of Mesnage et al. 2016. EFSA considered that there are severe shortcomings in the experimental design, as well as uncertainties on the suitability of the test material as described by Mesnage et al. (2016) and that the interpretation of the results is incomplete, since the authors did not take into account natural variability of the endpoints analysed. EFSA concluded that the publication by Mesnage et al. (2016) does not reveal any new information that would invalidate the previous conclusions on maize NK603 made by the EFSA GMO Panel and considered that the previous risk assessment conclusions on maize NK603 remained valid and applicable.

Comment 3
A comprehensive and systematic search of scientific peer-reviewed open literature has been performed covering the period 2007-2016. This analysis did not reveal concerns relating to human and animal health. (See also my general comment)

Comment 4
No comments

B.3.2. UPDATED BIOINFORMATICS

- similarity searches for known toxic and/or allergenic proteins, using up-to-date databases, for all ORFs between stop codons without applying a size limit.
- information on the similarities of DNA sequences inserted in the plant genome with microbial DNA sequences, with an assessment of potentially altered likelihood for horizontal gene transfer, together with an evaluation of the consequences for human and animal health and the environment.

Comment 1
No comments.

Comment 2
Bioinformatics analysis of the PAT protein using a BLASTp search against an up-to-date NCBI non-redundant protein database did not identify any sequence similarity with any known proteins and antinutritional factors that are harmful to humans or animals. (July 2016)

The results of these data indicate that no biologically relevant sequence similarities were observed between the CP4 EPSPS protein and allergen, toxin, or other biologically active proteins. (Feb. 2016)

Bioinformatics analysis of the Cry1F protein using a BLASTp search against an up-to-date NCBI non-redundant protein database did not identify any sequence similarity with any known proteins that are harmful to humans or animals. (March 2016)

Comment 3
The updated sequence similarity assessment to known allergens by bioinformatics analyses yielded no significant amino acid sequence similarities with known allergens. (See also my general comment)

B.3.3. ADDITIONAL DOCUMENTS OR STUDIES PERFORMED BY OR ON BEHALF OF THE APPLICANT

- any prohibition or restriction imposed by any third country in which the food/feed is placed on the market.
- all unpublished studies performed or sponsored by the applicant and not previously submitted to the EU, with a review and assessment of their relevance for molecular characterisation, human and animal safety and the environment.

Comment 1
No comments.

C. OVERALL ASSESSMENT

- potential identification of new hazards or modified exposure, or new scientific uncertainties, challenging the previous risk assessment.
- new studies in case required by the elements above.

Comment 1
Although alterations in the levels of enzymes of glycolysis and TCA cycle pathways have been found, a clear link between alterations in the NK603 maize (Mesnage et al., 2016) and the possible health effects following long-term consumption of this product remains to be established.

Comment 2
No further remarks.

D. MONITORING PLAN AND PROPOSAL FOR IMPROVING THE CONDITIONS OF THE ORIGINAL AUTHORISATION

Comment 1
Some vigilance is necessary because of the changes in proteins and metabolites of NK603 maize (Mesnage et al., 2016). The general surveillance should check whether unexpected, adverse effects will occur due to the long-term use of 1507 x NK603 maize.

References

Mesnage, R., Agapito-Tenfen, S.Z., Vilperte, V., Renney, G., Ward, M.,Séralini, G.E., Nodari, R.O., Antoniou, M.N. 2016. An integrated multi-omics analysis of the NK603 Roundup-tolerant GM maize reveals metabolism disturbances caused by the transformation process. Sci. Rep. 6, 37855; doi: 10.1038/srep37855.