Bioveiligheidsraad
Conseil de Biosécurité

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Secretariaat
Secrétariat

O./ref.: WIV-ISP/41/BAC/2017_0740

Advice of the Belgian Biosafety Advisory Council on application EFSA-GMO-RX-003 from Pioneer Overseas Corporation and Dow AgroSciences LLC under Regulation (EC) No. 1829/2003

Context

Application EFSA-GMO-RX-003 was submitted by Pioneer Overseas Corporation and Dow AgroSciences LLC on 4 August 2016 for the renewal of authorisation for the marketing of genetically modified (GM) maize 59122 for food and feed uses, import and processing (excluding cultivation) within the European Union (EU), within the framework of Regulation (EC) No. 1829/2003[1].

Maize 59122 contains genes derived from *Bacillus thuringiensis* that express Cry34Ab1 and Cry35Ab1, conferring resistance to rootworms, as well as the gene for the PAT protein from *Streptomyces viridochromogenes*, conferring tolerance to glufosinate-ammonium herbicides.

The placing on the market of maize 59122 for food/feed uses, except cultivation, is currently authorised by Commission Decision 2007/702/EC of 24 October 2007 (application EFSA-GMO-NL-2005-12), following a positive opinion of EFSA on 23/03/2007 (http://www.efsa.europa.eu/en/efsajournal/pub/470), and a positive advice of the BAC on 14/06/2007. The event sequence considered in the context of this renewal application was corrected for sequencing errors in three single nucleotides in comparison to the sequence assessed in the original application.

The application was officially acknowledged by EFSA on 20 September 2016 and a formal three-month consultation period of the Member States was started, 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 Biosafety and Biotechnology Unit (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.

The opinion of the EFSA Scientific Panel on GMOs was adopted on 18 May 2017 (EFSA Journal 2017;15(6):4861[2]), and published on 29 June 2017 together with the responses from

[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] See https://www.efsa.europa.eu/en/efsajournal/pub/4861

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the EFSA GMO Panel to comments submitted by the Member States during the three-month consultation period.
On 10 August 2017 the opinion of EFSA was forwarded to the Belgian experts. They were invited to give comments and to react if needed.

The comments formulated by the experts together with the opinion of EFSA, as well as the advices already adopted by the BAC on stacked events containing maize 1507 and the advices already adopted by the BAC on other GM single events expressing the Cry34Ab1, Cry35Ab1 and/or the PAT protein(s), form the basis of the advice of the Biosafety Advisory Council given below.

Scientific evaluation

1. Post-market environmental monitoring

The Biosafety Advisory Council welcomes the annual post-market environmental monitoring (PMEM) reports provided by the applicant during the period October 2007 to June 2015, and takes note of the absence of adverse effects reported by the applicant during the authorisation period of maize 59122.

2. Systematic search and evaluation of literature

The Biosafety Advisory Council welcomes the systematic literature search covering the complete duration of the event's authorisation conducted by the applicant following the principles outlined in the relevant EFSA guidance.
The Council agrees with the GMO panel of EFSA that none of the scientific publications relevant for the risk assessment of maize 59122 identified from this literature search raise any new concerns regarding the safety for human or animal health or the environment.

3. Updated bioinformatics

The Biosafety Advisory Council agrees with the GMO panel of EFSA that the updated bioinformatics analyses for GM maize 59122 do not indicate any safety concern, as no known endogenous genes are interrupted by the inserts, the newly expressed proteins do not present significant similarities to known toxins or allergens, and the expression of an open reading frame showing significant similarities to toxins or allergens is highly unlikely.

4. Additional documents or studies

The Biosafety Advisory Council welcomes the reports of additional studies performed by the applicant over the course of the authorisation period with regard to the evaluation of the safety of the food/feed and the risks of the food/feed to humans, animal or the environment from maize 59122.
The Council agrees with the GMO panel of EFSA that this new information does not raise any concern for human and animal health, and the environment.

5. Overall assessment

The Biosafety Advisory Council agrees with the GMO panel of EFSA that no new information has given rise to any concern for human or animal health or the environment.

6. Monitoring plan and proposal for improving the conditions of the original authorisation

Since the allergenicity of the whole GM maize has not been fully assessed, it is recommended to take up monitoring of allergenicity as part of the general surveillance.

Conclusion

Based on the scientific assessment of the dossier done by the Belgian experts, taking into account the opinion of EFSA, the previous advice of the BAC on maize 59122, the advices already adopted by the BAC on stacked events containing maize 59122 and the advices already adopted by the BAC on other GM single events expressing the Cry34Ab1, the Cry35Ab1 and/or the PAT protein, and considering the new information provided by the applicant, the Biosafety Advisory Council is of the opinion that in the context of its proposed uses, maize 59122 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.

Prof. Maurice De Proft
President of the Belgian Biosafety Advisory Council

Annex I: Compilation of comments of experts in charge of evaluating the application EFSA/GMO/RX-003 and Comments submitted on the EFSAnet on mandate of the Biosafety Council (ref. BAC_2016_0822)

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Compilation of comments of experts in charge of evaluating the application EFSA/GMO/RX-003
and
Comments submitted on the EFSAnet on mandate of the Biosafety Council

Mandate for the Group of Experts: Mandate of the Biosafety Advisory Council (BAC) of 5 October 2016.
Coordinator: Dr. Geert Angenon
Experts: Eddy Decuypere (KUL), Patrick du Jardin (ULg), 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-003** concerns an application for renewal submitted by the companies **Pioneer and Dow AgroSciences** for authorisation to place on the market genetically modified **maize 59122** 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 19 September 2016.

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
There is no reason why the authorisation of import and processing of genetically modified maize 59122 for food and feed use cannot be renewed. No new data or information became available, indicating that maize 59122 as such may not be safe for human and animal health in comparison with conventional maize.
However, the increased use of glyphosate-tolerant genetically modified crops and the resistance to Cry34/35Ab1 maize, and the presence of resistance to multiple Bt toxins by western corn rootworm, highlight the potential vulnerability of Bt crops. Therefore, extra attention should be paid to the sustainability of the use of maize 59122.

SBB Comment:
The assessment of pesticide use is not within the remit of the Biosafety Advisory Council.
Coordinator Comment:
59122 maize contains the *pat* gene from *Streptomyces viridochromogenes*, which encodes the PAT protein that confers tolerance to glufosinate-ammonium; it does not contain a glyphosate resistance gene.

Comment 2
No comments.

Comment 3
None

Comment 4
No comments.

B. DATA REQUIREMENTS

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

Comment 1
No questions.

Comment 2
None

Comment 3
Renewal of authorization of maize 59122, authorized since October 2007.

Comment 4
No comments.

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

Comment 1
No questions.

Comment 2
The analysis performed by the applicant seems OK. However, the extrapolations, estimations and assumptions made illustrate the difficulty to perform this monitoring exercise, hence the uncertainty of its conclusions. However, I see no safety issue here, but a regulatory issue.

Comment 3
Monitoring reports have been submitted regularly to the European Commission.
The applicant concludes that no adverse effects on human or animal health or on the environment have been reported during the eight -year period.
The report contains detailed statistics on the import of maize in EU member states.
The surveillance program is described in detail involving all interested parties among others the European Trade Organizations (importers, silo operators and processors). These organisations represent the whole processing chain.

I have no comments or questions about the overall conclusion of the applicant.

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 questions.

Comment 2
None

Comment 3
No remarks or concerns: the search string used was comprehensive in its coverage and included sufficient positive controls (known relevant papers) as checks for the accuracy of the search; the search did not reveal any concern for human and animal health of the genetically modified food.

Comment 4
No comments.

Comment 5
No comment on the molecular characterization.

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
An up-to-date similarity search was performed for the 3 proteins (July 2016). None of the protein sequences returned by the BLASTP search identified any safety concerns from the expression of Cry34Ab1, Cry35Ab1 and PAT protein in genetically modified plants.

Comment 2
Scopus and CAB are indeed the most important databases for scientific literature. No scientific literature was published between 2007 and 2016 that could raise any concern for human and animal health by the use of maize 59122. Therefor the conclusions of the previous safety assessment of maize 59122 have not to be changed

Comment 3
It is interesting to note that resequencing of the 59122 insert identified three mistakes in the original sequence previously risk assessed (in 2007). However, this raises no safety concern as the three nucleotide changes are located outside of the protein-coding regions, and considering that the updated bioinformatic analysis of all newly created ORFs was performed using the corrected sequence in the context of this renewal application. The PCR-based detection method is also unaffected by the sequence update.

Comment 4
No remarks or concerns regarding allergenicity of the introduced traits and/or the GM plant: the performed sequence similarity assessments to known allergens by bioinformatics analyses of the newly expressed proteins Cry34Ab1, Cry35Ab1 and PAT have been updated to 2016 allergen databases. This update yielded no significant amino acid sequence similarities with any known allergens.

Comment 5
No comments.

Comment 6
No comments.

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 questions.

Comment 2

The applicant lists studies (in table 9) performed for the purpose of authorizations outside of EU. A summary is given of the main results. Although no discrepancy is mentioned between these studies and those introduced in the dossier submitted to the EU regulatory bodies, hence raising no issue in the context of this dossier, I wonder how the experts could deal with such discrepancies in the absence of the full reports of these additional studies. For the same reason, the experts are not able to verify the conclusions of the applicant regarding these additional studies.

Comment 3
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
The resistance to Cry34/35Ab1 toxins and to multiple Bt toxins by western corn rootworm (Cullen et al., 2013; Tabashnik et al., 2013; Jakka et al., 2016) requires special attention to the sustainability of pest management and the use of maize 59122, considering the pending application for authorisation for cultivation of maize 59122 in the EU (see Part II Scientific Information, P.9, 2.3.1.1.).

Because of the controversy 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). The future use of maize 59122 may be modified according to the results of such a new examination.

SBB Comment:
The assessment of pesticide use is not within the remit of the Biosafety Advisory Council.
Coordinator Comment:
59122 maize contains the *pat* gene that confers tolerance to glufosinate-ammonium; it does not contain a glyphosate resistance gene.

Comment 2
No questions.

Comment 3
Although single events and stacks containing the same events are subjected to separate assessments and authorizations, it is difficult to separate both in the context of post-market monitoring. In the conclusions of the applicant, and having regard to the different stacked maize containing the 59122 event (cfr table 6), it is not clear to me whether the data given for the single event ("less than 0.6% of total maize imports") is representative of the total of 59122 or whether approved stacks also contribute to the imports of 59122, in which case it seems logical to take them into account in the exposure assessment. I could find no information in the dossier regarding the import of approved 59122-containing stacks. I see no safety issue here, since no hazards and risks were identified, but a consistency issue from a regulatory perspective.

Comment 4

No new potential hazards with regards to allergenicity of the GM plant and its derivatives have been identified that would invalidate the previous conclusions on the safety of maize 59122.

Comment 5
No comments.

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

Comment 1
No questions.

Comment 2
Could future monitoring reports address the comment above about the necessity to consider grouped data of both single events and stacks, which seem the only relevant for exposure assessment ? Again, this is more a regulatory issue than a safety concern in this dossier.

Comment 3
A question: does monitoring also include consumer health reports from other continents than Europe where the GM maize is less diluted with wild type maize? The inclusion of such reports in the monitoring plan might help to better (faster) recognize possible consumer (!) health problems such as allergic sensitization. Europe being largely self-sufficient regarding maize, imported GM maize (such as maize 59122) will be largely diluted with European maize.

References

Cullen, E.M., Gray, M.E., Gassmann, A.J., Hibbard, B.E. 2013. Resistance to Bt corn by western corn rootworm (Coleoptera: Chrysomelidae) in the U.S. corn belt. J. Integ. Pest Mngmt. 4, IPM13012 (6 pp).

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Myers, J.P., Antoniou, M.N., Blumberg, B., Carroll, L., Colborn, T., Everett, L.G., Hansen, M., Landrigan, P.J., Lanphear, B.P., Mesnage, R., Vandenberg, L.N., vom Saal, F.S., Welshons, W.V., Benbrook, C.M. 2016. Concerns over use of glyphosate-based herbicides and risks associated with exposures: a consensus statement. Environ. Health 15, Article 19 (13 pp).

Tabashnik, B.E., Brévault, T., Carrière, Y. 2013. Insect resistance to Bt crops: lessons from the first billion acres. Nat. Biotechnol. 31, 510-521.