Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Advice of the Belgian Biosafety Advisory Council on application EFSA-GMO-DE-2017-142 (maize MZIR098) from Syngenta under Regulation (EC) No. 1829/2003

30 September 2020
Ref. SC/1510/BAC/2020_0871

Context

Application EFSA-GMO-DE-2017-142 was submitted by Syngenta for the authorisation of the marketing of genetically modified (GM) maize MZIR098 for food and feed uses, import and processing (excluding cultivation) within the European Union, within the framework of Regulation (EC) No. 1829/2003[1].

Maize MZIR098 contains a single insert expressing the eCry3.1Ab, mCry3A and PAT proteins, conferring resistance to certain coleopteran pests and tolerance to glufosinate-ammonium-containing herbicides respectively.

The application was validated by EFSA on 11 August 2017 and a formal three-month consultation period of the Member States was started, lasting until 13 November 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 Biosafety and Biotechnology Unit (SBB). Seven 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 sent to EFSA on 13 November 2017.

The opinion of the EFSA Scientific Panel on GMOs was published on 26 June 2020 (EFSA Journal 2020;18(6):6171[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 10 July 2020, with an invitation to react if needed.

In delivering the present advice, the BAC considered in particular the comments formulated by the experts on application EFSA-GMO-DE-2017-142 and the opinion of EFSA.

[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/6171

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Scientific evaluation

1. Environmental risk assessment

The Biosafety Advisory Council is of the opinion that it is unlikely that the accidental release of maize MZIR098 (i.e. during transport and/or processing) into the European environment[3] will lead to environmental harm.

2. 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.

3. Assessment of food/feed safety and nutritional value

3.1. Assessment of compositional analysis

The Biosafety Advisory Council agrees with the GMO panel of EFSA that the compositional data of GM maize MZIR098, in comparison with its conventional counterpart, do not raise safety concerns.

3.2. Assessment of toxicity

The Biosafety Advisory Council agrees with the GMO panel of EFSA that the available data on the toxicity of GM maize MZIR098, in comparison with its conventional counterpart, does not raise safety concerns.

3.3. Assessment of allergenicity

The Biosafety Advisory Council has evaluated the safety of the newly expressed eCry3.1Ab, mCry3A and PAT 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.

3.4. Nutritional value

The Biosafety Advisory Council is of the opinion that the information provided is sufficient to conclude that the nutritional characteristics of maize MZIR098-derived food and feed are not expected to differ from those of conventional maize varieties.

4. Monitoring

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

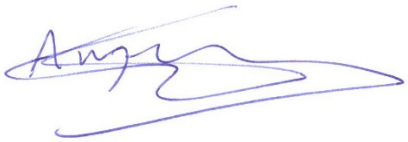
[3] As the application doesn't imply cultivation of the GM crop in the EU, a full environmental assessment as in the case of a cultivation file is not warranted.

Conclusion

Based on the whole set of data on maize MZIR098 provided by the applicant, the scientific assessment of the dossier done by the Belgian experts, the opinion of EFSA, and the answers of the EFSA GMO panel to the questions raised by the Belgian experts, the Biosafety Advisory Council:

1) Agrees with the GMO panel of EFSA that the potential environmental release of maize MZIR098 is unlikely to pose any threat to the European environment;
2) Agrees with the GMO panel of EFSA that in the context of its proposed uses, maize MZIR098 is unlikely to pose any risk to human and animal health;

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



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

Annex I: Compilation of comments of experts in charge of evaluating the application EFSA-GMO-DE-2017-142 and comments sent to EFSA (ref. BAC_2017_0887)

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Conseil de Biosécurité

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13/11/2017

Compilation of comments of experts in charge of evaluating the application EFSA/GMO/DE/2017/142
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 17 August 2017.
Coordinator: Prof. Geert Angenon
Experts: Patrick du Jardin (Ulg), Leo Fiems (ILVO), Johan Grooten (UGent), André Huyghebaert (UGent), Peter Smet (Consultant), Frank Van Breusegem (UGent), Jan Van Doorsselaere (Vives)
SBB: Didier Breyer, Fanny Coppens, Katia Pauwels.

- **INTRODUCTION**

Dossier **EFSA/GMO/DE/2017/142** concerns an application submitted by the company **Syngenta** for authorisation to place on the market genetically modified **maize MZIR098** 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 11 August 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 genetically modified plant considered in the application on its 1) molecular, 2) environmental, 3) allergenicity, 4) toxicity and/or 5) food and feed aspects. It was expected that the expert should evaluate if 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.

The comments are structured as in the "Guidance document of the scientific panel on genetically modified organisms for the risk assessment of genetically modified plants and derived food and feed" (EFSA Journal (2004), 99, 1-94). 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

PART I - GENERAL INFORMATION

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

Comment 1
MZIR098 maize may be as safe for human and animal health and the environment as conventional maize based on the results of the compositional analysis and the toxicological and allergenicity assessment.
However, multiple resistance of corn rootworm against Cry toxins (Gassmann et al., 2014; Wangila et al., 2015; Gassmann et al., 2016; Jakka et al., 2016; Zukoff et al., 2016) results in a lack of efficiency with regard to a sustainable crop protection and production. This may be due to the fact that the toxins in genetically modified Bt corn are not high dose against the northern corn rootworm, so that it is difficult to achieve the diagnostic dose (Oyediran et al., 2016). Furthermore, the non-recessive inheritance of resistance and the minimal fitness costs may provoke a rapid evolution of resistance to Cry proteins by corn rootworm (Paolino and Gassmann, A.J. 2017). Even if MZIR098 maize is not intended for cultivation in the EU, it highlights the potential vulnerability of genetically modified Bt crops.

Coordinator comment: resistance to Bt toxins is a known phenomenon and needs to be addressed by resistance management strategies, however this is not a biosafety risk.

PART II - SCIENTIFIC INFORMATION

1. HAZARD IDENTIFICATION AND CHARACTERISATION

1.1. INFORMATION RELATING TO THE RECIPIENT OR (WHERE APPROPRIATE) PARENTAL PLANTS

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

1.2. MOLECULAR CHARACTERISATION

1.2.1. Information relating to the genetic modification

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

1.2.2. Information relating to the genetically modified plant

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

Comment 1
In the bioinformatic analysis of the newly created ORFs internal to the insert (appendix 1.2.10), the applicant identified several hits with allergens exceeding the statistical significance threshold criteria. In order to evaluate the biological relevance of these results, the applicant assessed the likelihood of expression based on the location of the regions of similarity within the insert (transcribed vs. non transcribed strand, presence of ATG codon, intron vs. exon sequence, etc). Furthermore, the sequences showing similarity are all of low complexity, which lowers their significance. Taken together, I consider that all these data are not indicative of a risk of allergenicity.

Comment 2
Protein concentrations are all expressed on a fresh weight basis which makes comparing with other dossiers difficult. Can data be provided on a dry weight basis?

Comment 3
p31: …>99,99% confidence that there are no detectable extraneous plasmid…
Where does this mathematical number come from? Southern blots either show presence or absence of (pieces of) backbone.

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

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

1.2.4. Conclusions of the molecular characterisation

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

1.3. COMPARATIVE ANALYSIS

1.3.1. Choice of the conventional counterpart and additional comparators

Have evaluated this section and consider the information adequate: 5 experts

1.3.2. Experimental design and statistical analysis of data from field trials for comparative analysis

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

1.3.3. Selection of material and compounds for analysis

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

Comment 1
Comments with respect to the selection of compounds for analysis of grain:
- the OECD guidelines are followed,
- total dietary fiber and starch are included although not on the OECD list; the applicant recognises the importance of both constituents for human nutrition in contrast to other applications for maize
- no information about other carotenoids than beta-carotene; as mentioned before maize is a source of lutein and zeaxanthin in human nutrition; both are important for eye health,
- no information on phytosterols, constituents with a positive effect on cholesterol metabolism in humans,
- no information on tocopherols and tocotrienols; in response to this comment in a previous applications it was stated that information on alpha-tocopherol is adequate as it is the major constituents for vitamin E activity; no doubt about this reaction but the problem is not the vitamin E activity; the question is about the anti-oxidative activity of tocopherols and tocotrienols; it is well known that vitamin activity and anti-oxidative properties are inversely related; maize germ oil is a highly

unsaturated oil, stable in maize germs but unstable once isolated from the germs; under normal conditions the oil is protected against oxidation by tocopherols and tocotrienols; data on these constituents would confirm the functionality of maize germ oil in terms of oxidation stability.

I accept that the applicant followed the OECD guidelines from 2002 with some additions but the actual knowledge about maize oil and maize in general is more advanced than in 2002. A revision of the guidelines is urgently needed.

Results of the statistical analysis are discussed in detail with particular attention for cases of non-equivalence. The biological significance of the findings is discussed.

It is concluded that the levels of the vast majority of nutritional components of maize MZIR098 are equivalent to those in the non-transgenic reference lines and are not significantly different from those of in the non-transgenic, near-isogenic control maize

My addition to this conclusion is that maize MZIR098 is equivalent as far as major constituents are studied according to the OECD guidelines of 2003.

1.3.4. Comparative analysis of composition

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

Comment 1

Some compounds of MZIR098 maize were significantly different from the conventional maize. It may be recognized that if a compositional variation is detected, this should not be inferred as representing a de facto hazard. About half of the stack ranges with values outside of the prediction intervals occur among the minerals, which are not metabolized by the plant but are influenced by environmental conditions as soil type and fertilization (Kramer et al., 2016). Furthermore, a recent study reported that the heterogeneity is rising in maize since 2000, both between and within fields (Lobell and Azzari, 2017). However, differences are not considered as relevant, because they were within the range of reference varieties.

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Comment 2

See previous paragraph under 1.3.3.

1.3.5. Comparative analysis of agronomic and phenotypic characteristics

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

Comment 1

I have evaluated the agro/pheno characterization part. The applicant made it clear (see Appendix D of report 1.3.2) that the agronomic equivalence assessment could not use formal statistics for the evaluation of four plant characteristics: early stand count, days to 50% pollen shed, days to 50% silking and total lodging, due to the low number of values not showing the normal variation required for the ANOVA analysis of these endpoints. Although the descriptive statistics used are presumably not fully in line with the requirements of EFSA guidance and implementing regulation, I consider that the arguments are sufficient, taking into account the scope of the application (import and processing).

Comment 2

As mentioned in other applications, information on the resistance to mould infections would be welcome. Maize is known to be one of the major sources of mycotoxin exposure of humans and animals.

1.3.6. Effects of processing

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

1.3.7. Conclusion

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

Comment 1
I basically agree with the conclusion.

1.4. TOXICOLOGY

1.4.1. Testing of newly expressed proteins

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

Comment 1
The chance that the new proteins of MZIR098 maize (eCry3.1Ab, mCry3A and PAT) will pose serious risks for toxicity is negligible. There is no plausible or testable hypothesis for an interaction of the new proteins in MZIR098 maize (Steiner et al., 2013). WHO (1995) stated that, when two plants that are substantially equivalent to conventional varieties are crossed by conventional breeding, the stacked event is expected to be substantially equivalent to the single events.

Comment 2
I evaluated the protein equivalence testing: equivalence of the microbial-expressed proteins with the plant-expressed proteins, and identity with previously assessed Cry proteins (events 5307 and MIR604) are demonstrated.

1.4.2. Testing of new constituents other than proteins

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

1.4.3. Information on natural food and feed constituents

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

1.4.4. Testing of the whole genetically modified food or feed

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

1.4.5. Conclusion of the toxicological assessment

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

1.5. ALLERGENICITY

1.5.1. Assessment of allergenicity of the newly expressed protein

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

Comment 1
The risk analysis was performed in accordance with the requirements by EFSA. In line with previous risk assessments by EFSA and the history of safe use, this analysis did not reveal a risk for allergenicity of the newly expressed eCry3.1Ab, mCry3A and PAT proteins. Also the repeated dose 28-day oral toxicity and 90-day feeding studies performed as part of the toxicological risk assessment, did not indicate a health risk.

The studies were well performed and well reported. Accordingly, I comply with the applicant's conclusion that the newly expressed eCry3.1Ab, mCry3A and PAT proteins are unlikely to have any allergenic potential.

I have no further comments.

1.5.2. Assessment of allergenicity of the whole genetically modified plant

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

Comment 1
I comply with the applicant's conclusion that the results of the compositional analyses and 90-day rat feeding study along with the overall allergenic safety profile of maize-derived food make it unlikely that MZIR098 would have an increased allergenic potential as compared to conventional maize.

I have no further comments.

1.5.3. Conclusion of the allergenicity assessment

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

1.6. NUTRITIONAL ASSESSMENT

1.6.1. Nutritional assessment of the genetically modified food

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

1.6.2. Nutritional assessment of the genetically modified feed

Comment 1

Some compounds of MZIR098 maize were significantly different from conventional maize. Therefore, a general surveillance should be used to evaluate if the observed difference poses a risk to food and feed safety or the environment.

1.6.3. Conclusion of the nutritional assessment

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

2. EXPOSURE ASSESSMENT — ANTICIPATED INTAKE OR EXTENT OF USE

Comment 1
No combined MOE, as proposed by Wilkinson et al. (2000) and Meek et al. (2011), was presented for the 3 proteins in MZIR maize. However, no risk is expected due to the low concentrations.

3. RISK CHARACTERISATION

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

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

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

5. ENVIRONMENTAL RISK ASSESSMENT (ERA)

5.1. INTRODUCTION

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

5.2. GENERAL APPROACH OF THE ERA

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

5.3. SPECIFIC AREAS OF RISK

5.3.1. Persistence and invasiveness including plant-to-plant gene flow

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

5.3.2. Plant to micro-organisms gene transfer

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

5.3.3. Interactions of the GM plant with target organisms

Comment 1
Gassmann et al. (2014) and Jakka et al. (2016) reported a significant interaction between corn rootworm population type and maize hybrid.

5.3.4. Interactions of the GM plant with non-target organisms (NTOs)

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

5.3.5. Impacts of the specific cultivation, management and harvesting techniques

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

5.3.6. Effects on biogeochemical processes

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

5.3.7. Effects on human and animal health

Comment 1
No adverse effects of the new protein in MZIR maize (eCry3.1Ab, mCry3A and PAT) on human and animal health are expected.

5.3.8. Overall risk evaluation and conclusions

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

6. POST-MARKET ENVIRONMENTAL MONITORING PLAN (PMEM)

6.1. INTERPLAY BETWEEN ENVIRONMENTAL RISK ASSESSMENT, RISK MANAGEMENT AND PMEM

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

6.2. CASE-SPECIFIC GM PLANT MONITORING (STRATEGY, METHOD AND ANALYSIS)

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

6.3. GENERAL SURVEILLANCE FOR UNANTICIPATED ADVERSE EFFECTS (STRATEGY, METHOD)

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

6.4. REPORTING THE RESULTS OF PMEM

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

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

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

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