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DATUM	22 juni 2023
KENMERK	CGM/230622-01
ONDERWERP	Advies hernieuwing vergunning voor import van gg-maïs MON89034x1507xMON88017x59122

Geachte mevrouw Heijnen,

Naar aanleiding van een aanvraag voor de hernieuwing van de vergunning voor import en verwerking van genetisch gemodificeerde (gg-)maïs MON89034x1507xMON88017x59122 (GMFF-2022-9170), gezamenlijk ingediend door Bayer Agriculture BV en Corteva Agriscience Belgium B.V., deelt de COGEM u het volgende mee.

Samenvatting:
De COGEM is gevraagd te adviseren over de hernieuwing van de vergunning voor import en verwerking van genetisch gemodificeerde (gg-)maïs MON89034x1507xMON88017x59122 en een deel van diens nakomelingen (subcombinaties). De eerdere vergunning is in 2013 voor een periode van 10 jaar afgegeven. Deze gg-maïs is verkregen door vier gg-maïslijnen met elkaar te kruisen en brengt de *cry1A.105*, *cry2Ab2*, *cry1F*, *cp4epsps*, *cry3Bb1*, *cry34Ab1*, *cry35Ab1* en *pat* genen tot expressie. Deze gg-maïs is resistent tegen bepaalde insecten, en tolerant voor glyfosaat en glufosinaat-ammonium-bevattende herbiciden. De COGEM heeft in 2009 positief geadviseerd over de import en verwerking van deze gg-maïs. De hernieuwingsaanvraag bevat o.a. geactualiseerde bio-informatische analyses, een recente literatuurstudie en de resultaten van de verplichte 'post-market environmental monitoring' die sinds 2014 is uitgevoerd. Hieruit komen geen nieuwe zaken naar voren die de eerdere conclusie, dat import van deze gg-maïs een verwaarloosbaar klein milieurisico vormt, veranderen. Verwildering van maïsplanten is in Nederland nooit waargenomen. Bovendien komt de wilde verwant van maïs (teosinte) niet in de natuurlijke omgeving in Nederland voor, waardoor de kans dat de ingebrachte genetische eigenschappen zich naar een andere soort kunnen verspreiden, te verwaarlozen is.

De COGEM is van oordeel dat de risico's voor mens en milieu van import van gg-maïs MON89034x1507xMON88017x59122 en diens nakomelingen (alle subcombinaties) verwaarloosbaar klein zijn. Omdat een voedselveiligheidsbeoordeling door andere instanties wordt uitgevoerd, heeft de COGEM de risico's van incidentele consumptie niet beoordeeld.

De door de COGEM gehanteerde overwegingen en het hieruit voortvloeiende advies treft u hierbij aan als bijlage.

Hoogachtend,

Prof. dr. ing. Sybe Schaap
Voorzitter COGEM

c.c.

- Drs. Y. de Keulenaar, Hoofd Bureau ggo
- Ministerie van IenW, Directie Omgevingsveiligheid en Milieurisico's DG Milieu en Internationaal
- Ing. M.A.C. Möllers, Food-Feed loket

Renewal of the authorisation for import and processing of genetically modified maize MON89034x1507xMON88017x59122 and part of its subcombinations

COGEM advice CGM/230622-01

- The present application (GMFF-2022-9170) concerns the renewal of the authorisation for import and processing for use in feed and food of genetically modified (GM) maize MON89034x1507x MON88017x59122 and part of its subcombinations;
- GM maize MON89034x1507xMON88017x59122 and part of its subcombinations were previously authorised for import and processing in 2013;

- MON89034x1507xMON88017x59122 maize was developed by conventional crossbreeding of GM maize MON89034, 1507, MON88017 and 59122;
- GM maize MON89034x1507xMON88017x59122 expresses the genes *cry1A.105*, *cry2Ab2* (MON89034), *cry1F* (1507), *cp4epsps*, *cry3Bb1* (MON88017), *cry34Ab1*, *cry35Ab1* (59122) and *pat* (1507 and 59122). The *cry*-genes confer resistance to insect pests, and the *cp4epsps* and *pat* genes confer tolerance to glyphosate and glufosinate-ammonium containing herbicides, respectively;

- In the Netherlands, feral maize populations have never been observed and the appearance of volunteers - maize not deliberately planted - is rare;
- The wild relative of maize (teosinte) is not present in het natural environment of the Netherlands, therefore hybridisation of GM maize with other species is not possible;

- The molecular characterisation of maize MON89034x1507xMON88017x59122 has been updated and meets the criteria of COGEM;
- The updated bioinformatics analyses, literature review and monitoring reports do not give any indication of a potential environmental risk;

- COGEM is of the opinion that import and processing of maize MON89034x1507x MON88017x59122 and its subcombinations poses a negligible risk to the environment in the Netherlands;
- COGEM abstains from giving advice on the potential risks of incidental consumption since other organisations carry out a food/feed assessment.

1. Introduction

The present application (GMFF-2022-9170), a joint application filed by Bayer Agriculture BV and Corteva Agriscience Belgium B.V., concerns the renewal of the authorisation for food, feed, import and processing of genetically modified (GM) maize (*Zea mays*) MON89034x1507xMON88017x 59122 and part of its subcombinations. This authorisation was granted in 2013 (2013/650/EU).[1] Since market authorisations remain valid for a period of 10 years, the applicant filed an application for the renewal of the authorisation granted in 2013. The application contains, amongst others, monitoring reports, updated bioinformatics analyses, and a systematic literature search.

2. Previous COGEM advice

COGEM advised positively on import and processing of MON89034, 1507, MON88017, 59122, 1507x59122 and MON89043xMON88017.[2,3,4,5,6,7] In 2009, COGEM advised positively on import and processing of MON89034x1507xMON88017x59122.[8]

3. Environmental risk assessment

3.1 Characteristics of maize

Maize (*Zea mays*) is a member of the grass family *Poaceae*. It is a highly domesticated crop originating from Central America, but nowadays cultivated globally. Maize is wind pollinated[9,10] and has both male and female flowers that are spatially separated. The female flowers are not attractive to insect pollinators, because they do not produce nectar. Insect pollination of maize is highly limited but cannot be excluded.[11] Hybridisation of GM maize with other species than teosinte, the wild relative of maize, cannot occur.

Maize does not tolerate prolonged cold and frost,[12] and requires warm conditions in order to grow.[11,13] In cultivation areas with warm climatic conditions, volunteers – i.e. maize not deliberately planted – may be present the year following maize cultivation due to spilled cobs or kernels. However, these volunteers are usually killed by common mechanical pre-planting soil preparation practices.[11]

Maize is very sensitive to weed competition.[14] During the long process of domestication, maize has lost the ability to persist in the wild.[10] A soil seed bank, small seeds, and an extended period of flowering and seed production are characteristics often observed in persistent weeds.[15] Maize lacks all these characteristics. After ripening, the seeds (the kernels) adhere to the cob and do not scatter naturally.[11,16] Consequently, seed dispersal is severely hampered.

3.2 Receiving environment

In the Netherlands, the appearance of maize volunteers is rare, although maize plants occasionally have been observed outside agricultural fields.[17,18] Any volunteers emerging will be killed by frost at the onset of winter.[12] COGEM is not aware of any reports of feral maize populations in the Netherlands. Maize can hybridise with teosinte, the wild relative of maize. However, as teosinte is absent in maize fields and in nature in the Netherlands,[12] hybridisation of GM maize with teosinte will not occur in the Netherlands.

Conclusion: In the Netherlands, feral maize populations do not occur and hybridisation of maize with other species is impossible.

3.3 Description of the introduced genes, traits and regulatory elements

MON89034x1507xMON88017x59122 maize was developed by conventional crossbreeding of GM MON89034, 1507, MON88017 and 59122 maize. MON89034, MON88017 and 59122 were obtained by *Agrobacterium*-mediated transformation, using a plasmid containing a T-DNA insert with expression cassettes. GM maize 1507 was obtained by biolistics-mediated transformation using a DNA fragment.

MON89034 contains genes to produce Cry1A.105 and Cry2Ab2, which confer resistance to certain lepidopteran insects such as the fall armyworm (*Spodoptera* sp.), the black cutworm (*Agrotis ipsilon*) and the corn earworm (*Helicoverpa zea*). GM maize 1507 is modified to express a synthetic truncated *cry1F* gene and a *pat* gene. The Cry1F protein confers protection to damage by the European corn borer, PAT confers resistance to glufosinate-ammonium containing herbicides. MON88017 produces CP4 EPSPS and Cry3Bb1. CP4 EPSPS provides tolerance to glyphosate, Cry3Bb1 confers resistance to certain coleopteran insects such as the corn rootworm (*Diabrotica virgifera*). GM maize 59122 is modified to produce Cry34Ab1, Cry35Ab1 and PAT. The Cry34Ab1 and Cry35Ab1 proteins provide protection from feeding damage by the corn rootworm (*Diabrotica* spp.).

3.4 Updated bioinformatics analyses

The applicant updated the bioinformatic analyses of MON89034, 1507, MON88017 and 59122 using databases assembled in January 2022. For each GM maize, the location of the insert in the maize genome was determined. The potential disruption of endogenous genes was also assessed, using the most-recent version of the GenBank maize B-73 reference genome. Furthermore, the insert and the junctions with its 5’ and 3’ flanking regions were bioinformatically analysed from stop-to-stop codon in all six potential reading frames. The sequences were used for comparisons with updated toxin database and protein sequence databases. The results are discussed below.

Assessment of the insertion site of the MON89034 T-DNA indicated that the insert is likely to be located on chromosome 1. The sequences of the 5’ and 3’ regions were aligned to the B-73 reference genome. The sequences of the 5’ and 3’ regions did not align to adjacent regions of the B-73 reference genome. According to the applicant, the gap in the alignment is likely the result of germplasm differences between the transformed line and the B73 maize assembly. No endogenous genes were disrupted by the insert.

The analyses using updated databases show alignments with hypothetical proteins of rice (*Oryza sativa* Japonica group) of which no additional information was listed with the accession number, and an alignment which was punctuated with stop codons in the query sequence and required gaps to optimise the alignment. No alignments with known toxic proteins, harmful to humans or animals, were found.

The applicant updated the bioinformatic analyses of the GM maize 1507 insert. As the sequence of the insert in 1507 has previously been corrected, the applicant used both the originally reported 1507 insert sequence and the corrected 1507 insert sequence which differs by four base pairs (1) a decrease in Cs in a poly-C region, (2) a G-to-A substitution in the *cry*1F gene, (3) a C-to-T in the *pat* gene and (4) an increase in Cs in another poly-C region.

The applicant reports that the insert is likely to be located on chromosome 2 and did not disrupt endogenous genes. Analysis of the sequences using the updated databases show alignments with sequences annotated as hypothetical proteins or non-toxic proteins.

Assessment of the insertion site of the MON88017 T-DNA indicates that a putative and uncharacterized gene is disrupted at the 5' end of the insert. The gene encodes a protein that shares homology with *Arabidopsis thaliana* purine permease 11. Two permeases from the same family have been characterized to mediate adenine uptake and cytokinin transport, functions of remaining family members remain unclear. The applicant states that the disruption of this gene does not appear to have a negative impact on MON88017 plants.

Analysis of the sequences using the updated databases show alignments with hypothetical proteins of rice (*Oryza sativa*), which revealed to be the reverse complement strand of *ract1* promoter and intron derived from the rice actin gene. The *ract1* promoter is part of the *cry3Bb1* expression-cassette inserted in MON88017. The analysis also retrieved alignments which were punctuated with stop codons in the query sequence and required gaps to optimise the alignment. No alignments with any known toxic protein harmful to humans or animals were found.

Analysis of the 5' and 3' genomic borders of GM maize 59122 indicated that the insert is likely integrated in a locus on chromosome 1, encompassing a predicted maize mRNA for a pentatricopeptide repeat (PPR)-containing protein. The potential function of this protein and its role in 59122, are not further discussed by the applicant. According to the applicant, the potential risk of a likely disruption of a predicted mRNA encoding a PPR protein is negligible, as 59122 maize is substantially equivalent to non-transgenic maize. The applicant reports that for 59122, no alignments with any known toxic protein harmful to humans or animals were found.

The results of the bioinformatic analyses of all four events with the updated allergen, gliadin and glutenin protein sequence database were not assessed by COGEM, because the assessment of potential allergenicity is not part of the environmental risk assessment, but is included in the food/feed safety assessment which is carried out by EFSA and WFSR (see paragraph 4).

COGEM is of the opinion that the molecular characterisation of MON89034, 1507, MON88017 and 59122 maize was performed correctly and meets the requirements of COGEM.[19]

Conclusion: The bioinformatics analyses of maize MON89034x1507xMON88017x59122 have been updated and performed adequately. No indications for potential environmental risks were identified.

3.5 Systematic literature search and unpublished studies

An overview of unpublished studies performed by the applicant that were not previously submitted to the EU was not provided. According to the applicant there were no unpublished studies that bring new information that might influence the risk assessment.

The applicant performed a literature search using several bibliographic databases and internet pages of relevant key organisations involved in the risk assessment of GM plants covering a publication period from January 1st 2012 to July (databases) or August 2022 (internet pages). The literature search addressed the question “Does MON 89034 × 1507 × MON 88017 × 59122 maize and part of its sub-combinations, derived food/feed products and the inherited herbicide tolerance and insect protection traits have adverse effects on human and animal health and the environment?”

Five studies, of which three publications retrieved from literature databases and two records retrieved from internet pages of key organisations, were considered relevant. According to the applicant, none of these studies were found to contain new data relevant to the risk assessment.

Overall, no adverse effects on human and animal health, or the environment were identified in the literature searches and unpublished studies of the applicant.

Conclusion: The systematic literature search did not provide any indications that import of maize MON89034x1507xMON88017x59122 poses an environmental risk.

3.6 Annual monitoring reports

The applicant supplied annual reports on the post-market monitoring (PMEM) carried out between September 2014 and October 2021. These reports contain amongst others information on annual literature searches carried out by the applicant, and on the monitoring which is carried out by operators involved in import, handling and processing of viable GM maize. These operators are members of the European trade associations COCERAL, UNISTOCK or FEDIOL. They are expected to report any occurrence of unanticipated adverse effects arising from MON89034x 1507xMON88017x59122 maize, including adventitious populations resisting routine eradication procedures. No adverse health or environmental effects were reported by the trade associations involved in the monitoring of import and processing of MON89034x1507xMON88017x59122 maize.

According to the monitoring reports, no relevant publications that invalidate the initial conclusions on the risk assessment of MON89034x1507xMON88017x59122 maize were identified in the annual literature search.

The PMEM of import and processing carried out between September 2014 and October 2021 did not provide any indications that import and processing of MON89034x1507xMON88017x59122 maize poses a risk to the environment.

Conclusion: The information in the annual monitoring reports gives no indication of adverse effects or incidents resulting from import and/or processing of MON89034x1507xMON88017x 59122 maize.

4. Food/feed assessment

This application is submitted under Regulation (EC) 1829/2003, therefore a food/feed assessment is carried out by EFSA and national organisations involved in the assessment of food safety. In the Netherlands, a food and/or feed assessment for Regulation (EC) 1829/2003 applications is carried out by Wageningen Food Safety Research (WFSR). The outcome of the assessment by other organisations (EFSA, WFSR) was not known when this advice was completed.

5. Post-market environmental monitoring (PMEM)

The applicant did not propose any changes to the existing post-market environmental monitoring (PMEM) plan for maize line MON89034x1507xMON88017x59122. COGEM has published several recommendations for further improvement of the general surveillance (GS) plan[20,21] which is part of a PMEM plan, but considers the current GS (and PMEM) plan adequate for import and processing of maize MON89034x1507xMON88017x59122.

6. Overall conclusion

Overall, COGEM is of the opinion that import and processing of maize MON89034x1507xMON88017x59122 and all its subcombinations poses a negligible risk to the environment in the Netherlands. COGEM abstains from giving advice on the potential risks of incidental consumption since other organisations carry out a food/feed assessment.

7. Additional remark

The applicant performed a systematic literature search as well as literature searches which are part of the annual PMEM reports. COGEM notes that in the systematic literature search only three publications were considered relevant, and two of them were written by employees of the companies which are the authorisation holders of this stacked event. In the annual literature searches several publications were considered irrelevant because the study did not use MON89034x1507x MON88017x59122 or its sub-combinations. Some of these studies contained information on one of the single events of MON89034x1507xMON88017x59122. COGEM is of the opinion that studies on the parental lines of a stacked event should not be automatically excluded from further analysis, as they may contain information that is relevant.

References

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