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Assessment of genetically modified cotton 281-24-236 × 3006-210-23 for renewal authorisation under Regulation (EC) No 1829/2003 (application EFSA-GMO-RX-019)

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Abstract

Following the submission of application EFSA-GMO-RX-019 under Regulation (EC) No 1829/2003 from Corteva Agriscience LLC represented by Corteva Agriscience Belgium B.V., the Panel on Genetically Modified Organisms of the European Food Safety Authority was asked to deliver a scientific risk assessment on the data submitted in the context of the renewal of authorisation application for the insect resistant genetically modified cotton 281-24-236 × 3006-210-23, for food and feed uses, excluding cultivation within the European Union. The data received in the context of this renewal application contained post-market environmental monitoring reports, a systematic search and evaluation of literature, updated bioinformatic analyses, and additional documents or studies performed by or on behalf of the applicant. The GMO Panel assessed these data for possible new hazards, modified exposure or new scientific uncertainties identified during the authorisation period and not previously assessed in the context of the original application. The GMO Panel concludes that there is no evidence in renewal application EFSA-GMO-RX-019 for new hazards, modified exposure or scientific uncertainties that would change the conclusions of the original risk assessment on cotton 281-24-236 × 3006-210-23.

Keywords: cotton, 281-24-236 × 3006-210-23, renewal, Articles 11 and 23, Regulation (EC) No 1829/2003

Requestor: European Commission

Question number: EFSA-Q-2020-00793

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Summary

Following the submission of application EFSA-GMO-RX-019 under Regulation (EC) No 1829/2003 from Corteva Agriscience LLC represented by Corteva Agriscience Belgium B.V., the Panel on Genetically Modified Organisms of the European Food Safety Authority (GMO Panel) was asked to deliver a scientific risk assessment on the data submitted in the context of the renewal of authorisation application for the insect resistant genetically modified cotton 281-24-236 × 3006-210-23. The scope of the renewal application EFSA-GMO-RX-019 is for the renewal of the placing on the market of products containing, consisting of, or produced from cotton 281-24-236 × 3006-210-23, excluding cultivation within the European Union (EU).

In delivering its scientific opinion, the GMO Panel took into account application EFSA-GMO-RX-019, additional information provided by the applicant, scientific comments submitted by the EU Member States and relevant scientific publications. The data received in the context of the renewal application EFSA-GMO-RX-019 contained: post-market environmental monitoring reports, an evaluation of the literature retrieved by a systematic search, additional studies performed by or on behalf of the applicant and updated bioinformatics analyses. The GMO Panel assessed these data for possible new hazards, modified exposure or new scientific uncertainties identified during the authorisation period and not previously assessed in the context of the original application.

The GMO Panel concludes that there is no evidence in the renewal application EFSA-GMO-RX-019 for new hazards, modified exposure or scientific uncertainties that would change the conclusions of the original risk assessment on cotton 281-24-236 × 3006-210-23 (EFSA GMO Panel, 2010).

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1. Introduction

1.1. Background

On 2 December 2020, the European Food Safety Authority (EFSA) received from the European Commission (EC) application EFSA-GMO-RX-019 for the renewal of the authorisation of cotton 281-24-236 × 3006-210-23 (Unique Identifier DAS-24236-5 × DAS-21Ø23-5), submitted by Corteva Agriscience LLC represented by Corteva Agriscience Belgium B.V. (hereafter referred to as 'the applicant') according to Regulation (EC) No 1829/2003[1].

Following receipt of application EFSA-GMO-RX-019, EFSA informed the EU Member States (MS) and made the summary of the application available to the public on the EFSA website.[2]

EFSA checked the application for compliance with the relevant requirements of Regulation (EC) No 1829/2003 and Regulation (EU) No 503/2013[3] and, when needed, asked the applicant to supplement the initial application. On 21 May 2021, EFSA declared the application valid and made the valid application available to the MS and the EC.

Following the submission of application EFSA-GMO-NL-2005-16 and the publication of the EFSA scientific opinion (EFSA GMO Panel, 2010), the placing on the market of cotton 281-24-236 × 3006-210-23 for products containing, consisting of, or produced from this GM cotton, excluding cultivation in the EU, was authorised by Commission Decision 2011/891/EU.[4] A copy of this authorisation was provided by the applicant.[5]

From the validity date, EFSA and its scientific Panel on Genetically Modified Organisms (hereafter referred to as 'the GMO Panel') endeavoured to respect a time limit of six months to issue a scientific opinion on application EFSA-GMO-RX-019. Such time limit was extended whenever EFSA and/or its GMO Panel requested supplementary information to the applicant. According to Regulation (EC) No 1829/2003, any supplementary information provided by the applicant during the risk assessment was made available to the EU Member States and EC (for further details, see the section 'Documentation', below).

In accordance with Regulation (EC) No 1829/2003, EFSA consulted the nominated risk assessment bodies of the MS, including national Competent Authorities within the meaning of Directive 2001/18/EC.[6] The EU Member States had three months to make their opinion known on application EFSA-GMO-RX-019 as of date of validity.

1.2. Terms of Reference as provided by the requestor

According to Articles 6 and 18 of Regulation (EC) No 1829/2003, EFSA and its GMO Panel were requested to carry out a scientific risk assessment of cotton 281-24-236 × 3006-210-23 for the renewal of authorization for placing on the market of products containing, consisting of, or produced from GM cotton 281-24-236 × 3006-210-23 in the context of its scope as defined in application EFSA-GMO-RX-019.

According to Regulation (EC) No 1829/2003, this scientific opinion is to be seen as the report requested under Articles 6(6) and 18(6) of that Regulation including the opinions of the nominated risk assessment bodies of the MS.[7]

In addition to the present scientific opinion on cotton 281-24-236 × 3006-210-23, EFSA and its GMO Panel were also asked to report on the particulars listed under Articles 6(5) and 18(5) of

[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, pp. 1–23.
[2] Available online: https://open.efsa.europa.eu/questions/EFSA-Q-2020-00793
[3] Commission Implementing Regulation (EU) No 503/2013 of 3 April 2013 on applications for authorisation of genetically modified food and feed in accordance with Regulation (EC) No 1829/2003 of the European Parliament and of the Council and amending Commission Regulations (EC) No 641/2004 and (EC) No 1981/2006. OJ L157, 8.6.2013, pp. 1–48.
[4] Commission Decision of 22 December 2011 authorising the placing on the market of products containing, consisting of, or produced from genetically modified cotton 281-24-236 × 3006-210-23 (DAS-24236-5 × DAS-21Ø23-5) pursuant to Regulation (EC) No 1829/2003 of the European Parliament and of the Council. Official Journal of the European Union L 344/51, 28.12.2011.
[5] Dossier: Cotton 281-24-236 × 3006-210-23 – Annex I.
[6] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. OJ L 106, 12.3.2001, pp. 1–38.
[7] Opinions of the nominated risk assessment bodies of EU Member States can be found at the Open EFSA Portal https://open.efsa.europa.eu/questions, querying the assigned Question Number.

Regulation (EC) No 1829/2003. The relevant information is made available in the OpenEFSA portal,[8] including the information required under Annex II to the Cartagena Protocol, a labelling proposal, a post-market environmental monitoring (PMEM) plan as provided by the applicant; the method(s), validated by the Community reference laboratory, for detection, including sampling, identification of the transformation event in the food-feed and/or foods-feeds produced from it and the appropriate reference materials.

2. Data and Methodologies

2.1. Data

The data for application EFSA-GMO-RX-019 submitted according to EFSA requirements (EFSA GMO Panel, 2015; EFSA, 2019a) and provided by the applicant at the time of submission, or in reply to requests for additional information, are specified below.

In the frame of the contract OC/EFSA/GMO/2018/04 and OC/EFSA/GMO/2021/06, the contractor performed preparatory work and delivered reports on the methods applied by the applicant in performing literature search and updated bioinformatic analyses, respectively.

2.1.1. Post-market monitoring reports[9]

Based on the outcome of the initial food and feed risk assessment, a post-market monitoring plan for monitoring of GM food and feed was not required by the authorisation decision. The implementation of a PMEM plan, consisting of a general surveillance plan to check for any adverse effects on the environment arising from cotton 281-24-236 × 3006-210-23, was a condition for the authorisation. As no potential adverse environmental effects were identified in the environmental risk assessment of cotton 281-24-236 × 3006-210-23 (EFSA GMO Panel, 2010), case-specific monitoring was not considered necessary by the GMO Panel.

The applicant provided 10 annual PMEM reports covering a reporting period from October 2011 till June 2021. The annual PMEM plans submitted by the applicant included (1) commodity crop (GM and non GM) imports into the EU by country of origin and destination; (2) the description of a centralised system established by EuropaBio[10] for the collection of information recorded by various operators (federations involved in cotton grains import and processing) on any observed adverse effect(s) on human health and the environment arising from handling of cotton possibly containing cotton 281-24-236 × 3006-210-23; (3) the reports of the surveillance activities conducted by such operators; and (4) the review of relevant scientific peer-reviewed studies retrieved from literature searches.

2.1.2. Systematic search and evaluation of literature[11]

In addition to the separate searches provided as part of the annual PMEM reports, the applicant performed a systematic literature search covering the period from January 2009 until April 2022, in accordance with the recommendations on literature search outlined in EFSA (EFSA, 2010, 2019b).

Searches in electronic bibliographic databases and in websites of relevant organisations were performed to identify relevant publications. Altogether 2,535 publications (including the updated search) were identified (after removal of duplicates). After applying the eligibility/inclusion criteria defined a priori by the applicant, six publications were identified as relevant for food and feed safety assessment or molecular characterisation. The relevant publications are listed in Appendix A.

2.1.3. Updated bioinformatic data[12]

At the time of submission of the renewal dossier, the applicant provided a complete bioinformatic dataset for cotton 281-24-236 × 3006-210-23 event including an analysis of the insert and flanking sequences, an analysis of the potential similarity to allergens and toxins of the newly expressed proteins and of all possible open reading frames (ORFs) within the insert and spanning the junction sites, an analysis of possible horizontal gene transfer (HGT) (EFSA, 2017), and a safety assessment of

[8] https://open.efsa.europa.eu/questions/EFSA-Q-2020-00793
[9] Dossier: Cotton 281-24-236 × 3006-210-23 – Annex II; additional information: 8/7/2022, 26/8/2022.
[10] The responsibilities of EuropaBio in coordinating activities of technology providers on the post-market environmental monitoring of GM crops were taken over by CropLife Europe as of 1 January 2021.
[11] Dossier: Cotton 281-24-236 × 3006-210-23 – Annex III; additional information: 17/2/2022.
[12] Dossier: Cotton 281-24-236 × 3006-210-234 – Annex III-2; additional information: 18/11/2021, 8/7/2022.

the newly expressed proteins Cry1F, Cry1Ac and PAT regarding its capacity to trigger celiac disease (EFSA GMO Panel, 2017). The outcome of the updated bioinformatic analyses is presented in Section 3.3.

2.1.4. Additional documents or studies provided by the applicant[13]

In line with the renewal guidance requirements (EFSA GMO Panel, 2015; EFSA, 2019a), the applicant provided an overview on the worldwide approvals of cotton 281-24-236 × 3006-210-23 and searched for any available full reports of studies performed by or on behalf of the applicant over the course of the authorisation period and not previously submitted to the EU (Appendix B).

The relevance of the listed studies for molecular characterisation, human and animal safety and the environment was assessed by the applicant.

2.1.5. Overall assessment as provided by the applicant[14]

The applicant provided an overall assessment concluding that information provided in the application for renewal of authorisation of cotton 281-24-236 × 3006-210-23 for food and feed uses in the EU does not change the outcome of the original risk assessment (EFSA GMO Panel, 2010).

2.1.6. Monitoring plan and proposal for improving the conditions of the original authorisation[14]

The applicant indicated in the dossier that the post-market environmental monitoring plan is appropriate and does not need any changes.

2.2. Methodologies

The GMO Panel assessed the application for renewal of the authorisation of cotton 281-24-236 × 3006-210-23 for food and feed uses in accordance with Articles 11 and 23 of Regulation (EC) No 1829/2003. The GMO Panel took into account the requirements described in its guideline for the risk assessment of renewal applications of GM food and feed authorised under Regulation (EC) No 1829/2003 (EFSA GMO Panel, 2015). The comments raised by the nominated risk assessment bodies of EU Member States were taken into consideration during the scientific risk assessment.

3. Assessment

3.1. Evaluation of the post-market monitoring reports

During the general surveillance activities covering the authorisation period of cotton 281-24-236 × 3006-210-23, no adverse effects were reported by the applicant.

3.2. Evaluation of the systematic search and evaluation of literature

The GMO Panel assessed the applicant's literature searches on cotton 281-24-236 × 3006-210-23 and the newly expressed proteins Cry1F, Cry1Ac and PAT. The overall quality of the performed literature searches is acceptable.

The GMO Panel acknowledges that no publications raising a safety concern for human and animal health and the environment which would change the original risk assessment conclusions on cotton 281-24-236 × 3006-210-23 (EFSA GMO Panel, 2010) have been identified by the applicant.

3.3. Evaluation of the updated bioinformatic data

The updated bioinformatic analysis was performed with the newly determined sequences for the events 281-24-236 and 3006-210-23 (see Section 3.4; EFSA GMO Panel, 2022).

The results of the updated bioinformatic analyses confirm previous results indicating that the insertion of event 281-24-236 occurred into the 3′ untranslated region of the GA 20-oxidase gene while no known endogenous genes have been interrupted by the event 3006-210-23 (EFSA GMO Panel, 2010).

[13] Dossier: Cotton 281-24-236 × 3006-210-23 – Annex III-3 and Annex III-4; additional information: 18/11/2021, 17/2/2022.
[14] Dossier: Cotton 281-24-236 × 3006-210-23 – Part I.

Analyses of the amino acid sequence of the newly expressed Cry1F(synpro_L620Q), Cry1Ac and PAT proteins reveal no significant similarities to toxins, allergens or immunogenic gluten-related epitopes. The updated bioinformatic analyses indicated that the expression of any predicted ORF within the insert and spanning the junction between the insert and the flanking genomic regions and showing similarity with known allergens or toxins is highly unlikely in cotton 281-24-236 × 3006-210-23.

The bioinformatic analysis regarding the possibility of HGT revealed several DNA sequences that could provide sufficient length and identity to facilitate HGT by double homologous recombination. Given the results of this analysis and the genes expressed in the inserts, the GMO Panel confirms previous assessment of the event and concludes that the unlikely, but theoretically possible, HGT of recombinant genes from the events 281-24-236 and 3006-210-23 to bacteria does not raise any environmental safety concern (EFSA GMO Panel, 2010).

3.4. Evaluation of the additional documents or studies provided by the applicant

The GMO Panel evaluated the reports of the additional studies provided, including new sequencing studies for both events 281-24-236 and 3006-210-23 (Appendix B). The sequencing studies provided by the applicant at the time of submission, or in reply to requests for additional information, revealed that the newly reported nucleotide sequence for both events 281-24-236 and 3006-210-23 displayed several nucleotide changes compared to the sequences of the events previously assessed (EFSA GMO Panel, 2010). Importantly, one of these nucleotide changes in the sequence of the event 281-24-236 resulted in a single amino acid substitution at location 620 of the Cry1F(synpro) amino acid sequence, generating the Cry1F(synpro_L620Q) version.

In 2020, EC assigned to EFSA a mandate to assess these new sequencing information provided by Dow AgroSciences and to indicate whether, on the basis of these additional studies, the conclusions of the adopted opinion on cotton 281-24-236 × 3006-210-23 remain valid.[15] The GMO Panel risk assessed both the newly reported sequences for the events 281-24-236 and 3006-210-23 and the identified amino acid substitution in the Cry1F(synpro) protein, and confirmed that the conclusions of the original opinion for GM cotton 281-24-236 × 3006-210-23 remain valid (EFSA GMO Panel, 2022).

Overall, the new additional documents and studies provided by the applicant do not raise any concern for human and animal health and the environment, which would change the original risk assessment conclusions on cotton 281-24-236 × 3006-210-23 (EFSA GMO Panel, 2010, 2022).

3.5. Evaluation of the overall assessment as provided by the applicant

The GMO Panel evaluated the overall assessment provided by the applicant and confirms that there is no evidence in renewal application EFSA-GMO-RX-019 indicating new hazards, relevant changes in exposure or scientific uncertainties that would change the previous conclusions on cotton 281-24-236 × 3006-210-23.

3.6. Evaluation of the monitoring plan and proposal for improving the conditions of the original authorisation

The PMEM plan covers general surveillance of imported GM plant material, including cotton 281-24-236 × 3006-210-23. This general surveillance is coordinated by CropLife Europe and implemented by selected operators (federations involved in cotton grains import and processing). In addition, the applicant reviews relevant scientific publications retrieved from literature searches on an annual basis. The GMO Panel is of the opinion that the scope of the plan provided by the applicant is consistent with the scope of application EFSA-GMO-RX-019, but reminds that monitoring is related to risk management, and thus the final adoption and implementation of the PMEM plan falls outside the mandate of EFSA.

4. Conclusions

The GMO Panel concludes that there is no evidence in renewal application EFSA-GMO-RX-019 for new hazards, modified exposure or scientific uncertainties that would change the conclusions of the original risk assessment on cotton 281-24-236 × 3006-210-23 (EFSA GMO Panel, 2010).

[15] Available at https://open.efsa.europa.eu/questions/EFSA-Q-2020-00796

5. Documentation as provided to EFSA

- Letter from the European Commission to EFSA received on 2 December 2020 for the continued marketing of genetically modified cotton 281-24-236 × 3006-210-23 submitted in accordance with articles 11 and 23 of Regulation (EC) No 1829/2003 by Corteva Agriscience LLC represented by Corteva Agriscience Belgium B.V. (EFSA-GMO-RX-019)
- The application was made valid on 21 August 2021
- Additional Information (Clock 1) was requested on 1 September 2021
- Additional Information (Clock 1) was received on 18 November 2021
- Additional Information (Clock 2) was requested on 17 December 2021
- Additional Information (Clock 2) was received on 17 February 2022
- Additional Information (Clock 3) was requested on 4 March 2022
- Additional Information (Clock 3) was received on 8 July 2022
- Additional Information (Clock 4) was requested on 8 August 2022
- Additional Information (Clock 4) was received on 26 August 2022

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EFSA (European Food Safety Authority), Gennaro A, Gomes A, Herman L, Nogué F, Papadopoulou N and Tebbe C, 2017. Technical report on the explanatory note on DNA sequence similarity searches in the context of the assessment of horizontal gene transfer from plants to microorganisms. EFSA supporting publication 2017:EN-1273, 11 pp. https://doi.org/10.2903/sp.efsa.2017.EN-1273

EFSA (European Food Safety Authority), 2019a. Administrative guidance on the submission of applications for renewal of authorisation of genetically modified food and feed under Articles 11 and 23 of Regulation (EC) No 1829/2003. EFSA supporting publication 2019:EN-1668, 19 pp. https://doi.org/10.2903/sp.efsa.2019.EN-1668

EFSA (European Food Safety Authority), 2019b. Explanatory note on literature searching conducted in the context of GMO applications for (renewed) market authorisation and annual post-market environmental monitoring reports on GMOs authorised in the EU market - Note on literature searching to GMO risk assessment guidance. EFSA supporting publication, 2019:EN-1614, 62 pp. Available online: https://www.efsa.europa.eu/en/supporting/pub/en-1614

EFSA GMO Panel (EFSA Panel on Genetically Modified Organisms), 2010. Scientific Opinion on application (EFSA-GMO-NL-2005-16) for the placing on the market of insect resistant genetically modified cotton (*Gossypium hirsutum L.*) 281–24-236 × 3006-210-23 for food and feed uses, import and processing under Regulation (EC) No 1829/2003 from Dow AgroSciences. EFSA Journal 2010;8(6):1644, 32 pp. https://doi.org/10.2903/j.efsa.2010.1644

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Abbreviations

Cry1Ac	pesticidal crystal protein Cry1Ac from *Bacillus thuringiensis*
Cry1F	crystalline entomocidal protoxin Cry1F from *Bacillus thuringiensis*
GM	genetically modified
GMO	genetically modified organism
GMO Panel	EFSA Panel on Genetically Modified Organisms
HGT	horizontal gene transfer

ORFs	open reading frames
PAT	Phosphinothricin N-acetyltransferase
PMEM	post-market environmental monitoring

Appendix A – List of relevant publications identified by the applicant through systematic literature searches (January 2009 – April 2022)

References
Center for Environmental Risk Assessment IRF, 2011a. A review of the environmental safety of the Cry1Ac protein. Environmental Biosafety Research, 10, 27–49.
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Santos-Vigil KI, Ilhuicatzi-Alvarado D, Garcia-Hernandez AL, Herrera-Garcia JS and Moreno-Fierros L, 2018. Study of the allergenic potential of Bacillus thuringiensis Cry1Ac toxin following intra-gastric administration in a murine model of food-allergy. International Immunopharmacology, 61, 185–196.
Schafer BW, Embrey SK and Herman RA, 2016. Rapid simulated gastric fluid digestion of in-seed/grain proteins expressed in genetically engineered crops. Regulatory Toxicology and Pharmacology, 81, 106–112.

Appendix B – List of additional studies performed by or on behalf of the applicant over the course of the authorisation period and not previously submitted to the EU with regard to the evaluation of the safety of the food and feed for humans, animal or the environment from cotton 281-24-236 × 3006-210-23

Study identification	Title
–	Compliance check of the sequencing information of cotton GM event DAS-24236-5 in the stacked event DAS-24236-5 × DAS-21023-5 (EFSA-GMO-NL-2005-16, CRL-VL-14/05)
–	Compliance check of the sequencing information of cotton GM event DAS-21023-5 in the stacked event DAS-24236-5 × DAS-21023-5 (EFSA-GMO-NL-2005-16, CRL-VL-14/05)
–	Outline of recent sequencing on DAS-24236-5 × DAS-21023-5 cotton, certified by the EURL
–	Cry1F(synpro_L620Q) protein safety information 281-24-236 × 3006-210-23 cotton (EFSA-GMO-NL-2005-16)