SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 25 September 2019

doi: 10.2903/j.efsa.2019.5846

Assessment of genetically modified maize MIR604 for renewal authorisation under Regulation (EC) No 1829/2003 (application EFSA-GMO-RX-013)

EFSA Panel on Genetically Modified Organisms (GMO),
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Abstract

Following the submission of application EFSA-GMO-RX-013 under Regulation (EC) No 1829/2003 from Syngenta Crop Protection NV/SA, the EFSA Panel on Genetically Modified Organisms (GMO) 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 maize MIR604, for food and feed uses, excluding cultivation within the EU. 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. Under the assumption that the DNA sequence of the event in maize MIR604 considered for renewal is identical to the corrected sequence of the originally assessed event, the GMO Panel concludes that there is no evidence in renewal application EFSA-GMO-RX-013 for new hazards, modified exposure or scientific uncertainties that would change the conclusions of the original risk assessment on maize MIR604.

Keywords: Maize, MIR604, renewal, Articles 11 and 23, Regulation (EC) No 1829/2003

Requestor: European Commission (DG SANTE)

Question number: EFSA-Q-2018-00644

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Acknowledgements: The Panel wishes to thank the members of its standing Working Groups on Molecular Characterisation, Food/Feed and Environmental Risk Assessment for the preparatory work on this scientific opinion, and the EFSA staff members Silvia Federici, Antonio Fernandez Dumont, Andrea Gennaro, Irene Muñoz Guajardo, and Konstantinos Paraskevopoulos for the support provided to this scientific opinion.

Suggested citation: EFSA GMO Panel (EFSA Panel on Genetically Modified Organisms), Naegeli H, Bresson J-L, Dalmay T, Dewhurst IC, Epstein MM, Firbank LG, Guerche P, Hejatko J, Moreno FJ, Mullins E, Nogué F, Rostoks N, Sánchez Serrano JJ, Savoini G, Veromann E, Veronesi F, Álvarez F, Ardizzone M and Raffaello T, 2019. Scientific Opinion on the assessment of genetically modified maize MIR604 for renewal authorisation under Regulation (EC) No 1829/2003 (application EFSA-GMO-RX-013). EFSA Journal 2019;17(11):5846, 11 pp. https://doi.org/10.2903/j.efsa.2019.5846

ISSN: 1831-4732

The EFSA Journal is a publication of the European Food Safety Authority, an agency of the European Union.

Summary

Following the submission of application EFSA-GMO-RX-013 under Regulation (EC) No 1829/2003[1] from Syngenta Crop Protection NV/SA, the EFSA Panel on Genetically Modified Organisms (GMO) 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 (GM) maize MIR604. The scope of the application EFSA-GMO-RX-013 is for the renewal of the placing on the market of products containing, consisting of, or produced from maize MIR604, excluding cultivation within the European Union (EU).

In delivering its scientific opinion, the GMO Panel took into account application EFSA-GMO-RX-013, 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-013 contained: post-market environmental monitoring reports, an evaluation of the literature retrieved by a systematic search, updated bioinformatics analyses, and additional 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.

Under the assumption that the DNA sequence of the event in maize MIR604 considered for renewal is identical to the corrected sequence of the originally assessed event, the GMO Panel concludes that there is no evidence in the renewal application EFSA-GMO-RX-013 for new hazards, modified exposure or scientific uncertainties that would change the conclusions of the original risk assessment on maize MIR604 (EFSA, 2009).

[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. 1–23.

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1. Introduction

1.1. Background

On 23 August 2018, the European Food Safety Authority (EFSA) received from the European Commission application EFSA-GMO-RX-013 for the renewal of the authorisation of maize MIR604 (Unique Identifier SYN-IR6Ø4-5), submitted by Syngenta Crop Protection NV/SA (hereafter referred to as 'the applicant') according to Regulation (EC) No 1829/2003.[2]

Following receipt of application EFSA-GMO-RX-013, EFSA informed the Member States (MS) and made the summary of the application available to the public on the EFSA website.[3]

EFSA checked the application for compliance with the relevant requirements of Regulation (EC) No 1829/2003 and Regulation (EU) No 503/2013[4] and, when needed, asked the applicant to supplement the initial application. On 5 November 2018, EFSA declared the application valid and made the application available to the MS and the European Commission.

Following the submission of application EFSA-GMO-UK-2005-11 and the publication of the EFSA scientific opinion (EFSA, 2009), the placing on the market of maize MIR604 for products containing, consisting of, or produced from this GM maize, excluding cultivation in the EU, was authorised by Commission Decision 2009/866/EC.[5] A copy of this authorisation was provided by the applicant.[6]

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 6 months to issue a scientific opinion on application EFSA-GMO-RX-013. 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 European Commission (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.[7] The MS had three months to make their opinion known on application EFSA-GMO-RX-013 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 maize MIR604 for the renewal of the authorisation for placing on the market of products containing, consisting of, or produced from GM maize MIR604 in the context of its scope as defined in application EFSA-GMO-RX-013.

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.[8]

In addition to the present scientific opinion on maize MIR604, EFSA and its GMO Panel were also asked to report on the particulars listed under Articles 6(5) and 18(5) of Regulation (EC) No 1829/2003. The relevant information is made available in the EFSA Register of Questions,[9] 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

[2] 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. 1–23.
[3] Available online: http://registerofquestions.efsa.europa.eu/roqFrontend/questionDocumentsLoader?question=EFSA-Q-2018-00644
[4] 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 L 157, 8.6.2013, p. 1–48.
[5] Commission Decision of 30 November 2009 authorising the placing on the market of products containing, consisting of, or produced from genetically modified maize MIR604 (SYN-IR6Ø4-5) pursuant to Regulation (EC) No 1829/2003 of the European Parliament and of the Council. Official Journal of the European Union L 314/102, 30.11.2009.
[6] Dossier: Maize MIR604 – Section 2.1
[7] 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, p. 1–38.
[8] Opinions of the nominated risk assessment bodies of EU Member States can be found at the EFSA Register of Questions, http://registerofquestions.efsa.europa.eu/roqFrontend/login, querying the assigned Question Number.
[9] http://registerofquestions.efsa.europa.eu/roqFrontend/questionDocumentsLoader?question=EFSA-Q-2018-00644

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-013 provided by the applicant at the time of submission, or in reply to requests for additional information, are specified below.

In the context of this renewal application, no new sequencing study was submitted among the additional documents or studies performed by or on behalf of the applicant. In accordance with the GMO Panel guidelines for renewal of applications of GM food and feed authorised under Regulation (EC) No 1829/2003 (EFSA GMO Panel, 2015a), the GMO Panel evaluated the data provided in the context of this maize MIR604 renewal application under the assumption that the MIR604 event sequence is identical to the corrected sequence of the originally assessed event (EFSA GMO Panel, 2015b).

2.1.1. Post-market monitoring reports[10]

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 maize MIR604, was a condition for the authorisation. As no potential adverse environmental effects were identified in the environmental risk assessment of maize MIR604 (EFSA, 2009), case-specific monitoring was not considered necessary by the GMO Panel.

The applicant provided nine annual PMEM reports covering a reporting period from July 2009 till June 2018. 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 for the collection of information recorded by various operators (federations involved in maize grains import and processing) on any observed adverse effect(s) on human health and the environment arising from handling of maize possibly containing maize MIR604; (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 nine separate searches provided as part of the annual PMEM reports, the applicant performed a systematic literature search covering the period from January 2007 till March 2019, in accordance with the recommendations on literature search outlined in EFSA (2010, 2017a).

Searches in electronic bibliographic databases and in websites of relevant organisations were performed to identify relevant publications. Altogether, 2968 publications were retrieved (after removal of duplicates). After applying the eligibility/inclusion criteria defined *a priori* by the applicant, 16 publications were identified as relevant for food and feed safety assessment, molecular characterisation and environmental safety assessment. The list of relevant publications is provided 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 maize MIR604 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, and an analysis of possible horizontal gene transfer (HGT) (EFSA, 2017b). Additionally, upon EFSA request during the risk assessment, the applicant provided bioinformatic analysis using up-to-date databases to identify possible gene interruption, to asses potential for horizontal gene transfer, and to assess the capacity of

[10] Dossier: Maize MIR604 – Section 2.2; additional information: 15/5/2019.
[11] Dossier: Maize MIR604 – Section 2.3.1; additional information: 2/5/2019.
[12] Dossier: Maize MIR604 – Section 2.3.2; additional information: 15/5/2019.

the newly expressed proteins mCry3A and PMI 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, 2015a), the applicant provided an overview on the worldwide approvals of maize MIR604 and the full reports of all 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 maize MIR604 for food and feed uses in the EU does not change the outcome of the original risk assessment (EFSA, 2009).

2.1.6. Monitoring plan and proposal for improving the conditions of the original authorisation[15]

The applicant indicated in the dossier that the PMEM plan is appropriate and does not need any changes.

2.2. Methodologies

The GMO Panel assessed the application for renewal of the authorisation of maize MIR604 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, 2015a). The comments raised by the nominated risk assessment bodies of the EU Member States were taken into consideration during the scientific risk assessment.[9]

3. Assessment

3.1. Evaluation of the post-market monitoring reports

During the general surveillance activities covering the authorisation period of maize MIR604, 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 search on maize MIR604 and the newly expressed proteins mCry3A and PMI. The overall quality of the performed literature search is acceptable; however, the GMO Panel considers that future searches could be fine-tuned. The GMO Panel recommends the applicant for future searches to:

- define more clearly the eligibility/inclusion criteria for assessing the relevance of publications;
- ensure that enough search term variation is used (covering possible synonyms, related terms, acronyms, spelling variants, old and new terminology, brand and generic names, lay and scientific terminology, common typos, translation issues);
- ensure that enough truncation is used and used consistently;
- include controlled vocabulary (subject indexing) in the searches when available (in addition to text words);
- adapt the search to the size of the retrieved publications (and thus not combine search sets when one of the search sets already yields only a small number of publications).

[13] Dossier: Maize MIR604 – Section 2.3.3; additional information: 15/5/2019.
[14] Dossier: Maize MIR604 – Section 3.
[15] Dossier: Maize MIR604 – Section 4.

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 maize MIR604 (EFSA, 2009) have been identified by the applicant.

3.3. Evaluation of the updated bioinformatic data

The results of the updated bioinformatic analyses of maize MIR604 confirm that no known endogenous genes were disrupted by the insert. Analyses of the amino acid sequence of the newly expressed mCry3A and PMI proteins show no relevant similarities to toxins, allergens or immunogenic gluten-related epitopes. In addition, bioinformatic analyses of the newly created ORFs within the insert or spanning the junctions with genomic DNA confirm previous conclusions indicating that the expression of ORFs showing similarities to toxins or allergens for the event MIR604 is highly unlikely (EFSA, 2009; EFSA GMO Panel, 2019).

The updated bioinformatic analysis for maize event MIR604 does not reveal any DNA sequence that could provide sufficient length and identity which could facilitate double homologous recombination (HR), confirming the previous conclusions (EFSA GMO Panel, 2019). Given the results of this analysis and that the recombinant DNA in maize MIR604 does not confer selective advantages or increased fitness to microorganisms, the GMO Panel identified no safety concern linked to an unlikely but theoretically possible HGT.

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

The GMO Panel evaluated the full study reports of the additional studies provided (Appendix B). This new information does not raise any concern for human and animal health and the environment, which would change the original risk assessment conclusions on maize MIR604.

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-013 indicating new hazards, relevant changes in exposure or scientific uncertainties that would change previous conclusions on maize MIR604.

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 maize MIR604. This general surveillance is coordinated by EuropaBio and implemented by selected operators (federations involved in maize 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-013, 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

Under the assumption that the DNA sequence of the event in maize MIR604 considered for renewal is identical to the corrected sequence of the originally assessed event (EFSA GMO Panel, 2015b), the GMO Panel concludes that there is no evidence in renewal application EFSA-GMO-RX-013 for new hazards, modified exposure or scientific uncertainties that would change the conclusions of the original risk assessment on maize MIR604 (EFSA, 2009).

Documentation as provided to EFSA

1) Letter from the European Commission to EFSA received on 23 August 2018 concerning a request for the continued marketing of genetically modified maize MIR604 in accordance with articles 11 and 23 of Regulation (EC) No 1829/2003 by Syngenta Crop Protection NV/SA (EFSA-GMO-RX-013).
2) Application EFSA-GMO-RX-013 validated by EFSA, 5 November 2018.
3) Request for supplementary information to the applicant, 28 November 2018.

4) Request for supplementary information to the applicant, 21 December 2018.
5) Receipt of supplementary information from the applicant, 22 February 2019.
6) Request for supplementary information to the applicant, 10 April 2019.
7) Receipt of supplementary information from the applicant, 2 May 2019.
8) Receipt of supplementary information from the applicant, 15 May 2019.
9) Receipt of spontaneous information from the applicant, 5 September 2019.

References

EFSA (European Food Safety Authority), 2009. Scientific Opinion - Application (Reference EFSA-GMO-UK-2005-11) for the placing on the market of insect-resistant genetically modified maize MIR604 event, for food and feed uses, import and processing under Regulation (EC) No 1829/2003 from Syngenta Seeds S.A.S. on behalf of Syngenta Crop Protection AG. EFSA Journal 2009;7(7):1193, 26 pp. https://doi.org/10.2903/j.efsa.2009.1193

EFSA (European Food Safety Authority), 2010. Application of systematic review methodology to food and feed safety assessments to support decision making. EFSA Journal 2010;8(6):1637, 90 pp. https://doi.org/10.2903/j.efsa.2010.1637

EFSA (European Food Safety Authority), Devos Y, Guajardo IM, Glanville J and Waigmann E, 2017a. Explanatory note on literature searching conducted in the context of GMO applications for (renewed) market authorization and annual post-market environmental monitoring reports on GMOs authorised in the EU market. EFSA supporting publications 2017:EN-1207, 48 pp. https://doi.org/10.2903/sp.efsa.2017.en-1207

EFSA (European Food Safety Authority), Gennaro A, Gomes A, Herman L, Nogue F, Papadopoulou N and Tebbe C, 2017b. 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 publications 2017:EN-1273, 11 pp. https://doi.org/10.2903/sp.efsa.2017.en-1273

EFSA GMO Panel (EFSA Panel on Genetically Modified Organisms), 2015a. Guidance for renewal applications of genetically modified food and feed authorised under Regulation (EC) No 1829/2003. EFSA Journal 2015;13(6):4129, 8 pp. https://doi.org/10.2903/j.efsa.2015.4129

EFSA GMO Panel (EFSA Panel on Genetically Modified Organisms), 2015b. Statement on the risk assessment of new sequencing data on GM maize event MIR604. EFSA Journal 2015;13(10):4255, 6 pp. https://doi.org/10.2903/j.efsa.2015.4255

EFSA GMO Panel (EFSA Panel on Genetically Modified Organisms), Naegeli H, Birch AN, Casacuberta J, De Schrijver A, Gralak MA, Guerche P, Jones H, Manachini B, Messean A, Nielsen EE, Nogue F, Robaglia C, Rostoks N, Sweet J, Tebbe C, Visioli F, Wal J-M, Eigenmann P, Epstein M, Hoffmann-Sommergruber K, Koning F, Lovik M, Mills C, Moreno FJ, van Loveren H, Selb R and Fernandez Dumont A, 2017. Guidance on allergenicity assessment of genetically modified plants. EFSA Journal 2017;15(5):4862, 49 pp. https://doi.org/10.2903/j.efsa.2017.4862

EFSA GMO Panel (EFSA Panel on Genetically Modified Organisms), Naegeli H, Bresson J-L, Dalmay T, Dewhurst IC, Epstein MM, Firbank LG, Guerche P, Hejatko J, Moreno FJ, Mullins E, Nogué F, Rostoks N, Sánchez Serrano JJ, Savoini G, Veromann E, Veronesi F, Ardizzone M, Álvarez F, Fernandez Dumont A, Gennaro A, Lanzoni A, Neri FM, Papadopoulou N, Paraskevopoulos K, De Sanctis G, Raffaello T, Federici S and Koukoulanaki M, 2019. Scientific Opinion on assessment of genetically modified maize Bt11 × MIR162 × MIR604 × 1507 × 5307 × GA21 and subcombinations, for food and feed uses, under Regulation (EC) No 1829/2003 (application EFSA-GMO-DE-2011-103). EFSA Journal 2019;17(3):5635, 36 pp. https://doi.org/10.2903/j.efsa.2019.5635

Abbreviations

GM	genetically modified
GMO	genetically modified organisms
GMO Panel	EFSA Panel on Genetically Modified Organisms
HGT	horizontal gene transfer
ORFs	open reading frames
PMEM	post-market environmental monitoring

Appendix A – List of relevant publications identified by the applicant through the systematic literature search (January 2007 – March 2019)

Reference

Chen E and Defontes C, 2014. Transgenic plants expressing modified CRY3A. Official Gazette of the United States Patent & Trademark Office Patents (Jun 24).

Chen E and Defontes C. 2012. Modified Cry3A toxins and nucleic acid sequences coding therefor. Official Gazette of the United States Patent & Trademark Office Patents (Aug 21).

Chen E and Stacy C, 2007a. Modified Cry3A toxins and nucleic acid sequences coding therefor." Official Gazette of the United States Patent & Trademark Office Patents, (Jun 12).

Chen E and Stacy C, 2007b. Modified Cry3A toxins. Official Gazette of the United States Patent & Trademark Office Patents (Oct 2).

Chen E and Stacy C, 2009. Modified Cry3A toxins and nucleic acid sequences coding therefor. Official Gazette of the United States Patent & Trademark Office Patents (Aug 4).

Chen E and Stacy C, 2011. Modified Cry3A toxins and nucleic acid sequences coding therefor. Official Gazette of the United States Patent & Trademark Office Patents (Aug 30).

Chen E and Stacy C, 2012. Modified Cry3A toxins and nucleic acid sequences coding therefor. Official Gazette of the United States Patent & Trademark Office Patents (Jul 10).

Haegele JW and Peterson PA, 2007. The flow of maize pollen in a designed field plot. Maydica, 52, 117–125.

Steiner H-Y, Chen E, Meghji M, 2008. Corn event MIR604. Official Gazette of the United States Patent & Trademark Office Patents (Apr 22).

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Tutel'ian VA, Gapparov M M, Avren'eva LI, Aksiuk IN, Guseva GV, Kravchenko LV, L'Vova LS, Saprykin VP, Tyshko NV, Chernysheva ON, 2009. "[Medical and biological safety assessment of genetically modified maize event MIR604: Report 1. Toxicologo-hygienic examinations]." Voprosy Pitaniya, 78, 24–32.

Tyshko NV, Britsina MV, Gmoshinsky IV, Zhanataev NS, Zorin SN, Mazo VK, Ozeretskovskaia MN, Semenov BF, 2009. [Medical and biological safety assessment of genetically modified maize event MIR604: Report 2. Genotoxicologic, immunologic and allergologic examinations]. Voprosy Pitaniya, 78, 33–38.

Wang X, Zhang S, Hu D, Zhao X, Li Y, Liu T, Wang J, Hou X, Li Y, 2014. BcPMI2, isolated from non-heading Chinese cabbage encoding phosphomannose isomerase, improves stress tolerance in transgenic tobacco. Molecular Biology Reports, 41, 2207–2216.

Zhang M, Zhuo X, Wang J, Yang C, Powell CA, Chen R, 2015. Phosphomannose isomerase affects the key enzymes of glycolysis and sucrose metabolism in transgenic sugarcane overexpressing the manA gene. Molecular Breeding, 35, 100.

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 maize MIR604

Study identification	Title
SSB-219-10	Quantification of mCry3A and MIR604 PMI in event MIR604 maize tissues grown in Romania in 2008
SSB-005-10	Quantification of mCry3A and MIR604 PMI in event MIR604 maize tissues grown in Spain in 2008
SSB-112-10 (Vols 1 and 2)	Compositional analysis of forage and grain from an MIR604 hybrid maize grown during 2008 in Europe
EPD-100-10-A1	Agronomic assessment of event MIR604 maize under European growing conditions in 2008