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SCIENTIFIC OPINION

Opinion on application reference EFSA-GMO-RX-Bt11 for renewal of the authorisation of existing products produced from insect-resistant genetically modified maize Bt11, under Regulation (EC) No 1829/2003 from Syngenta[1]

Scientific Opinion of the Panel on Genetically Modified Organisms

(Question No EFSA-Q-2007-146)

Adopted on 28 January 2009

PANEL MEMBERS[*]

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SUMMARY

This document provides the opinion of the Scientific Panel on Genetically Modified Organisms (GMO Panel) of the European Food Safety Authority (EFSA) on an application submitted under Regulation (EC) No 1829/2003 (reference EFSA-GMO-RX-Bt11) for renewal of the authorisation of existing products derived from genetically modified maize Bt11.

The scope of this application covers the continued marketing of existing food and food ingredients containing, consisting of or produced from maize Bt11, food additives produced from maize Bt11, feed containing, consisting of or produced from maize Bt11 (feed materials and feed additives) to be used as any other maize grain but not for cultivation, and other products containing or consisting of maize Bt11 with the exception of cultivation which were lawfully placed on the market in the Community before the date of entry into force of Regulation (EC) No 1829/2003. After the date of entry into force of Regulation (EC) No

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[*] (minority opinion) This opinion is not shared by 0 members of the Panel. / (conflict of interest) 0 members of the Panel did not participate in (part of) the discussion on the subject referred to above because of possible conflicts of interest.

1829/2003 these products were notified to the European Commission according to Articles 8 and 20 of that Regulation and included in the Community Register of genetically modified food and feed[2].

Maize Bt11 was developed to provide protection against specific lepidopteran pests. The maize also contains a gene providing tolerance to the herbicide glufosinate ammonium.

The EFSA GMO Panel has previously issued a scientific opinion related to notification C/F/96/05.10 for the placing on the market of insect-resistant genetically modified maize Bt11, for cultivation, feed and industrial processing under Directive 2001/18/EC (EFSA, 2005). In this opinion the Panel concluded that maize Bt11 is unlikely to have an adverse effect on human and animal health or the environment in the context of its proposed uses.

In delivering its present opinion, the GMO Panel considered information provided in the renewal application (reference EFSA-GMO-RX-Bt11) as well as additional information submitted by the applicant on request of the Panel. In accordance with the Guidance Document for renewal of authorisations of existing GMO products (EFSA, 2006a), the Panel has taken into account the new information, experience and data, which have become available during the authorisation period.

New information was provided in this renewal application with regards to 1) a review of peer-reviewed scientific data on Bt11 maize; 2) a report on areas and quantity of production, importation, use in Europe of Bt11 maize and information on known and estimated human and animal exposure; 3) an updated molecular characterisation, including sequence data for the flanking regions; 4) an updated information on the levels of expression of the specific proteins and metabolites resulting from the genetic modification and on the composition of the GMO; 5) an updated information on allergenicity and toxicology; and 6) a post-market environmental monitoring plan.

The updated molecular and bioinformatic analyses provided for the maize Bt11 event do not indicate any safety concerns and the GMO Panel maintains its previous opinion on the safety of this event,

New information from an updated literature review and from additional studies performed by the applicant does not prompt the Panel to change its previous opinion that maize Bt11 is as safe and as nutritious as its non-GM counterparts.

The application for renewal of authorisation of existing products derived from maize Bt11 excludes cultivation of the crop in the EU. There is therefore no requirement for scientific assessment of possible environmental effects associated with the cultivation of maize Bt11. The scope of the post-market environmental monitoring plan provided by the applicant is in line with the intended uses of maize Bt11 since cultivation is excluded and is in line with the EFSA Guidance Document (EFSA, 2006b) and the Opinion of the GMO Panel on post-market environmental monitoring (EFSA, 2006c).

The GMO Panel concludes that the new information provided by the applicant and the review of the literature that has been published since the previous scientific opinion of the GMO Panel does not require changes of the previous scientific opinion on maize Bt11 and addresses

[2] http://ec.europa.eu/food/dyna/gm_register/gm_register_auth.cfm?pr_id=1

the scientific comments raised by the Member States. Therefore, the Panel reiterates the previous conclusion that genetically modified maize Bt11 is unlikely to have an adverse effect on human and animal health or the environment in the context of its proposed uses. This also applies to the products which are the subject of the present application.

Key words: GMO, maize, *Zea mays*, Bt11, insect-resistant, herbicide-tolerant, Cry1Ab, PAT, feed safety, food safety, human health, Regulation (EC) No 258/97, Regulation (EC) No 1829/2003, Directive 90/220/EEC, Directive 2001/18/EC, renewal, existing product.

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BACKGROUND

On 29 June 2007, EFSA received from the European Commission an application for renewal of the authorisation of existing products derived from maize Bt11 (EFSA-GMO-RX-Bt11) submitted by Syngenta within the framework of Regulation (EC) No 1829/2003 on genetically modified food and feed (EC, 2003). The scope of this application covers the continued marketing of existing food and food ingredients containing, consisting of or produced from maize Bt11, food additives produced from maize Bt11, feed containing, consisting of or produced from maize Bt11 (feed materials and feed additives) to be used as any other maize grain but not for cultivation, and other products containing or consisting of maize Bt11 with the exception of cultivation which were lawfully placed on the market in the Community before the date of application of Regulation (EC) No 1829/2003. After the date of application of Regulation (EC) No 1829/2003, the products were notified to the Commission according to Articles 8 and 20 of that Regulation and included in the Community Register of genetically modified food and feed[3].

The EFSA GMO Panel has previously issued a scientific opinion related to notification C/F/96/05.10 for the placing on the market of insect-resistant genetically modified maize Bt11, for cultivation, feed and industrial processing under Directive 2001/18/EC (EFSA, 2005). The Panel concluded that maize Bt11 is unlikely to have an adverse effect on human and animal health or the environment in the context of its proposed uses (EFSA, 2005).

After receiving the application EFSA-GMO-RX-Bt11 and in accordance with Articles 5(2)(b) and 17(2)b of Regulation (EC) No 1829/2003, EFSA informed the Member States and the European Commission and made the summary of the application available to the public on the EFSA website. EFSA initiated a formal review of the application to check compliance with the requirements laid down in Articles 8 and 20 of Regulation (EC) No 1829/2003. On 17 March 2008 EFSA declared the application as valid in accordance with Articles 6(1) and 18(1) of Regulation (EC) No 1829/2003[4].

EFSA made the valid application available to Member States and the European Commission and consulted nominated risk assessment bodies of the Member States, including the national Competent Authorities within the meaning of Directive 2001/18/EC (EC, 2001) following the requirements of Articles 6(4) and 18(4) of Regulation (EC) No 1829/2003, to request their scientific opinion. The Member State bodies had three months after the date of receipt of the valid application (until 16 June 2008) within which to make their scientific comments known.

On 15 July 2008 and 5 September 2008 the GMO Panel asked the applicant for additional data or clarifications on Bt11 maize. EFSA received the requested information on 6 August 2008 and 28 October 2008, respectively. After receipt and assessment of the full data package, the GMO Panel finalised its opinion.

The GMO Panel carried out the scientific assessment of the renewal application on maize GM Bt11 according to the Guidance document for renewal of authorisation of existing products (EFSA, 2006a) taking into consideration the scientific comments of the Member States and the additional information provided by the applicant.

[3] http://ec.europa.eu/food/dyna/gm_register/gm_register_auth.cfm?pr_id=1
[4] See section Documentation provided to EFSA

In giving its opinion on maize Bt11 to the European Commission, the Member States and the applicant, and in accordance with Articles 6(1) and 18(1) of Regulation (EC) No 1829/2003 EFSA has endeavoured to respect a time limit of six months from the receipt of the valid application. As additional information was requested by the GMO Panel, the time limit of 6 months was extended accordingly, in line with Articles 6(1), 6(2), 18(1), and 18(2) of Regulation (EC) No 1829/2003.

According to Regulation (EC) No 1829/2003, the EFSA opinion shall include an assessment report stating the reasons for its opinion and the information on which the opinion is based, including the opinions of the competent authorities when consulted in accordance with Article 6(4) and 18(4) of Regulation (EC) No 1829/2003. This document is to be seen as the report requested under Articles 6(6) and 18(6) of that Regulation and thus will be part of the overall opinion in accordance with Articles 6(5) and 18(5).

TERMS OF REFERENCE

The GMO Panel was requested to issue a scientific opinion for renewal of the authorisation of existing products produced from genetically modified maize Bt11, that were previously notified according to Articles 8(1)(a)(b) and 20(1)(a)(b) of Regulation (EC) No 1829/2003 on genetically modified food and feed, and that have now been submitted under Article(s) 8(4) and 20(4) of Regulation (EC) No 1829/2003. This application fulfils the requirements of Articles 11(2) and 23(2) of Regulation (EC) No 1829/2003.

The GMO Panel was not requested to give an opinion on information required under Annex II to the Cartagena Protocol. Furthermore, the GMO Panel did also not consider proposals for labelling and methods of detection (including sampling and the identification of the specific transformation event in the food/feed and/or food/feed produced from it), which are matters related to risk management.

ACKNOWLEDGEMENTS

The European Food Safety Authority wishes to thank the members of the Working Groups on Molecular Characterisation, Food-Feed and Environment for the preparation of this opinion.

ASSESSMENT

1. Introduction

Summary of the conclusions of the previous scientific opinion (EFSA, 2005)

Regarding the information which has already been evaluated in the context of the previous applications on maize Bt11, the GMO Panel refers to the respective opinion (EFSA, 2005). The scientific assessment included the transformation process, the vectors used and the transgenic constructs in the genetically modified plants. A comparative analysis of agronomic traits and composition was undertaken and the safety of the new proteins and the whole food/feed was evaluated with respect to toxicology and allergenicity. A nutritional assessment and an environmental assessment including monitoring plans were undertaken. The Panel concluded that maize Bt11 is unlikely to have an adverse effect on human and animal health or the environment in the context of its proposed uses (EFSA, 2005).

The assessment presented here is based on the information provided by the applicant in its application for renewal EFSA-GMO-RX-Bt11, including 1) a review of peer-reviewed scientific data on maize Bt11 for import and food/feed uses; 2) a report on areas and quantity of production, importation, use in Europe of maize Bt11 and information on known and estimated human and animal exposure; 3) an updated molecular characterisation, including sequence data for the flanking regions; 4) an updated information on the levels of expression of the specific proteins and metabolites resulting from the genetic modification and on the composition of the GMO; 5) an updated information on allergenicity and toxicology; and 6) a post-market environmental monitoring plan, as well as the additional information submitted by the applicant in reply to questions from the GMO Panel.

2. ISSUES RAISED BY THE MEMBER STATES

Issues raised by Member States are addressed in Annex G of the EFSA overall opinion.

3. EVALUATION OF RELEVANT NEW SCIENTIFIC DATA

3.1. Molecular Characterisation

The GMO Panel received an updated sequence analysis of both the insert and the original plasmid used for transformation. The nucleotide sequence of the entire Bt11 insert in sweet corn was determined which enabled a direct comparison to the previously reported sequence (from field corn). A total of eight nucleotide differences were identified when the Bt11 insert sequence was compared to the previously reported Bt11 sequence. The applicant attributed this discrepancy to sequencing errors in the original datasets. The GMO Panel supports this re-evaluation.

An updated bioinformatic analysis (2008) confirmed the original analysis carried out by the applicant and supports the conclusion that the genomic sequences in both 5' and 3' regions flanking the insert of Bt11 event show homology to highly repetitive, knob-associated sequences. The data do not indicate any safety concerns with regard to the interruption of known genes or from the potential production of new toxins or allergens.

Additional data were provided to support the conclusion that the traits were inherited in a Mendelian manner. In addition, an updated Southern analyse, using probes which covered the entire insert, confirmed that the Bt11 maize contains a single copy event at a single locus.

The application provided a table summarising Cry1Ab and PAT protein expression levels in all the field trials. The overall data confirmed that variations in the protein levels measured for a given tissue type are relatively small and that the range of levels measured raises no safety concerns. With regards PAT protein minute amounts (*e.g.* nanogram per gram) were measured in leaves, silk and tassel but levels were below the limit of detection in kernels, pollen, root and stalk.

3.1.1. Conclusions

The updated molecular and bioinformatic analyses provided for the maize Bt11 event do not indicate any safety concerns and the GMO Panel maintains its previous opinion on the safety of this event.

3.2. Food and Feed safety assessment

In addition to the information available in the original application and that was taken into account by the GMO Panel in its previous opinion (EFSA, 2005), the applicant provided updated information on the utilisation of Bt11 maize in Europe and an estimation of human and animal exposure to the newly expressed proteins.

The applicant also provided a report of the peer reviewed scientific data on Bt11 that have become available since the previous opinion of the GMO Panel. The Panel also considered additional, recently published literature. An extensive survey has been made including not only maize Bt11 but also other GM events in which the Cry1Ab insecticidal protein has been inserted, *e.g.* Bt 176 but mainly maize MON 810. According to the applicant, in maize Bt11, only the first 615 amino acid residues of the full length Cry1Ab protein are expressed while a longer Cry1Ab protein is expressed in maize MON 810. The GMO Panel has taken into consideration all the published information while assessing the truncated newly expressed protein Cry1Ab in maize Bt11.

The articles analysed pertained to compositional analysis, toxicology and allergenicity and nutritional equivalence.

3.2.1. Utilisation of Bt11 maize in Europe - Estimation of human exposure

The applicant provided data on import and use of Bt11 in Europe and an estimation of human and animal exposure. Most of this Bt11 maize (ca. 60%) was imported into Spain and Portugal but also into UK and the Netherlands. No imports of sweet Bt11 maize have been

recorded and most of the imported Bt11 maize is supposed to have been used for animal feeding. However a maximum (potential) estimated daily intake of the Cry1Ab and PAT proteins was calculated taking into account an average maize consumption of 150 g/person and per day and a mean expression level in kernels of 5 µg/g of Cry1Ab and 0.008 µg/g of PAT (which actually is the limit of detection). These quantities result in an exposure of 0.01 and 0.00002 mg/kg body weight/day for the Cry1Ab and PAT protein respectively.

3.2.2. Compositional analysis

No new information was made available to the Panel that would indicate differences in the composition in major nutrients and anti nutrients of products derived from Bt11 and non-GM maize. In particular, Jung and Sheaffer (2004) showed that the insertion of the Cry1Ab transgene had no impact on lignin concentration and forage quality traits of Bt11 maize when compared with non-GM counterparts. A survey of numerous field trials in 2000-2002 showed that contamination by mycotoxins (*e.g.* fumonisin and aflatoxin) was frequently lower in Bt maizes expressing Cry1Ab than in non-GM maizes (Hammond *et al.*, 2004).

3.2.3. Toxicology

The potential toxicity of GM maize expressing the Cry1Ab protein has been assessed in recent published 90-day sub-chronic toxicity study in rodents. Hammond et al. (2006) fed rats with diets containing either MON 810 maize grain at levels of 11% and 33% or non-GM maize (33%) as a control. No adverse effects or clinical changes of biological relevance were observed.

Detailed published studies on the transfer of transgenic DNA, survival of transgenic proteins and DNA in gastric fluids and the impact of Cry1Ab protein on rumen microbiota and intestinal epithelial cells were analysed. In particular, Ferrini et al. (2007) investigated the survival *in vitro* of *bla* and *cry1Ab* genes in Bt176 maize in gastric juice from human patients suffering from gastro-oesophageal reflux or celiac disease and in gastric fluid samples having the pH modified by addition of sodium carbonate. They observed that in these particular conditions, part of the *cry1Ab* gene can survive in the gastric fluid and fragments of transgenic DNA can reach the intestine. Onose et al. (2008) tested the possible toxicity of the natural Cry1Ab protein from *B. thurengiensis* in rats with an impaired gastrointestinal function and in rats where gut damage was induced by treatment with famotidine and indomethacin. No significant toxicological effects of the Cry1Ab were observed on the animals during the 4 week experimental period and after necropsy.

Regarding the mechanism of action of the Cry1Ab protein, *in vitro* studies by Shimada et al., (2006a) using brush border membrane vesicles showed that Cry1Ab can bind to mammalian intestinal cells but this binding does not damage cell membrane integrity, even at high concentrations.

In conclusion, no significant effects requiring further studies were observed.

3.2.4. Allergenicity

Batista *et al.,* (2005) assessed allergenicity using a survey on a human population. The authors monitored the antibody response to newly expressed proteins (including Bt proteins such as Cry1Ab) present in GM crops authorised in the EU (including events Bt11, Bt176 and MON810) in a population of sensitive humans. None of the tested volunteers had detectable IgE against the transgenic proteins.

In addition the applicant performed updated searches for amino acid sequence homology of the Cry1Ab and PAT proteins as expressed in Bt11 with sequences of known toxins and allergens.

Regarding toxins, the searches were performed using the BLASTP algorithm and the NCBI (2006) Protein Database. Among the 392 high scoring hits with E values below the 0.39 found for the PAT protein, none was identified as a known or putative toxin. Among 273 entries returned by the database search for Cry1Ab, most were identified as Bt derived insecticidal delta endotoxins. Four additional hits were found but none related to a known or putative toxin other than delta endotoxins.

For allergens, two different searches were performed using the in house SBI allergen database (updated in July 2006). The first search used the FASTA search algorithm to assess sequence identity greater than 35% over successive 80-amino acid peptides of the Cry1Ab and PAT sequences to known allergens. The second was a search for alignments of eight or more contiguous amino acids in common with sequences of known allergens. These updated bioinformatic analyses showed no significant sequence homology of either PAT or Cry1Ab protein with known allergens (including gliadins), in line with the conclusions drawn in the original application.

3.2.5. Nutritional assessment

The impacts of diets containing the GM events on performances of various target animals, e.g. chicken broilers, calves, lactating cows, sheep, piglets and finishing pigs, fish, were analysed in feeding studies. The overall performances were similar in animals fed the GM crops as compared to those that received the non-GM counterpart. No intact Cry1Ab protein or gene was detected in tissues of target animals fed diets containing Bt11 maize.

3.2.6. Conclusions

In conclusion, new information from this updated literature review and from additional studies performed by the applicant does not prompt the Panel to change its previous opinion that Bt11 maize is as safe and as nutritious as the non-GM counterparts.

3.3. Environmental assessment

In addition to the information available in the original application and used by the GMO Panel in its previous opinion (EFSA, 2005), the applicant provided a post market environmental monitoring plan. The GMO Panel considered also the available published literature on Bt11 maize.

The general surveillance plan proposed by the applicant includes i) the description of an approach involving operators, reporting to the applicants any observed adverse effect of GMOs on human health and the environment, ii) a coordinating system newly established by EuropaBio, and iii) the use of networks of existing surveillance systems. The applicant will submit a general surveillance report on an annual basis and a final report at the end of the consent. In case of confirmed adverse effects, the applicant will immediately inform the European Commission and the Member States.

The GMO Panel is of the opinion that the general approaches and measures of the monitoring plan proposed by the applicant are in line with the EFSA opinion on post-market environmental monitoring (EFSA, 2006c) as well as with the intended uses of maize Bt11. Since the environmental risk assessment identifies no potential adverse environmental effects, no case-specific monitoring is necessary. The GMO Panel agrees with the proposal made by the applicant on the reporting intervals of the general surveillance plan. The GMO Panel advises that appropriate management systems should be in place to prevent seeds of maize Bt11 entering cultivation as the latter requires specific approval under Directive 2001/18/EC or Regulation (EC) No 1829/2003.

3.3.1. Conclusions

The post market environmental monitoring plan provided by the applicant is in line with the intended uses of maize Bt11. The GMO Panel advises that appropriate management systems should be in place to prevent seeds of maize Bt11 entering cultivation as the latter requires specific approval under Directive 2001/18/EC or Regulation (EC) No 1829/2003.

CONCLUSIONS AND RECOMMENDATIONS

The GMO Panel was requested to issue a scientific opinion for renewal of the authorisation of existing products produced from genetically modified maize Bt11 (EFSA-GMO-RX-Bt11) under of Regulation (EC) No 1829/2003. The scope of this application covers the continued marketing of existing food and food ingredients containing, consisting of or produced from maize Bt11, food additives produced from maize Bt11, feed containing, consisting of or produced from maize Bt11 (feed materials and feed additives) to be used as any other maize grain but not for cultivation, and other products containing or consisting of maize Bt11 with the exception of cultivation which were lawfully placed on the market in the Community before the date of application of Regulation (EC) No 1829/2003 and included in the Community Register of genetically modified food and feed.

In its previous opinion the GMO Panel concluded that the maize Bt11 is unlikely to have adverse effects on human and animal health or the environment in the context of its proposed use (EFSA, 2005).

The updated molecular and bioinformatic analyses provided for the maize Bt11 event do not indicate any safety concerns and the GMO Panel maintains its previous opinion on the safety of this event,

New information from this updated literature review and from additional studies performed by the applicant does not prompt the Panel to change its previous opinion that Bt11 maize is as safe and as nutritious as the non-GM counterparts.

The post market environmental monitoring plan provided by the applicant is in line with the intended uses of maize Bt11. The GMO Panel advises that appropriate management systems should be in place to prevent seeds of maize Bt11 entering cultivation as the latter requires specific approval under Directive 2001/18/EC or Regulation (EC) No 1829/2003.

The GMO Panel concludes that the new information provided by the applicant and the review of the literature that has been published since the previous scientific opinion of the GMO panel does not require changes of the previous scientific opinion on maize Bt11 and addresses the scientific comments raised by the Member States. Therefore, the Panel reiterates the previous conclusion that genetically modified maize Bt11 is unlikely to have an adverse effect on human and animal health or the environment in the context of its proposed uses. This also applies to the products which are the subject of the present application.

DOCUMENTATION PROVIDED TO EFSA

1. Letter from the European Commission, dated 29 June 2007, concerning a request for renewal of authorisation for the placing on the market of maize Bt11 in accordance with Regulation (EC) No. 1829/2003.
2. Acknowledgement letter, dated 20 July 2007, from EFSA to the European Commission (ref. SR/DC/eb (2007) – 2266731).
3. Letter from EFSA to applicant, dated 20 December 2007, with request for clarifications under completeness check (Ref. SR/KL/shv (2007) 2588242).
4. Letter from applicant to EFSA, dated 29 February 2008, providing EFSA with an updated version of the application EFSA-GMO-RX-Bt11 submitted by Syngenta under Regulation (EC) No. 1829/2003.
5. Letter from EFSA to applicant, dated 17th March 2008, delivering the 'Statement of Validity' for application EFSA-GMO-RX-Bt11 maize Bt11 submitted by Syngenta under Regulation (EC) No. 1829/2003 (ref. SR/KL/md (2008) 2871626).
6. Letter from EFSA to applicant, dated 15 July 2008, with request for clarifications/additional information (ref. PB/KL/md (2008) 3171843).
7. Letter from applicant to EFSA, dated 06 August 2008, providing additional information upon EFSA request.
8. Letter from EFSA to applicant, dated 05 September 2008, with request for clarifications/additional information (ref. PB/KL/md (2008) 3276591).
9. Letter from applicant to EFSA, dated 28 October 2008, providing additional information upon EFSA request.

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