Biosafety Advisory Council

07-12-2007

Secretariat

O./ref.: WIV-ISP/BAC/2007_SC_614
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Title: Advice of the Belgian Biosafety Advisory Council on the applications **EFSA/GMO/UK/2005/19 and EFSA/GMO/RX/GA21** of Syngenta under Regulation (EC) No. 1829/2003

Context

Application EFSA/GMO/UK/2005/19

The application EFSA/GMO/UK/2005/19 was submitted by Syngenta on 8 August 2005 for the marketing (import and processing) of the glyphosate-tolerant genetically modified maize GA21 for food and feed applications under Regulation (EC) No. 1829/2003[1]. It was officially acknowledged by EFSA on 7 April 2006.

On the same date EFSA started the formal three-month consultation period of the Member States, in accordance with Articles 6.4 and 18.4 of Regulation (EC) No. 1829/2003 (consultation of national Competent Authorities within the meaning of Directive 2001/18/EC designated by each Member State in the case of genetically modified organisms (GMOs) being part of the products).

Within the framework of this consultation, the Belgian Biosafety Advisory Council, under the supervision of a coordinator and with the assistance of its Secretariat, contacted experts to evaluate the dossier, chosen from the common list of experts drawn up by the Biosafety Advisory Council and the Division of Biosafety and Biotechnology (SBB). Six experts answered positively to this request, and formulated a number of comments to the dossier synthesised by the coordinator. See Annex I for an overview of all the comments and for the list of comments actually placed on the EFSAnet on 5 July 2006.

[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)

The opinion of the EFSA Scientific Panel on GMOs was adopted on 13 September 2007 (The EFSA Journal, 2007, 541, 1-25)[2], and published together with the responses from the EFSA GMO Panel to comments submitted by the experts during the three-month consultation period.

On 4 October 2007 the opinion of EFSA was forwarded to the Belgian experts. They were invited to give comments and to react if needed to the answers given by the EFSA GMO Panel, in particular in case the comments formulated in their initial assessment of the dossier were not taken into account in the opinion of EFSA.

The comments formulated by the experts together with the opinion of EFSA including the answers of the EFSA GMO Panel form the basis of the advice of the Biosafety Advisory Council given below.

Application EFSA/GMO/RX/GA21

The application EFSA/GMO/RX/GA21 was submitted by Syngenta on 28 June 2007 for the renewal of the authorisation of maize GA21 as existing products (food additives, feed materials and feed additives produced from GM maize GA21) within the framework of Regulation (EC) No. 1829/2003. It was officially acknowledged by EFSA on 6 September 2007.

All data required for the risk assessment of this application have also been provided in application EFSA/GMO/UK/2005/19. In consequence, the Biosafety Advisory Council issues a single comprehensive advice covering both applications.

Scientific evaluation

1) According to the Biosafety Advisory Council, *no major risks were identified neither concerning the molecular characterisation nor the environment*[3].
2) The Biosafety Advisory Council is of the opinion that the compositional analysis of the maize does not raise any health safety concerns.
3) Following the comments submitted by the Belgian experts, the Biosafety Advisory Council considers that the assessment of the potential *allergenic risk* should have been completed with additional data concerning the allergenicity of the whole crop or kernels.
4) Following the EFSA guidelines, animal trials are not required in this context. The applicants did perform animal trials but owing to an insufficient power of the statistical analysis and/or the sensitivity of the trials, the results of the animal trials were not conclusive and did *not allow to draw a sound scientific opinion*.

[2] see: http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178648864472.htm

[3] As the application doesn't imply a cultivation of the plant in EU, a full environmental assessment is not required in EFSA procedure and was not achieved.

General conclusion

1) Based on the scientific assessment of the dossier done by the Belgian experts,
Taking into account the opinion of EFSA, the answers of the EFSA GMO Panel to the questions raised by the Belgian experts, and considering the data presently available,
On the basis of the compositional analysis, the Biosafety Advisory Council, can agree with the overall conclusion of the GMO panel of EFSA that: "it is unlikely that maize GA21 will have any adverse effects on human and animal health or on the environment in the context of its intended uses".

2) The Biosafety Advisory Council is of the view that:
a) in the future, EFSA should systematically request from the applicants the evaluation of the potential allergenicity of the whole GM plant or kernels. This can be achieved through simple experiments, i.e. by comparing IgE-binding patterns of native and GM plant protein extracts and/or by measuring the content in known major allergens.
b) the power of the statistical analysis and/or the sensitivity of the tests performed on animals for toxicological and nutritional assessment need to comply with standards of good statistics in order to allow scientifically sound conclusions. Indeed, in order to support the results of the compositional analysis, animal trials must be conducted adequately.

Because of these remarks, some members of the BAC are not convinced that the health safety of this transgenic maize has been proven,

p.o.

Prof. D. Reheul
President of the Biosafety Advisory Council.

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Annex I : Full comments of experts in charge of evaluating application EFSA/GMO/UK/2005/19 and comments submitted on the EFSAnet (ref: BAC_2006_PT_399)

Bioveiligheidsraad
Conseil de Biosécurité

05 July 2006

Secretariaat
Secrétariat

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Comments of experts in charge of evaluating the application EFSA/GMO/UK/2005/19
and
Comments submitted on the EFSAnet on mandate of the Biosafety Council

Mandate for the Group of Experts: mandate of the Biosafety Advisory Council (BAC) of 11 May 2006
Coordinator: Prof. dr. ir. Dirk Reheul
Experts: Pascal Cadot (KUL), Rony Geers (KUL), Jean-Pierre Maelfait (Instituut voor Natuurbehoud), Peter Smet (Consultant), Frank Van Breusegem (VIB), Johan Van Waes (CLO)
Domains of expertise of experts involved: Genetics, genome analysis, genetic engineering, immunology, alimentary allergology, animal feed, labelling of food/feed, consumer information, ecology, plant-insect relations, nature conservation, agronomy, crop protection, crop production management, herbicide tolerance biosafety research, maize
Secretariat: Adinda De Schrijver, Martine Goossens

INTRODUCTION

Dossier **EFSA/GMO/UK/2005/19** concerns an application of the company **Syngenta** for the marketing of the genetically modified **maize GA21** for food and feed applications under Regulation (EC) 1829/2003.
The application has been officially acknowledged by EFSA on 07 April 2006.
The scope of the application is:
☒ GM plants for food use
☒ Food containing or consisting of GM plants
☒ Food produced from GM plants or containing ingredients produced from GM plants
☒ GM plants for feed use
☒ Feed produced from GM plants
☒ Import and processing (Part C of Directive 2001/18/EC)
☐ Seeds and plant propagating material for cultivation in European Union (Part C of Directive 2001/18/EC)

Depending on their expertise, the experts were asked to evaluate the genetically modified plant considered in the application on its 1) molecular, 2) environmental, 3) allergenicity, 4) toxicity and/or 5) food and feed aspects. It was expected that the expert should evaluate if the information provided

in the application is sufficient in order to state that the marketing of the genetically modified plant for its intended uses, will not raise any problems for the environment or human or animal health. If information is lacking, the expert was asked to indicate which information should be provided and what the scientifically reasoning is behind this demand.

The comments are structured as in the "Guidance document of the scientific panel on genetically modified organisms for the risk assessment of genetically modified plants and derived food and feed" (EFSA Journal (2004), 99, 1-94). Items are left blank when no comments have been received either because the expert(s) focused on other related aspects, or because for this dossier the panel of experts who accepted to evaluate the dossier didn't have the needed expertise to review this part of the dossier.

List of comments received from the experts

A. GENERAL INFORMATION

Comments/Questions of the expert(s)

Comment 1
See D.9.7

Comment 2
According to the dossier the scope of application does not include cultivation of event GA21 maize in the EU. It can however be worth to give some remarks on the different topics, dealing with cultivation and survivability of seeds, in the case that the applicant should ask in the near future for an extension for the scope of cultivation.

Comment 3
Appendix 1: Portfolio
"…offers outstanding glyphosate tolerance…. Even at six times the recommended rate."
Are there any data available concerning the herbicide consumption on a GMO field compared to an otherwise identical non-GMO field? By comparing these data, it is important to look at the following items:

- What types of herbicides are used in each case (GMO vs non-GMO)
- Consumption (amount per surface unit)
- Toxicological and ecotoxicological profile of the herbicides used.

If the environmental load (concerning toxicology and ecotoxicology) seems to be higher on a GMO field, relative to a (identical) non-GMO field, then, to my point of view, it is important to look at these consequences as well.

Comment 4
The general information provided is complete / no questions.

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

Comments/Questions of the expert(s)

Information is sufficient / no questions.

C. INFORMATION RELATING TO THE GENETIC MODIFICATION

Comments/Questions of the expert(s)

Information is complete. The detailed and clear description provides all data necessary to make a full assessment of the molecular aspects of the genetic modification.

D. INFORMATION RELATING TO THE GM PLANT

D.1 Description of the traits and characteristics which have been introduced or modified

Comments/Questions of the expert(s)

Sufficient information / no questions.

D.2. Information on the sequences actually inserted or deleted

Comments/Questions of the expert(s)

All necessary information is presented, including the complete sequence of the 20,5 kb fragment containing the inserted sequence.

D.3. Information on the expression of the insert

Comments/Questions of the expert(s)

Sufficient information / no questions.

D.4. Information on how the GM plant differs from the recipient plant in: reproduction, dissemination, survivability

Comments/Questions of the expert(s)

Remarks concerning the survivability of seeds of maize: In the dossier it is mentioned that seed can only survive under a narrow range of climatic conditions. Volunteers are killed by frost. This is correct but from our experience maize seeds can survive in the soil during a not so severe winter. It can happen that out of full ears, fallen on the ground at harvest and after labouring of the land, covered with soil, some seeds survive and give plantlets during the next season. So here in the case of GMO-plants it will be necessary to have a follow up of the fields in the next year to detect for surviving plants. This information is only relevant if at a certain moment the scope would be extended to cultivation in Europe.

D5. Genetic stability of the insert and phenotypic stability of the GM plant

Comments/Questions of the expert(s)

Comment 1

Are the GMO-plants already tested in more northern countries, with a cold spring and in many cases with bad conditions in autumn? Will the variety behaviour under such conditions be phenotypic the

same? What will be the reaction after a herbicide control on plants grown in spring under not optimal conditions?

Comment 2
Genetic stability is demonstrated by Southern Blot analysis. Sufficient details are provided.

D.6. ANY CHANGE TO THE ABILITY OF THE GM PLANT TO TRANSFERR GENETIC MATERIAL TO OTHER ORGANISMS

Comments/Questions of the expert(s)

Chances to transfer genetic material to other organisms are negligible.

D.7. INFORMATION ON ANY TOXIC, ALLERGENIC OR OTHER HARMFUL EFFECTS ON HUMAN OR ANIMAL HEALTH ARISING FROM THE GM FOOD/FEED

D.7.1 Comparative assessment

Comments/Questions of the expert(s)

In this chapter it is mentioned that Event GA 21 was compared with relevant control maize lines that had not been genetically modified. Commercial varieties were also included in the comparison where possible. What does it mean? The GA 21 is tolerant to glyphosate. So I think it is not possible to compare with commercial varieties, unless they are also tolerant to glyphosate (= are also genetically modified).

D.7.2 Production of material for comparative assessment

Comments/Questions of the expert(s)

D.7.3 Selection of material and compounds for analysis

Comments/Questions of the expert(s)

D.7.4 Agronomic traits

Comments/Questions of the expert(s)

In the dossier it is mentioned that the scope of application does not include cultivation, but the applicant add that measurement and observation of agronomic characteristics can add to the assessment of unintended effects of the genetic modification. Furthermore it is noted that "While some differences between transgenic and control were found to be significant, there were no consistent trends in the data across locations or hybrids that would indicate that any of these differences were due to the presence of the transgene".
My question and remark: Can the applicant give some more information about "which differences were significant". Are these for quantitative or qualitative characteristics? In the last case this can be important to have information of the content of the GM seeds (the same as for the non GM seeds?), because food and feed from seeds and plants will be imported.

D.7.5 Product specification

Comments/Questions of the expert(s)

D.7.6 Effect of processing

Comments/Questions of the expert(s)

D.7.7 Anticipated intake/extent of use

Comments/Questions of the expert(s)

D.7.8 Toxicology

Comments/Questions of the expert(s)

D. 7.8.1 Safety assessment of newly expressed proteins

Comments/Questions of the expert(s)

Appendix 19
Blood clinical chemistry: statistical analysis of some parameters is based on two measurements. To what extent is it meaningful to perform statistical analysis in these cases?

Appendix 22
83% (w/w) of the test substance is protein. What about the remainder?

D.7.8.2 Testing of new constituents other than proteins

Comments/Questions of the expert(s)

D.7.8.3 Information on natural food and feed constituents

Comments/Questions of the expert(s)

D.7.8.4 Testing of the whole GM food/feed

Comments/Questions of the expert(s)

Appendix 23

- "Adjusted mean bodyweights for males fed diets containing 41.5% Event GA21 positive transgenic grain from maize that has been sprayed with glyphosate were statistically significantly lower compared to the respective controls in week 6, 10, 12, 13 and 14."
- "Food utilisation in males was statistically significantly lower in the 41.5% Event GA21 positive transgenic maize grain group (from plants sprayed with glyphosate) in weeks 5-8 and overall (weeks 1-13) compared to control."
- "Hind limb grip strength was statistically significantly lower in males fed diet containing 41.5% Event GA21 positive transgenic maize grain (sprayed with glyphosate) compared to control."

These items are mentioned by way of precaution. Personally, I do not believe there seems to be a problem, but it may be worth discussing it.

D.7.9 Allergenicity

Comments/Questions of the expert(s)

In section 7.9.1, it is said that maize is widely consumed with no history of allergenicity. This is not true as allergic reactions (including anaphylaxis) to maize have been documented, and allergens have been described (Pasini et al. 2002; Pastorello et al. 2003; Weichel et al 2006a; Weichel et al. 2006b).

The reviewer agrees when the applicant states that the amino-acid sequence of mEPSPS does not match the sequence of any known allergen (including gliadins).
Although not a formal proof of the absence of allergenicity, the applicant performed a test for the resistance to digestion of mEPSPS, where it is shown that the protein is readily degraded in the presence of simulated gastric fluid.
The resistance to heat (thus cooking) has also been evaluated, although this cannot be considered as a test for proving the absence of allergenicity. As an example, one of the major allergens of maize is heat-resistant (Pastorello et al. 2003).
In addition, eleven maize allergens have recently been determined (Weichel et al. 2006a), but none seems to correspond to the native EPSPS protein, excluding further this and alike proteins as potentially allergenic.
As a conclusion, the reviewer agrees when it is said that mEPSPS is unlikely to be allergenic.

Section 7.9.2
The potential allergenicity of the whole crop has not been evaluated. Given that maize can be considered as an allergenic source, and given that the introduction and expression of the new trait might influence the expression of other proteins (including allergens), it is recommended to assess, by using patient's serum for example, whether there is no increase in the expression of known maize allergens, or no induction of new maize allergens not yet observed. This can be achieved by comparing IgE-binding patterns of native and GA21 corn protein extracts.

D.7.10 Nutritional assessment of GM food/feed

Comments/Questions of the expert(s)

D.7.11 Post-market monitoring of GM food/feed

Comments/Questions of the expert(s)

D.8. MECHANISM OF INTERACTION BETWEEN THE GM PLANT AND TARGET ORGANISMS (IF APPLICABLE)

Comments/Questions of the expert(s)

D.9. POTENTIAL CHANGES IN THE INTERACTIONS BETWEEN THE GM PLANT WITH THE BIOTIC ENVIRONMENT RESULTING FROM THE GENETIC MODIFICATION

D.9.1. Persistence and invasiveness

Comments/Questions of the expert(s)

Comment 1
It is mentioned that maize is highly domesticated and cannot survive without human intervention, especially under normal European climatic conditions. How must we interpret the term "normal": southern Europe conditions (warm and dry) are more favourable for maize plants compared to northern Europe (cold and wet in spring).

Comment 2
Main text page 29
"In the unlikely event that small amounts of grain accidentally found there way into the environment…"
I do not agree with this. When harvested, the grains are mechanically removed from the cob. During this process inevitable losses occur, which are eaten by birds and other animals.
In any case, this is not an unlikely event.

Comment 3
Information provided: sufficient

D.9.2 Selective advantage or disadvantage

Comments/Questions of the expert(s)

Information provided: sufficient

D.9.3 Potential for gene transfer

Comments/Questions of the expert(s)

Comment 1
Negligible

Comment 2
Information provided: sufficient

D.9.4 Interactions between the GM plant and target organism

Comments/Questions of the expert(s)

Information provided: sufficient

D.9.5 Interactions of the GM plant with non-target organism

Comments/Questions of the expert(s)

Information provided: sufficient

D.9.6 Effects on human health

Comments/Questions of the expert(s)

D.9.7 Effects on animal health

Comments/Questions of the expert(s)

1) File 19: GA21-0104: Single dose oral toxicity study in the mouse.
A total of 20 animals were studied, i.e. 10 control, 10 treated. The observed coefficient of variation with respect to body weight was 14%, and the difference between the mean values was about 3%. In order to have an opportunity to find a statistically significant difference at $P<0.05$ with a power of 80%, the number of animals should have been 120 per group (Berndtson, 1991). Hence, conclusions made in relation to growth, feed intake, clinical observations, … are not valid.

2) File 23: Event GA21 maize grain: 90 day whole food safety study in rats.
A total of 144 animals were studied, i.e. 6 treatment groups with 12 female and 12 male rats. The observed coefficient of variation with respect to body weight was 9%, and the difference between the mean values was about 8%. In order to have an opportunity to find a statistically significant difference about 33 animals per group instead of 24 should have been available (Berndtson, 1991). Hence, conclusions made on the investigated variables are not valid.

3) File 24: Evaluation of event GA21 Transgenic maize (corn) in Broiler Chickens.
A total of 300 birds per treatment were available, while a total of 42 would have been enough to find a statistically significant difference of 2% between the mean values having a coefficient of variability of 8% (Berndtson, 1991). However, the authors explained the observed statistical difference by the fact that the birds were selected at random and not by a treatment effect. This is not a correct conclusion,

since at random selection is a prerequisite for a sound statistical analysis. Hence, the observed differences have to be explained by treatment effects.

D.9.8 Effects on biogeochemical processes

Comments/Questions of the expert(s)

Information provided: sufficient

D.9.9 Impacts of the specific cultivation, management and harvesting techniques

Comments/Questions of the expert(s)

In this paragraph it is mentioned that the scope of application does not include cultivation of maize plants of Event GA 21 in the EU. Nevertheless I give here some remarks in the case that the applicant should ask in the near future for an extension for the scope of cultivation. In the framework of the EU-regulation 2002/53 a new variety have to be submitted to DUS (Distinctness, Uniformity, Stability) and VCU (Value for Cultivation and Use) tests before the variety can be commercialised. The new variety has to be compared with the best existing standard varieties. So my question here is : can the GM- maize be incorporated in normal VCU trials, for example treated with specific herbicides for maize and will the agronomical value be the same as tested in trials, where herbicides for which the variety is tolerant were used?

D.10. POTENTIAL INTERACTIONS WITH THE ABIOTIC ENVIRONMENT

Comments/Questions of the expert(s)

Information provided: sufficient

D.11. ENVIRONMENTAL MONITORING PLAN

D.11.1 General

Comments/Questions of the expert(s)

Comment 1

If seeds were imported by train containers for making food and feed, some monitoring has to be done if there are no maize plants along the railway roads. As already mentioned under a moderate winter seeds of maize can survive and can give plantlets in the next spring; so these plants have to be destroyed.

Comment 2

Information provided: sufficient

D.11.2 Interplay between environmental risk assessment and monitoring

Comments/Questions of the expert(s)

Information provided: sufficient

D.11.3 Case-specific GM plant monitoring

Comments/Questions of the expert(s)

Information provided: sufficient

D.11.4 General surveillance of the impact of the GM plant

Comments/Questions of the expert(s)

Information provided: sufficient

D.11.5 Reporting the results of monitoring

Comments/Questions of the expert(s)

In my opinion, it is very important that the General Surveillance report is made available for the scientific community and the general public.

References

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