GenØk - Centre for Biosafety

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Assessment of the technical dossier submitted under EFSA/GMO/BE/2011/81 for approval of transgenic rapeseed MS8, RF3, and MS8xRF3 from Bayer CropScience AG

Submitted to

Direktoratet for Naturforvaltning

by

Centre for Biosafety – GenØk
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KONKLUSJON PÅ NORSK

Hovedkonklusjon og anbefalinger

Vi har i vår gjennomgang funnet flere svakheter av begrepsmessig art, mangel på informasjon, feilaktige konklusjoner og mangelfulle empiriske data som hver for seg og til sammen ikke støtter søkers påstand om sikker bruk av MS8, RF3 AND MS8XRF3 rapeseed. Søker har ikke fremskaffet noe av den informasjonen som er nødvendig for å kunne vurdere samfunnsnytte og bærekraftighet, noe som er påkrevd i den norske genteknologiloven for godkjenning i Norge. Disse manglene gjør at vi mener at denne søknaden er ufullstendig i sin nåværende form. Vi anbefaler derfor å avslå søknaden samt at en ny søknad bare bør vurderes om søker har adressert de mangler vi har belyst.

SUMMARY OF THE ASSESSMENT OF THE TECHNICAL DOSSIER RELATED TO EFSA/GMO/BE/2011/81

As a designated National Competence Center for Biosafety, our mission at GenØk in advice giving is to provide independent, holistic and useful analysis of technical and scientific information/reasoning in order to assist authorities in the safety evaluation of biotechnologies proposed for use in the public sphere.

The following information is respectfully submitted for consideration in the evaluation of product safety and corresponding impact assessment of events MS8, RF3 and MS8XRF3, setting out the risk of adverse effects on the environment and health, including other consequences of proposed release under the pertinent Norwegian regulations.

This submission is structured to address specific provisions for an impact assessment required under the Norwegian Gene Technology Act of April 1993, focusing on the requirements in Appendix 2 - Principles for environmental risk assessment pursuant to sections 13-16 of the regulations, and Appendix 4 - Evaluation of ethical considerations, sustainability and benefit to society, cf section 17 of the "Regulations relating to impact assessment pursuant to the Gene Technology Act" of December 2005, pursuant to section 11 cf section 8. The information presented here may be applicable to more than one provision in different appendices.

We have targeted our critique to address the information needs under the relevant provisions that relate to our particular area of competence in biotechnology assessment as comprehensively as possible. Lack of commentary on our part towards any information under consideration should not be interpreted as specific endorsement of that information.

This submission was built in large part using the **Biosafety Assessment Tool** (https://bat.genok.org/bat/) produced by the University of Canterbury and GenØk – Centre for Biosafety. This is a free-to-the-public resource for hazard identification and risk assessment of genetically modified organisms.

All page numbers not directly referenced refer to the document Part 1 of the technical dossier "Application for authorization to place on the market MS8, RF3 AND MS8XRF3 rapeseed in the European Union, according to Regulation (EC) No. 1829/2003 on genetically modified food and feed", submitted by the Applicant.

Key findings

After a analysis of many of the portions of the dossier on MS8, RF3 AND MS8XRF3 submitted by the Applicant, we outline a number of shortcomings in the dossier that do not justify the Applicant's conclusion of safety, based on the given data. Our input focuses on a critique of the Applicant's dossier and covers two broad issues:

1. Insufficient information to support safe use related to inappropriate assumptions, faulty reasoning, or scientifically unjustified interpretations of the data by the Applicant

2. Missing information in relation to requirements under the Norwegian Gene Technology Act

Within each specific point we suggest the appropriate action to address the deficiencies where possible. In the concluding section of our assessment is a recommendation on the decision for approval.

Lastly, Codex Alimentarius guidelines allow Norway to ask for specific data of the type we identify and recommend obtaining. Norway therefore may request such information without concern of a challenge from the World Trade Organisation.

We also wish to orient you towards two other critical pieces of information related to this assessment, focused on health and toxicological consequence of use of this product and its co-products (e.g. herbicides) for its intended use.

First, the Austrian Environment Authority conducted a scientific evaluation related to these events when the applicant originally applied for import only use. They found compelling scientific grounds not to warrant the approval of these events within its boarders (EFSA subsequently evaluated the Austrian submission, and yet rejected it on the basis that the report did not contain evidence that proved their assertions – inappropriately shifting the burden of proof on risks, not on safety). Their report (english follows the german summary) is submitted along with this assessment.

Second, it is worth noting that in a previous assessment for import use conducted by the VKM titled "Helse- og miljørisikovurdering av genmodifisert oljeraps – linje MS8, RF3 og MS8xRF3 fra Bayer CropScience AG (C/BE/96/01)", found that the applicants own toxicological data was out of date and not relevant for the evaluation of health consequences associated with use as food or animal feed[1].

Recommendations

Based on our findings, we propose a number of specific recommendations, summarized here and detailed in the critique below.

1. The applicant's submission, and its interpretations should be conducted on the basis not only as "accidental, unintentional presence" in food, but as if the event applied for use in food was to be wholly consumed at any level of consumption. The application should be analyzed in such a manner that conforms not to the smallest level of exposure that would be allowed with the approval, but the largest.

[1] "Søkers dokumentasjon knyttet til toksisitet er av eldre dato, og ikke relevant for å belyse helsemessige konsekvenser ved bruk av rapslinjene som fôr.", VKM report 08/307

2. We recommend that applicant submits newly designed toxicity and allergenicity studies relevant to the application at hand.

3. We recommend that applicant provide information pertaining to the functional status of the transgenic protein after processing and also on the effects of MS8, RF3 AND MS8XRF3 inhalation in animals that are used as models of acute respiratory syndrome, compared with inhalation of the proper conventional comparator. This should include an analysis of allergenicity and toxicity.

4. The Applicant should submit required information on the social utility of MS8, RF3 AND MS8XRF3 and its contribution to sustainable development, in accordance with the Norwegian Gene Technology Act.

Overall recommendation

Based on our detailed assessment, we find that the informational, empirical and deductive deficiencies identified in the dossier do not support claims of safe use, social utility and contribution to sustainable development of MS8, RF3 AND MS8XRF3. **Critically, the Applicant has not included any of the required information to assess social utility and sustainability as required in Appendix 4 of the Norwegian Gene Technology Act, which would be necessary for consideration of approval in Norway.** Hence at minimum, the dossier is deficient in information required under Norwegian law. A new application or reapplication should only be reconsidered with the delivery of the information requests recommended here, including any additional information deemed significant by the Norwegian authorities.

Therefore, in our assessment of MS8, RF3 AND MS8XRF3, we conclude that based on the available data, including the safety data supplied by the Applicant, the Applicant has not substantiated claims of safety satisfactorily or provide the required information under Norwegian law to warrant approval in Norway at this time.

ASSESSMENT OF THE TECHNICAL DOSSIER RELATED TO EFSA/GMO/BE/2011/81

About the event

The transgenic rapeseed MS8, RF3 AND MS8XRF3, developed by Bayer CropScience AG, has been genetically engineered as a hybid development system in rapeseed. The event RF3 rapeseed also has the *bar* gene (from *Streptomyces hygroscopicus*) encoding for a phosphinothricin acetyl transferase (PAT) that confers tolerance to herbicides containing glufosinate-ammonium.

Assessment

We note that previous assessments by competent authorities or expert committees in the EU and Norway do not share the conclusions made by the applicant. We also wish to orient you towards two critical pieces of information related to this assessment, focused on health and toxicological consequence of use of this product and its co-products (e.g. herbicides) for its intended use.

First, the Austrian Environment Authority conducted a scientific evaluation related to these events when the applicant originally applied for import only use. They found compelling scientific grounds not to warrant the approval of these events within its boarders (EFSA subsequently evaluated the Austrian submission, and yet rejected it on the basis that the report did not contain evidence that proved their assertions – inappropriately shifting the burden of proof on risks, not on safety). Their report (english follows the german summary) is submitted along with this assessment.

Second, it is worth noting that in a previous assessment for import use conducted by the VKM titled "Helse- og miljørisikovurdering av genmodifisert oljeraps – linje MS8, RF3 og MS8xRF3 fra Bayer CropScience AG (C/BE/96/01)", found that the applicants own toxicological data was out of date and not relevant for the evaluation of health consequences associated with use as food or animal feed[2].

1. Insufficient information to support safe use related to inappropriate assumptions, faulty reasoning, or scientifically unjustified interpretations of the data by the Applicant

1.1 Inappropriate narrowing of the scope and analysis of application

[2] "Søkers dokumentasjon knyttet til toksisitet er av eldre dato, og ikke relevant for å belyse helsemessige konsekvenser ved bruk av rapslinjene som fôr.", VKM report 08/307

It should be noted that the applicant has not supplied new data in relation to this application, merely analyzed existing data in relation to human and animal consumption. Further, the analysis is explicitly noted as limited in framing by the applicant. The Applicant perplexingly then concludes that "no new data has been found that impacts the conclusions of the previous risk assessments".

The Applicant states that:

"The scope of this application has been selected in order to cover accidental, unintentional presence of traces of MS8/RF3 oilseed rape grain in food. It complements existing scopes for the designated use of MS8/RF3 oilseed rape that have already been notified and authorized in the EU." (p. 6).

Yet we are unaware of any EFSA approvals or assessments that differentiates between levels of expected food use. Therefore we find the limitations by the applicant to conduct its analysis in a frame "to cover accidental, unintentional presence" in food as unjustified. If the applicant is to be granted approval for food use, there are no such restrictions as food under a limited circumstance. Hence, the applicant should conduct its analysis of safety on the basis the event would be wholly consumed as food and not consumed as a result of incidental presence in food.

The Applicant's interpretations on this basis can be found on p. of the dossier:

"Bayer CropScience AG is unaware of any additional data that would change the previous conclusions of EFSA on the safety of MS8/RF3 oilseed rape or that would indicate that the previous conclusions cannot be extended to the scope of the current application, i.e. use of food containing or consisting of MS8/RF3 oilseed rape and food produced from MS8/RF3 oilseed rape or containing ingredients produced from MS8/RF3 oilseed rape (with the exception of processed oil) *with the aim to cover for accidental, unintentional presence of traces of MS8/RF3 oilseed rape grain in food*." [emphasis added]

Analyzing and the interpreting with such a narrow scope so narrowly may lead to the underestimation of potential exposure, and hence potential risks from the consumption of this event.

Recommendation: The applicant's submission, and its interpretations should be conducted on the basis not only as "accidental, unintentional presence" in food, but as if the event applied for use in food was to be wholly consumed at any level of consumption. The application should be analyzed in such a manner that conforms not to the smallest level of exposure that would be allowed with the approval, but the largest.

1.2 Existing food safety/ exposure studies related to this application are insufficient to conclude safety of this product

1.2.1 Assessment of the study by Pfisher, 1999[3]

We agree with the prior assessments of the VKM that the studies do not contain sufficient and/or relevant information to assess the safety of these events for human and animal consumption.

We find several fatal flaws in the aforemention study used in support of a conclusion of safe use. Specifically:

- Study design: Control and testing diets are insufficient to correlate the observed increase of lipids in blood. More test and control groups would be necessary to arrive at a scientifically supportable conclusion on elevated lipid levels.

- Study design: The groups of animals are too small to draw any statistical conclusions.

- Study design: Animal weights within groups are to variable to draw statistically meaningful conclusions. The rats used in the experiment are of different sizes at the beginning of the experiment, indicating they are likely from different age groups.

- Study design: Blood samples were taken just once after the feeding experiment. There is no baseline taken for comparison. The test animals were for 18h in a metabolic cage prior to when blood sample was taken, a high stress condition that may introduce secondary variables into the blood values.

- Missing information: The animals having PAT in the diet appear to have altered histology of the spleen, but no explanation given (only that changes were ”expected” in the strain of rats selected).

1.2.2 Assessment of the acute toxicity study of the BAR gene by Kennel, 2005[4].

Once again we find reason to agree with the prior assessments of the VKM that the studies referenced by the applicant do not contain sufficient and/or relevant information to assess the safety of these events for human and animal consumption.

We find several fatal flaws in the aforementioned study used in support of a conclusion of safe use. Specifically:

- Study design. 14 days are reported to have lapsed between injection of the test protein and histological and blood analyses. Shorter time intervals for analysis after injection would be necessary to capture shorter-term responses.

[3] Pfisher 1999 (GmbH internal report M-140484-07-1)

[4] Kennel 2002 (Bayer Crop Science M-211118-02-1)

- Conclusions: The study authors place significant weight on the lack of mortality to conclude no toxic effect, yet clearly toxic effects do not necessarily need to be fatal to be acute. Only properly designed feeding studies using processed rapeseed and based on actual consumption patterns in the target population could clarify this point.

- Study design: Test protein used is not derived from plant-sources but a bacterial analog. Comparisions between feeding studies and direct test protein injection lacks scientific validity.

- Conclusions: The authors conclude that the protein is not allergenic based on the in silico study, yet immunogenic responses do not necessarily follow a dose-response curve.

We recommend that applicant submits newly designed toxicity and allergenicity studies relevant to the application at hand.

1.3 Lack of comprehensive exposure analysis

In their analysis, the applicant has only considered dietary exposure pathways in its assessment of possible adverse effects from MS8, RF3 AND MS8XRF3. Inhalation exposure can be expected to be a significant pathway for many people, and a more direct cause of potential adverse effects. The identified use of MS8, RF3 AND MS8XRF3 as a highly processed product, involves milling the grain to rapeseed flour. Humans may more likely have direct, non-dietary exposure to rapeseed flour than through dietary exposure, yet the applicant did not take this into account.

Inhalation experiment would provide possible direct lung cell exposure to any rapeseed flour, including MS8, RF3 AND MS8XRF3. Moreover, inhalation sensitization to allergens can be more important than dietary sensitization. In relation to soya exposure:

"[I]it has to be considered that transgenic plants may be used in industrial processing; hence other exposure routes and sensitization scenarios might become important. For example, manufacturing large amounts of transgenic soybeans containing a food allergen may induce respiratory sensitization due to the generation of allergen-containing dust" (Spok et al., 2005).

We recommend that the applicant provide information pertaining to the functional status of the transgenic protein after processing and also on the effects of MS8, RF3 AND MS8XRF3 inhalation in animals that are used as models of acute respiratory syndrome, compared with inhalation of the proper conventional comparator. This should include an analysis of allergenicity and toxicity.

2. Missing information in relation to requirements under the Norwegian Gene Technology Act

2.1. Social utility and sustainability aspects

In addition to the EU regulatory framework for GMO assessment, an impact assessment in Norway follows the Norwegian Gene Technology Act. In accordance with the aim of the Norwegian Gene Technology Act, production and use of the GMO shall take place in an ethically and socially justifiable way, under the principle of sustainable development. This is further elaborated in section 10 of the Act (approval), where it is stated that

> *"significant emphasis shall also be placed on whether the deliberate release represent a benefit to the community and a contribution to sustainable development"*.

These issues are further detailed in the regulation on consequence assessment section 17 and its annex 4. The Applicant has not provided relevant information that allows an evaluation of the issues laid down in the aim of the Act, regarding ethical values, social justification of the GMO within a sustainable development. Given this lack of necessary information for such an evaluation, the Applicant has not demonstrated a benefit to the community and a contribution to sustainable development from the use of MS8, RF3 AND MS8XRF3. The Applicant should thereby provide the necessary data in order to conduct a thorough assessment on these issues, or the application should be refused.

It is also important to evaluate whether alternative options, (e.g. the parental non-GM version of this MS8, RF3 AND MS8XRF3 has achieved the same outcomes in a safer and ethically justified way.

Further, the Norwegian Gene Technology Act, with its clauses on societal utility and sustainable development, comes into play with a view also to health and environmental effects in other countries, such as where GMOs are grown. For instance, it is difficult to extrapolate on hazards or risks taken from data generated under different ecological, biological, and genetic contexts as regional growing environments, scales of farm fields, crop management practices, genetic background, interactions between cultivated crops, and surrounding biodiversity are all likely to affect the outcomes. Hence it cannot be expected that the same effects will apply between different environments and across continents.

Recommendation: The Applicant should submit required information on the social utility of MS8, RF3 AND MS8XRF3 and its contribution to sustainable development, in accordance with the Norwegian Gene Technology Act.

2.2 Ethical considerations

The events RF3 and MS8XRF3 contain the *bar* gene (from *Streptomyces hygroscopicus*) encoding for a phosphinothricin acetyl transferase (PAT) that confers tolerance to herbicides containing glufosinate-ammonium, a class of herbicides that are banned in Norway.The evaluation of co-products, that is, secondary products that are specifically designed and intended to be used in conjunction with the GMO, is considered important in the risk assessment of a GMO (Dolezel et

al, 2009). Therefore, considerations of the co-products also warrant an evaluation of safe use, particularly when there is precedence in policy concerning its used independently.

While it is understood that the Applicant has not applied for deliberate release of RF3 AND MS8XRF3 in Norway, the acceptance of a product in which the intended use includes the use of a product banned in Norway would violate basic ethical and social utility criteria, as laid out in the Act. That is, we find that it would be ethically incongruous to support a double standard of safety for Norway on one hand, and safety for countries from which Norway may import its food on the other. This line of reasoning is consistent with the provisions under the Act to assess ethical, social utility and sustainable development criteria not only for Norway, but for countries from which Norway imports food.

Therefore, we find it difficult to arrive at justified use of these events without engaging in such an ethical double standard. Specifically, this issue is relevent particularly in revised regulations of 2005 Section 17 "Other consequences of the production and use of genetically modified organisms" points 2 and 3 "ethical considerations that may arise in connection with the use of the genetically modified organism(s), and "any favourable or unfavourable social consequences that may arise from the use of the genetically modified organism(s)", respectively.

RF3 AND MS8XRF3 as a stand-alone products may prove to be perfectly as safe as its conventional counterpart, this can not be concluded on the basis of the infromation presented in this application.

Available information for risk assessment evaluation

This evaluation is for the most part based on the Applicant's own submitted information. The directly relevant scientific literature is very limited in some cases, yet we have tried to extract relevant indirect information from the peer-reviewed literature.

All product-related safety testing should have an independent and unbiased character. This goes both for the production of data for risk assessment, and for the evaluation of those data. The lack of compelling or complete scientific information to support the claims of the Applicant highlights the need for independent evaluation of safety studies and molecular information provided, including the raw data produced by the Applicant. We therefore request that mechanisms become elucidated that would allow any scientific information used in pursuit of regulatory approval to be transparent. This would include any information provided by the Applicant used to justify confidentiality claims on any scientific data. We encourage the authorities to insist on this level of transparency and accessibility to all scientific data (including raw data) to ensure the scientific validity of the information presented.

Conclusion

Above we highlight a number of conceptual, empirical and informational deficiencies in the dossier that do not justify a conclusion of safe use, social utility and contribution to sustainable development of MS8, RF3 AND MS8XRF3. Critically, the Applicant has not

included any of the required information to assess social utility and sustainability as required in Appendix 4 of the Norwegian Gene Technology Act, which would be necessary for consideration of approval in Norway. Taken together, these deficiencies fail to address the necessary safety regulations under Norwegian Law, and thus the application is incomplete and should not be approved. A new application or reapplication should only be reconsidered with the delivery of the information requests recommended here, including any additional information deemed significant by the Norwegian authorities.

Therefore, in our assessment of MS8, RF3 AND MS8XRF3 we conclude that based on the available data, including the safety data supplied, the Applicant has not substantiated claims of safety satisfactorily to warrant approval in Norway at this time.

References

BAT. Biosafety Assessment Tool (GenØk and University of Canterbury). www.bat.genok.org/bat.

Codex, 2003. Principles For The Risk Analysis Of Foods Derived From Modern Biotechnology; Codex Alimentarius Commission, CAC/GL 44-2003

Codex (2003a). Codex Work on Foods Derived from Biotechnology. In CAC/GL 45-2003. Codex. http://www.who.int/foodsafety/biotech/codex_taskforce/en/.

Dolezel M, Miklau, M., Eckerstorfer, M., Hilbeck, A., Heissenberger, A., Gaugitsch, H., 2009. Standardising the Environmental Risk Assessment of Genetically Modified Plants in the EU / Standardisierung der Umweltrisikoabschätzung gentechnisch veränderter Pflanzen in der EU. BfN – pp. 259.

Spok, A., Gaugitsch, H., Laffer, S., Pauli, G., Saito, H., Sampson, H., Sibanda, E., Thomas, W., van Hage, M. and Valenta, R. (2005). Suggestions for the assessment of the allergenic potential of genetically modified organisms. Int. Arch. Allergy Immunol. *137*, 167-180.