



GenØk - Centre for Biosafety

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**Assessment of the technical dossier submitted under
EFSA/GMO/BE/2011/98 for approval of transgenic soya FG72
from Bayer CropScience AG**

Submitted to

Direktoratet for Naturforvaltning

by

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SUMMARY OF THE ASSESSMENT OF THE TECHNICAL DOSSIER RELATED TO EFSA/GMO/BE/2011/98

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 FG72 soya, 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 following quoted text that is not directly referenced refers to the technical dossier “Request for Authorization of Herbicide Tolerant Genetically Modified Soybean FG72 for food and feed uses, and import and processing, in accordance with articles 5 and 17 of Regulation (EC) N° 1829/2003 GM Food and GM Feed”, submitted by the Applicant.

Key findings

After a analysis of many of the portions of the dossier on FG72 submitted by the Applicant, we outline a number of inadequacies in the information submitted in the dossier that do not justify the Applicant’s conclusion of safety. Our input focuses on a critique of the Applicant’s dossier and covers two broad issues:

1. Improper assumptions, reasoning, or interpretations of data that do not support a the conclusions given, or other insufficient or missing information and/or data by the Applicant related to the dossier
2. Missing or insufficient information in relation to requirements under the Norwegian Gene Technology Act

Within each specific point we make a recommendation on the appropriate action to address the deficiencies where possible. In the concluding section of our assessment is an overall 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.

Recommendations

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

The Direktoratet for naturforvaltning is encouraged to request the following:

1. The Applicant should provide follow-up analysis of unexpected hybridization patterns to ensure a complete understanding of copy number and arrangements of inserted sequences in FG72.
2. The Applicant's analysis should include the effect of the transformation not only on functional genes, but also on non-coding or regulatory disruptions. Given the deletion and insertions reported after integration of the transgenic DNA into the host genome, the Applicant should provide a survey of the actual RNAs produced or absent at the integration junctions and in the DNA surrounding the insert, preferably using high throughput transcriptome sequencing techniques (Heinemann et al., 2011).
3. The Applicant should provide further details on the methods of purification to ensure comprehensive identification of all protein isoforms that may be present, or conduct the analysis with FG72-derived m2epsps protein. Further, assays to better elucidate the biological significance of differences in protein sequence compositions observed, and further PTM modifications that may be present, should be performed.
4. The Applicant should re-perform the acute toxicity of Rascle 2009 M-358598-01 study utilizing sufficient number of animals within both sexes, so that statistically meaningful results for the detection of differences.

5. The Applicant should re-perform the 90-day feeding to include a complete histological analysis of all groups, along with FG72 diets that simulate the level of real-world exposure to herbicide residues expected on the grain from intended use of the GMO.
6. The Applicant should submit required information on the social utility of FG72 and its contribution to sustainable development, in accordance with the Norwegian Gene Technology Act.
7. Strong consideration should be given to ethical principles when Norway considers one or more of the co-products intended for use with FG72 as harmful. Acceptance of the use of this product would amount to a double-standard of safety between products produced in Norway and the products Norway selects for purchase and import.

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 FG72. **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 FG72, 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/2011/98

About the event

The transgenic soya FG72, developed by Bayer CropScience AG has been genetically engineered with to contains the hppdPfw336 and 2mepsps genes, which produce the proteins HPPD W336 (4-hydroxyl phenyl-pyruvate-dioxygenase) and 2mEPSPS (5-enolpyruvylshikimate-3-phosphate synthase) that confer resistance to two herbicides, isoxaflutole and glyphosate, respectively.

The herbicide isoxaflutole is banned for use in Norway.

Assessment findings

1. Improper assumptions, reasoning, or interpretations of data that do not support a the conclusions given, or other insufficient or missing information and/or data by the Applicant related to the dossier

1.1 Characterization and analysis of the transformation event producing FG72

The molecular analysis of transformation event reveals a complex integration that involves duplication, rearrangement and translocation of a part of the transgene integration cassette

1.1.1 Southern analysis

The Applicant reports an integration scenario for FG72 that includes a rearrangement that and translocation of a portion of the inserted cassette. From page 35 of the dossier:

“However, a number of fragments did run atypically on the agarose gel. This is probably caused by secondary DNA structures. A number of expected fragments could not be visualized, due to either a too small overlap between the fragments and the hybridization probe and/or to the ratio fragment length and probe length.”

The Applicant’s assertions here have no empirical support. Modification of hybridization conditions and probe design would provide greater clarity on the significance of this finding in relation to the expected outcomes. Therefore a conclusion of expected southern hybridization patterns is not justified.

Recommendation: The Applicant should provide followup analysis of unexpected hybridization patterns to ensure a complete understanding of copy number and arrangements

of inserted sequences in FG72.

1.1.2 Analysis of ORFs and endogenous gene disruptions

Genomic analysis of the inserted cassette reveals the formation of 2 new junctions created by the rearrangement and translocation of two regulatory elements, a partial 3_{prime} histonAt at the 3 prime end and a translocation of 158 bases of Ph4a748 promoter sequence at the 5 prime end, respectively.

The Applicant reports the creation of forty-six new ORFs within the transgenic locus and 19 interrupted ORFS in the non-transgenic sequences. Further, 18 promoters were identified in the non-transgenic sequences, where three were interrupted by the insertion event.

However, the applicant's analysis suggests that since these findings did not occur in known functional genes, or did not lead to the creation of known allergens or toxins, and the changes were of inconsequential. That is, the analysis only considers the creation of new ORFs as the only means which new allergens, toxins may be introduced as a result of the transformation. Further the limited analytical criteria held by the Applicant does not consider regulatory sequences that may have been disrupted or altered in a way that will affect gene expression or regulation in the host plant.

Codex takes this into account when requesting that

“In addition, information should be provided: [...] E) to indicate whether there is any evidence to suggest that one or several genes in the host plant has been affected by the transformation process” (§ 33 Codex 2003a).

The limitation of this analysis to functional genes and fully formed ORFs does not have support from the scientific literature, or in Codex guidelines. In addition to the direct disruption of genes or regulatory sequences at the insertion site, deletions and rearrangements in chromosomal sequences around the insertion site may affect important regulatory process that may be as important as function gene disruption (Latham et al., 2006 and references therein). Zolla et al (2008) conclude that:

“[I]t is also evident that the insertion of a single gene does not result in a unique newly expressed protein, but rather in many differently expressed genes with respect to the control. This could be due to the fact that, when the transgene enters the nucleus, many genetic loci are randomly affected by the insertion procedure”. (p. 1854 Zolla et al., 2008).

Thus, in addition to new junctions caused by insertions of recombinant DNA and thus possible novel RNAs in the transcriptome and proteins in the proteome, there may be a loss of endogenous RNAs and proteins that have no apparent effect on agronomic qualities but may have an effect on the expression or accumulation of toxins or anti-nutrients. The bioinformatic analysis provided by the Applicant does not substitute for a survey of actual RNAs produced at the junctions or for a survey of deleted RNAs.

Recommendation: The Applicant's analysis should include the effect of the transformation not only on functional genes, but also on non-coding or regulatory disruptions. Given the deletion and insertions reported after integration of the transgenic DNA into the host genome, the Applicant should provide a survey of the actual RNAs produced or absent at the integration junctions and in the DNA surrounding the insert, preferably using high throughput transcriptome sequencing techniques (Heinemann et al., 2011).

1.2 Use of bacterially produced transgenic proteins in place of FG72 plant produced proteins for safety assessment

The Applicant claims that:

“Since it is not feasible to produce an adequate amount of protein for these studies from transgenic FG72 soybean plants, it was necessary to demonstrate the equivalence between the E.coli-produced protein and the plant produced protein in order to utilize the safety data.” (Martone, 2009).

While this may have been more accurate some years ago, the development of protein isolation and purification technologies have dramatically improved the efficiency of these procedures in recent years. Further, the immunoaffinity column purification method used by the Applicant would have to capacity to produce sufficient quantities of FG72-derived transgenic protein for safety testing.

Of course, microbial production system present the most cost-effective means for producing the protein when one takes up-front costs in mind, however we argue the time and costs the Applicant used to assess the equivalence of bacterially produced and plant produced proteins likely exceeds that it would have taken if the Applicant had endeavored to purify FG72-produced transgenic target proteins in the first place.

To characterize 2mEPSPS protein, the E.coli produced protein was used. A study done by Martone A (2009) was done to proof the equivalence between FG72 and E.coli derived 2mEPSPS. They conclude that there is no difference between the 2mEPSPS proteins from the two sources in molecular weight, mobility and immune-reactivity. A closer look at the study of bioequivalence of the m2epsps reveals that the data does not support the conclusion of equivalence.

First, the antigen used to raise anti-m2epsps antibody/antibodies, and the antibodies themselves utilized in the immunoreactivity assay lacks description, e.g. whether the antigen was derived from an E. coli expression system in the former or if it is a monoclonal or polyclonal antibody in the latter. It is impossible to say, using the evidence provided, that the antibodies would in fact detect all isoforms of recombinant-m2epsps that might be produced in-planta, were they present in the sample. In our view, the Applicant has only succeeding in profiling only a single epitope on an unglycosylated recombinant-m2epesps isoform. This

brings into question the subsequent inference of equivalence and use of *E. coli*-derived m2epsps as a surrogate for FG72-derived m2epsps.

Second, the Developer's means of determining glycosylation status of the two proteins via hybridization of glycoproteins to probes is not the ideal method for sensitive detection of protein glycosylation. A more complete profile is possible using oligosaccharide mapping, liquid chromatography, and mass spectrometry (Werner et al, 2007). Glycosylation PTM are often implicated in increased allergenicity of a protein and should be analyzed (Codex, 2003).

Third, for MALDI-TOF spectrometry shows that 72% of the protein sequence of FG72 soybean produced 2mEPSPS is identical to the protein sequence of *E. coli* produced 2mEPSPS. The rest has not been detected or analyzed due to "partial degradation and not able to analyze". Only a small amount of the N-terminal peptide was detected in *E. coli* produced 2mEPSPS by N-terminal sequencing. Also some of the FG72 produced 2mEPSPS protein may be blocked at the N-terminus. But they do not investigate this further. However, on page 17, Martone (Martone A, 2009) says that this can be due to a modification or low concentration. But this is not further checked.

Further, this level of coverage sufficient to establish the identity of a protein is not necessarily sufficient to exclude-translational modifications 100% coverage is necessary to establish equivalence.

If the aim is to positively identify a protein, it is usually sufficient to detect 50-60% of the amino acids in the protein sample and compare them to a database or the calculated expected results. On the other hand, if the aim is to establish that a protein is identical and has not been altered (e.g. by PTM), then complete coverage is necessary [...]. Moreover, MS can fail to distinguish between, for example, two monosaccharide PTMs of identical molecular weight (Küster, B. et al., 2001). (https://bat.genok.org/bat/?sp=html/topic_guides/ch3_insert_to_trait/proteome_and_metabolome/proteome_testing/ms.html)

Fourth, small differences in protein size between the bacterial and plant versions of m2epsps may be linked to structural differences or differences in post-translational modifications (which would make the protein run slower on the gel, and hence seem "larger". It is well known that eukaryotes produce significantly more PTMs on proteins than prokaryotes particularly glycosylations. PTM serve particular functions in protein folding, targeting, degradation etc., and hence may affect the bioactivity of this protein differentially. Further, many of the PTMs differ/vary between species, tissues, stage of development and according to environmental variables such as temperature and light intensity (Gomord, V. et al., 2005; Küster, B. et al., 2001).

Small differences in amino acid composition between the bacterial and plant versions of m2epsps (lack of terminal methionine in the FG72 version) may be linked further effect the biological activity of the protein. Indeed, changes of single amino acids can drastically alter the characteristics of proteins (e.g. Doyle and Amasino, 2009, Hanzawa et al., 2005, Zubieta

et al., 2008), a fact that underpins the field of directed evolution (reviewed in e.g. Bloom and Arnold, 2009, Tracewell and Arnold, 2009). One of the characteristics that can be changed is immunogenicity. For example, several groups reported significant decreases of IgE binding to a major peanut allergen after mutating single nucleotides (Glaspole et al., 2005, King et al., 2005, Ramos et al., 2009). Even more surprising, in some cases not even an amino acid change is necessary to alter the characteristics of a protein. Kimchi-Sarfaty et al. demonstrated that even synonymous single nucleotide polymorphisms (i.e. differences in the nucleotide sequence of a gene that do not alter the resulting amino acid sequence) can change the substrate specificity of the resulting protein, potentially by affecting its folding patterns during translation (Kimchi-Sarfaty et al., 2007). Changes in the tertiary structure alone can turn benign proteins into toxins (Bucciantini et al., 2002, Ellis and Pinheiro, 2002, Ross and Poirier, 2005), as demonstrated for the Prp proteins causing Creutzfeldt-Jacob disease and mad cow disease (Caughey and Baron, 2006).

Fifth, the study fails to assay the potential PTM differences, particularly glycosylation, between the two versions of the m2epsps proteins. The study authors state the fact that glycosylation of proteins (of which N- and O- linked glycans often impart immunoreactive effects in mammals) occur in plant produced proteins but not in bacterially produced proteins. The authors justify this in the claim that glycosylation in these proteins is not likely as they are chloroplast directed and are not processed in the endoplasmic reticulum, as site for glycosylation. However, this is only true for N-linked glycosylation, glycopation and O-linked glycosylation occur in the golgi apparatus and cytoplasm, respectively. The applicant could equally use mass spectrometry not only for amino acid sequence identification, but also for the identification of PTM differences.

In summary, the standard set by the Developer for bioequivalence is unacceptably low and not justifiable, based on current scientific knowledge for the use of *E. coli*-produced m2epsps protein in studies to assess its safety in FG72 soybean.

Recommendation: The Applicant should provide further details on the methods of purification to ensure comprehensive identification of all protein isoforms that may be present, or conduct the analysis with FG72-derived m2epsps protein. Further, assays to better elucidate the biological significance of differences in protein sequence compositions observed, and further PTM modifications that may be present, should be performed.

1.3 In vitro digestibility of 2mepsps and HPPDW336 in simulated gastric and intestinal fluids

The proteins 2m EPSPS and HPPD W336 are rapidly degraded in simulated intestinal/gastric fluids. However, digestibility is not a suitable tool to look for allergenic potential of a protein. Resistance to digestion might also not be suitable, thus sensitization/boosting of the allergenic response through the respiratory tract might be of higher importance in allergenic sensitization studies (Spok, A et al 2005, p173).

1.4 Allergenicity and toxicity assessment of whole GM food/feed

The Applicant claims that a detailed allergenicity assessment is not necessary because of 1) equivalence in compositional analysis to conventional soybean Jack, 2) molecular analysis of FG72 and wt proteins and 3) because no concerns are raised in relation to the toxicology evaluation of neither 2mEPSPS nor HPPD W336. They conclude that “no increased allergenicity is anticipated”. However the Applicant conducts a poultry feeding study over 42 days, and a 90-day toxicity study in rats.

1.4.1 Toxicity studies in rats and poultry

The Applicant presents an acute toxicity study in mice (Rasclé 2009 M-358598-01). We find the study incomplete and deficient in experimental design and interpretation. For instance, only 5 female animals were used for the study, a number is far too low generating statistically meaningful results for the detection of differences. Further, there is no apparent reason given for the elimination of the male gender in the experiment, where gender differences in responses may be important. The Applicant does not perform any blood sample during the study, important to evaluate the wellbeing of the animals. The safety of the protein HPPD W336 is based solely on an incomplete necropsy and microscopy examination of the spleens. Based on the data these organs showed signs of extramedullary haematopoiesis in all the animals in the control group. This condition is usually related with bone marrow damage of diverse origin, among them cholesterolemia, arteriosclerosis (experimentally), and various toxins and infections (Close et al., 1958; Kwon et al., 2009; Matsumoto et al., 2008; Nagano et al.). Most interesting is the fact that extramedullary haematopoiesis may be gender dependent in singular studies (Shinzawa et al.), which cannot be analyzed based on the nature of the study design. This circumstance presented in the control animals suggested an unknown factor in the animals under study and should have been enough reason to question the results and to repeat the experiment.

Recommendation: The Applicant should re-perform the acute toxicity of Rasclé 2009 M-358598-01 study utilizing sufficient number of animals within both sexes, so that statistically meaningful results for the detection of differences.

Another toxicity study is presented using broiled chicken as animal model (Stafford 2009). Although the number of animals in each group is high, and allows reaching an acceptable statistical power, only 21 animals for gender and treatment were analyzed. The study concentrated on the growing potential of the different diets, comparing the weight of the different parts of the chicken with commercial value. No data is presented about the state of the different internal organs. In general the use of broiled chicken for low doses, long term toxicology studies is controversial since the animals present high mortality and a diverse and severe pathological conditions, complicating interpretation of the results.

Finally, a much more detailed and relevant 90 days feeding trial in rats is presented. The study compares 4 different diets (2 with two different concentrations of FG72 soybean, their jack counterpart and commercial feeding). The study concluded that there are no differences between the FG 72 feeding and their isolate. We find that a number of features of the study design undermine the ability to draw meaningful conclusions from the study.

There are very few differences between the two control diets. We do not understand why the 4 different diets have not been compared directly in the study. It is interesting however to note that the group that presented more pathological signs was the one feed with the commercial diet. Still, diet 3 (15% FG 72) had the highest proportion of pelvic epithelium hyperplasia (a condition presented in several toxicity studies with unknown origin (Greaves, 2012)). Only very few samples from diet 2 (5% FG 72 + 10% Jack counterpart) are analyzed microscopically. The Applicant seems to assume a dose dependent effect. While this is the usual response towards toxins there is exceptions to the rule. The number of positive mononuclear cell infiltrations or disturbance of the microcirculation in the periportal areas of the liver is half of those samples analyzed. We strongly recommend the applicant to finish the microscopic examination of the samples in all the groups.

An important aspect of the feeding trial that seems to have been overlooked involves the possible presence of herbicide residues that would be present on the grain in real world conditions of consumption. The diets given to the animals in any of the above described studies presented do not describe any levels of isoxaflutole or of glyphosate. However, since the herbicide-treated soy will be the product humans and animals will be exposed to, it should be taken into account in feeding trials, which are performed to provide evidence of the safety of FG 72.

Recommendation: The Applicant should re-perform the 90-day feeding to include a complete histological analysis of all groups, along with FG72 diets that simulate the level of real-world exposure to herbicide residues expected on the grain from intended use of the GMO.

1.4.2 Allergenicity studies

A study done by Rouquie (2011) where 6 soy allergic people were tested for their serum response profiles to known endogenous soybean allergens claims that there was no differences between the response profile to FG72, conventional soybean Jack and two other non GM lines. The overall response differed however a lot between individuals (as expected) and to the four samples of maize tested against. There was no clear pattern between the serum samples tested, or between GM or non GM samples. Also, a control group of non-allergic people lacked in the study. Based on this, one cannot conclude that there is no difference in the response profiles to GM or non GM soy here.

Another study by Goodman and Panda (2011) says that there is no obvious difference in IgE binding pattern between soy allergic and not allergic people in the study. Again, the individual IgE responses vary a lot, as expected and especially within the group of soybean allergic individuals. Interestingly, both allergic and non allergic individuals seems to have a response to one of the none –GM soybean lines. The response to soybean derived antigens must therefore be further analysed in a normal control group of a bigger size. Positive in this study is that they have a control group present.

2. Missing or insufficient 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 FG72. 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 FG72 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 FG72 and its contribution to sustainable development, in accordance with the Norwegian Gene Technology Act.

2.2 Ethical considerations: Isoxaflutole and glyphosate as co-products in the intended use of FG72

The event FG72 contains genes that confer specific resistance to herbicide/pesticide name a class of herbicides that are banned in Norway. The evaluation of co-products, that is, secondary products that are specifically designed and intended for use 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.

In depth studies of the toxicity of isoxaflutole reveal acute toxicities in rat model studies, including developmental toxicities (US EPA, 2011)

While it is understood that the Applicant has not applied for deliberate release of FG72 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 relevant 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.

FG72 as a stand-alone product may prove to be perfectly as safe as its conventional counterpart, yet with consideration of co-product usage this can not be concluded on the basis of the information presented in this application.

Recommendation: Strong consideration should be given to ethical principles when Norway considers one or more of the co-products intended for use with FG72 as harmful. Acceptance of the use of this product would amount to a double-standard of safety between products produced in Norway and the products Norway selects for purchase and import.

Conclusion

Available information for risk assessment evaluation

This evaluation is based on the Applicant’s own submitted information, along with our own expertise in related fields. The relevant scientific literature is very limited in some cases, yet we have tried to extract information from the peer-reviewed literature that may inform the scientific validity of the information under consideration. In situations where lack of knowledge, complexity and uncertainty are high, particularly in relation to unknown adverse

effects that may arise as a result of approval for release of a living modified organism into the environment or food supply, the available information may not be sufficient to warrant approval. Further information may address some of these issues, however an accurate description of uncertainties provided by the applicant would provide a more useful basis for assessing the level of risk that may come with regulatory approval of the LMO, taken on a case-by-case basis.

In all cases, 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 the data.

The lack of compelling or complete scientific information to support the claims of the Applicant documented here highlights the need for independent evaluation of the dossier as performed here, including the raw data produced by the Applicant. We therefore support better transparency and independent review of information to ensure high standards within the regulatory process. 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.

Overall recommendation

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 FG72. 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 FG72 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.

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