GenØk - Centre for Biosafety

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Direktoratet for naturforvaltning
Tungasletta 2
7485 Trondheim
Dato: 20.07.2012

Vedlagt er inspill fra GenØk – Senter for Biosikkerhet om høringer EFSA/GMO/DE/2011/99 for Bt11x59122xMIR604x1507xGA21 fra Syngenta Crop Protection AG

Hvis du har noe spørsmål, vennligst ta kontakt.

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Assessment of the technical dossier submitted under EFSA/GMO/DE/2011/99 for approval of Bt11x59122xMIR604x1507xGA21 from Syngenta Crop Protection AG

Submitted to

Direktoratet for Naturforvaltning

by

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SUMMARY OF THE ASSESSMENT OF THE TECHNICAL DOSSIER RELATED TO EFSA/GMO/DE/2011/99

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 Bt11x59122xMIR604x1507xGA21, 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.

Specific recommendations

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

- The Applicant should demonstrate the lack of interactive effects between the transgenic proteins in this stacked event through proper scientific testing and evidence gathering, rather than justify the lack of testing based on assumptions-based reasoning of no effects.

- Under environmental risk assessment, interactions between the proteins should be addressed in more detail and experiments should account for the high total amount of Bt protein in Bt11x59122xMIR604x1507xGA21 maize and for possible interactions of the mixture of Cry1Ab, Cry1F, mcry3A, Cry34Ab1/Cry35Ab.

- The Applicant should also address the potential of non-target effects of Bt toxins

- The regulator is encouraged to consider the safety of co-products intended to be used with the GM event in the evaluation of safety.

- The applicant should have used additional methods to detect the stacked event Bt11x59122xMIR604x1507xGA21and not only detection methods used to detect the single events in the stack.

- The stability of the inserts should be thoroughly examined, ideally over several generations; to show that unintended recombination does not occur.

- Since the 3´ region of the GA21 maize insert is positioned next to the sequence of a known retrotransposon, the genetic stability and the potential for changes in gene expression should be investigated.

- Since comparative Southern Blot analyses were the only method used for the molecular characterization (the inserts and flanks were not re-sequenced in the stacked event) the experiments and resulting data should be of the highest possible quality. There should be a consistency in the used positive controls and the Applicant should use a comprehensive set of smaller probes to in order to evaluate the genetic stability of the Bt11x59122xMIR604x1507xGA21 event.

- The applicant notes that the difference in protein expression is significant without exploring what it can be caused by or what the effect of it might be. Followup studies should be performed.

- The possibility of cross-resistance and change in effect on target/non-target species should be examined.

- The potential adjuvancy of Cry proteins should be further addressed since some scientific studies have shown that the Cry1Ac protein is a potent systemic and mucosal adjuvant.

- The Applicant should submit required information on the social utility of Bt11x59122xMIR604x1507xGA21 and its contribution to sustainable development, in accordance with the Norwegian Gene Technology Act.

Therefore, in our assessment of Bt11x59122xMIR604x1507xGA21, we conclude that based on the available data, including the safety data and monitoring plans supplied by the Applicant, the Applicant has not substantiated claims of environmental 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/DE/2011/99

About the event

The genetically modified maize line Bt11x59122xMIR604x1507xGA21, developed by Syngenta Crop Protection AG, has been produced by conventional breeding between event lines Bt11-, 59122-, MIR604-, 1507- and GA21 maize.

The combined trait product expresses the following proteins: *Cry1Ab*, *Cry1F, Cry34Ab1, Cry35Ab1, mcry3A, PAT*, *pmi* and mEPSPS. These proteins give resistance against certain Lepidoptera pests (*Cry1F* and *Cry1Ab*), protection against corn rootworm larvae (*mcry3A*, *CRY34Ab1* and *CRY35Ab1*), tolerance to the glufosinate-ammonium and glyphosate herbicides (*PAT* and *CP4EPSPS*) and allows the transformats to utilize mannose as a primary carbon source (*pmi*).

Assessment findings

Stacked events

If more than one gene from another organism has been transferred, the created GMO has stacked genes (or stacked traits), and is called a **gene stacked event** like in this case.A stacked organism has to be regarded as a new event, even if no new modifications have been introduced. The gene-cassette combination is new and only minor conclusions could be drawn from the assessment of the parental lines, since unexpected effects (e.g. synergistic effects of the newly introduced proteins) cannot automatically be excluded.

Stacked events are in general more complex and it has been an increased interest in the possible combinatorial and/or synergistic effects that may produce unintended and undesirable changes in the plant – like the potential for up- and down regulation of the plants own genes. Interactions with stacked traits cannot be excluded that the group of expressed toxins in the plant can give specific immunological effects or adjuvant effects in mammals (Halpin 2005, Schrijver et al, 2006).

Bt11x59122xMIR604x1507xGA21 maize combines several classes of Bt proteins active against insects pest like Lepidoptera and Western Corn Rootworm. It is well known that synergistic and additive effects both between Bt toxins and other compounds do occur (Then, 2010). Then (2010) reviews and discusses the evidence for changes in activity and specificity of Bt proteins dependent on synergistic interactions with extrinsic features. Such changes may critically influence the bioactivity and hence the potential for unintended effects and must be carefully considered in the development and risk assessments of stacked events. Robust data are necessary to identify whether the combined presence of transgenes influences expression levels.

Recommendation:

- The Applicant should demonstrate the lack of interactive effects between the transgenic proteins in this stacked event through proper scientific testing and evidence gathering, rather than justify the lack of testing based on assumptions-based reasoning of no effects.

- Environmental risk assessment interactions between the proteins should be addressed in more detail

Safety of Cry genes

As mentioned, Bt11x59122xMIR604x1507xGA21 maize combines 5 different classes of Bt proteins named Cry toxins (Cry1Ab, Cry1F, mcry3A, Cry34Ab1/Cry35Ab1). These toxins are claimed and believed to be safe, however lately the potential of non-target effects of Bt toxins concerning mode of action have been addressed (Gilliand et al 2002, Crickmore 2005, Hilbeck and Schmidt 2006, Mesnage et al, 2012). A review by (Hilbeck and Schmidt 2006) on all Bt-plants found 50% of studies documenting negative effects on tested invertebrates.

In relation to non-target and environmental effects, in two meta-analyses of published studies on non-target effects of Bt proteins in insects, (Lövei and Arpaia 2005) documented that 30% of studies on predators and 57% of studies on parasitoids display negative effects to Cry1Ab transgenic insecticidal proteins. A review by (Hilbeck and Schmidt 2006) on all Bt-plants found 50% of studies documenting negative effects on tested invertebrates.
Another quantitative review by (Marvier et al. 2007) suggested a reduction in non-target biodiversity in some classes of invertebrates for GM (Bt) cotton fields vs. non-pesticide controls, yet found little reductions in biodiversity in others. More recent research on aquatic environments has sparked intense interest in the impact of Bt-crops on aquatic invertebrates *Daphnia magna* (Bøhn et al. 2008), and caddisflies (Rosi-Marshall et al. 2007). These publications warrant future study, given the potential load of novel target proteins that may end up in agricultural runoff and end up in aquatic environments. Further, (Douville et al. 2007) present evidence of the persistence of the transgenic insecticidal protein Cry1Ab in aquatic environments and suggest that that sustained release of this potently bioactive compound from Bt maize production could result in negative impact on aquatic biodiversity. Impacts on soil microflora and fauna, including earthworms (Zwahlen et al. 2003), mychorizzal fungi (Castaldini et al. 2005) and microarthropods in response to Cry endotoxins have also been reported (Wandeler et al 2002, Griffiths et al 2006, Cortet et al 2007).
The significance of tri-trophic effects of accumulation, particularly of insecticidal Cry toxins (Harwood et al. 2006, Obrist et al. 2006) is, however, yet to be firmly established. It has been demonstrated that sub-chronic dosages of Cry proteins may affect both foraging behavior and learning ability in non-target bees (Ramirez-Romero et al. 2008), and may have indirect effects on recipient populations, and, given the key-stone role of bees as pollinators, on both primary production and on entire food-webs.

In relation to health impacts, a publication by (Dona and Arvanitoyannis 2009) reviews the potential health implications of GM foods for humans and animals, including incidences and effects of increased immunogenicity, amounts of anti-nutrients, possible pleiotropic and epigenetic effects, including possible reproductive and developmental toxicity. They conclude

that while there is strong evidence for health concerns on many fronts, exposure duration many have not been long enough to uncover important effects. Studies should also include subjects with immunodeficiency or exposed to other stress agents.

Indications of harm to non-target organisms in the environment, and possible impacts to human and animal health prompted the Austrian Authorities to invoke a safeguard clause to ban the use of Cry1Ab-containing maize even MON810 (Umweltbundesamt, 2007). We refer to this report as a detailed analysis of potential adverse effects from a Cry1Ab-producing GMO.

Recommendation:

- The regulator is encouraged to address the potential of non-target effects of Bt toxins
- Under environmental risk assessment, interactions between the proteins should be addressed in more detail and experiments should account for the high total amount of Bt protein in Bt11x59122xMIR604x1507xGA21 maize and for possible interactions of the mixture of Cry1Ab, Cry1F, mcry3A, Cry34Ab1/Cry35Ab1

Herbicides as co-products

Glyphosate tolerance

Event GA21 maize produces a modified m*CP4EPSPS* gene from *Agrobacterium sp. line CP4* that confers tolerance to herbicides products containing glyphosate. In recent years glyphosate has received more risk-related attention due to negative effects on both aquatic and terrestrial ecosystems (Blackburn and Boutin 2003, Ono et al 2002, Solomon and Thompson 2003) and studies in animals and cell cultures indicate possible health effects in rodents, fish and humans (Marc et al 2002, Axelrad et al 2003, Dallegrave et al 2003, Jiraungkoorskul et al 2003, Richard et al 2005).

Glufosinate-ammonium tolerance

The events 1507 maize contain the *pat* gene from *Streptomyces viridochromogenes* that confers tolerance to herbicides containing glufosinate-ammonium, a class of herbicides that are banned in Norway and in EU (except a limited use on apples) due to both acute and chronic effects on mammals including humans. Glufosinat ammonium is harmful by inhalation, swallowing and by skin contact. Serious health risks may result from exposure over time. Effects on humans and mammals include potential damage to brain, reproduction including effects on embryos, and negative effects on biodiversity in environments where glufosinate ammonium is used (Hung 2007; Matsumura et al. 2001; Schulte-Hermann et al. 2006; Watanabe and Sano 1998). According to EFSA, the use of glufosinate ammonium will lead to exposures that exceed acceptable exposure levels during application.

Recommendation:

- The regulator is encouraged to consider the safety of co-products intended to be used with the GM event in the evaluation of safety.

Molecular characterization:

Detection of the stacked event Bt11x59122xMIR604x1507xGA21

In part V of the application "Information on the Event-specific Methods" the applicant presents the PCR methods for the detection of the event. "The methods for quantitative, event-specific detection of Event Bt11 DNA, Event 59122 DNA, Event MIR604 DNA, Event 1507 DNA, and Event GA21 DNA in the hybrid Bt11× 9122×MIR604×1507×GA21 maize are based on seven real-time PCR systems: two maize-specific reference PCR systems, an event-specific PCR system for detection of Bt11 DNA, an event-specific PCR system for detection of 59122 DNA, an event-specific PCR system for detection of MIR604 DNA, an event-specific PCR system for detection of 1507 DNA, and an event-specific PCR system for detection of GA21 DNA."

This method is based on the detection of the single events and cannot be considered a Bt11x59122xMIR604x1507xGA21 event specific detection method since a sample of the stacked event will be indistinguishable from a sample containing a combination of the single events.

Recommendation:

- The applicant should have used additional methods to detect the stacked event Bt11x59122xMIR604x1507xGA21and not only detection methods used to detect the single events in the stack.

Gene stability & potential for recombination

The single parental events combined to produce the Bt11×59122×MIR604×1507×GA21 maize contain similar genetic elements such as the CaMV 35S promoter (Bt11, 59122, 1507), NOS terminator (Bt11, MIR604, GA21), CaMV 35S terminator (1507, 59122) and *pat* (Bt11, 5911, 1507). The CaMV 35S promoter and NOS terminator are suggested to be able to act as "hotspots" for recombinations (Kohli A et al, 1999, Collonier C et al 2003). The stability of the inserts should therefore be thoroughly examined, ideally over several generations; to show homologous recombination does not occur.

The Applicant states that "Bioinformatic analysis indicated that the 3´ region of the GA21 maize insert is positioned next to the sequence of a retrotransposon element (pol protein)". It is known that retrotransposons can regulate the expression of nearby sequences. Furthermore retrotransposons are known to be mobile genetic elements and a close proximity to a retrotransposon might affect the genetic stability of the insertion over time (BAT).

Recommendation:

- The stability of the inserts should be thoroughly examined, ideally over several generations; to show that unintended recombination does not occur.

- Since the 3´ region of the GA21 maize insert is positioned next to a known retrotransposon element, the genetic stability and the potential for changes in gene expression should be investigated.

Southern blot analysis

In order to evaluate the genetic stability of the Bt11x59122xMIR604x1507xGA21 event comparative Southern Blot analyses were conducted. Since comparative Southern Blot analyses were the only method used for the molecular characterization (the inserts and flanks were not re-sequenced in the stacked event) the experiments and resulting data should be of the highest possible quality. There should be a consistency in the used positive controls.

For the first two Southern Blots using a *mcry3A*- specific probe (Figure 19A and B of Appendix 3) nontransgenic maize combined with the probe were used as the positive control. For the third Southern blot however the digested pZM26 vector was used. The respective digested vectors used for the creation of the single events are the logical positive controls and should therefore be used.

Furthermore Southern Blot probes should not exceed 500 bp since long probes have the ability to bind to a DNA fragment even if single nucleotide changes have occurred. At the same time a long probe binding to a short insert might be washed of because of the binding being not strong enough. This might lead to false negative results. Therefore several probes should be used to cover the full length of the insert (BAT).

In order to make the interpretation of fragment sizes a Southern blot should contain 2 size markers, one on each side. If two markers were present in Figure 17 it would be possible to clarify whether there is a size difference in the bands in lane 4 and the respective band in lane 8 or if the observed difference is a result of a uneven gel run.

Longer exposure times for some Southern blots (e.g. Fig. 7C, 9A) are recommended since some bands described by the applicant are hardly visible.

In addition Southern blot analyses are not an ideal method to assess the genetic stability for GA21 since it is known to contain multiple copies of the *mepsps* three of them resulting in same sized fragments after digestion. These fragments will be in the same band in a Southern Blot. Since a Southern blot is not a quantitative method additional copies might not be detected.

Recommendation:

- The Applicant should provide additional data using a comprehensive set of smaller probes to in order to evaluate the genetic stability of the Bt11x59122xMIR604x1507xGA21 event.

- The Applicant should provide additional methods since Southern blot analyses are not an ideal method to assess the genetic stability for GA21 since it is known to contain multiple copies of the *mepsps*.

- In order to make the interpretation of fragment sizes a Southern blot should contain 2 size markers, one on each side and also longer exposure times for some Southern blots are recommended since some bands described by the applicant are hardly visible.

Assessment of the newly expressed protein

Analysis of the proteins expressed in the stack Bt11x59122xMIR604x1507xGA21 was performed by comparing the expression levels of the proteins isolated from the stack to the corresponding single events. The proteins were not isolated from plants treated with GMO specific herbicides. This should have been included as a control.

The concentration of the newly expressed proteins from the stacked event is reported to be equal to the expression levels measured in the hybrids, single events and individual event hybrids, in general. However, the Cry34Ab1 in V5 leaves and roots (Table D.3 (a)-2 (p.73 Technical Dossier part I) shows a difference between the single and the stacked event. The applicant notes that the difference is significant without exploring what it can be caused by or what the effect of it might be. This should have been done. Especially an adverse effect on-non target species, as evaluated as a potential effect by De Schrijver et al (2007), is not addressed.

In the stack of Bt11x59122xMIR604x1507xGA21 maize, five Cry proteins are expressed. Special concern or vigilance should be paid to GM stacks that combine events that have similar type of mode of action through their expressed transgenic proteins. Also, the Cry proteins can attach to the same receptor, changing their mode of action.

In theory, the presence of two toxins can result in cross-resistance and a changed effect on target and also non-target species (Schnepf et al 1998, Hua et al 2001, Estela et al 2004, Li et al 2004).

Recommendation:

- The applicant notes that the difference in protein expression is significant without exploring what it can be caused by or what the effect of it might be. This should have been done.

- The possibility of cross-resistance and a change in effect on target/non-target species should be examined.

Allergenicity and toxicity assessment.

The transgenic proteins produced in the stack Bt11x59122xMIR604x1507xGA21 are considered safe due to lack of acute toxicity, rapid digestion and no significant homology to known toxins by the analysis performed for the single proteins. For that reason, a 28 day toxicity study is considered to be unnecessary for the assessment of safety of these proteins.

However, the potential adjuvancy of Cry proteins has previously been addressed by the GMO panel of the Norwegian Scientific Committee for Food Safety. Some scientific studies (Moreno-Fierros et al 2003, Rojas-Hernandez et al 2004) have shown that the Cry1Ac protein is a potent systemic and mucosal adjuvant, which is an enhancer of immune responses. In the evaluation of GM maize, MIR604 x GA21, the panel found that it was difficult to evaluate if

kernels from this stack would cause more allergenic reactions than kernels from unmodified maize. This stack is part of the stack in this application, Bt11x59122xMIR604x1507xGA21 (H99).

The Panel continues with: "*As the different Cry proteins are closely related, and in view of the experimental studies in mice, the GMO Panel finds that the likelihood of an increase in allergenic activity due to Cry1Ab and mCry3A proteins in food and feed from maize Bt11 x MIR604 x GA21 cannot be excluded. Thus, the Panel's view is that as long as the putative adjuvant effect of Cry1Ab and mCry3A with reasonable certainty cannot be excluded, the applicant must comment upon the mouse studies showing humoral antibody response of Cry1A proteins and relate this to a possible adjuvant effect of the Cry1Ab and mCry3A proteins expressed. Furthermore, although Cry1Ab and mCry3A proteins are rapidly degraded in gastric fluid after oral uptake, there is also the possibility that the protein can enter the respiratory tract after exposure to e.g. mill dust. Finally, rapid degradation is no absolute guarantee against allergenicity or adjuvanticity" (EFSA/GMO/UK/2007/48, Norwegian Scientific comitee for Food Safety, 12/06-08).*
We also agree with these concerns.

For GM stacked events there has not been enough evaluation of the potential for change in expression level of the different proteins as compared to the single events. And according to Kuiper et al (2001), the information on the expression level of the transgenic proteins in the stacked event is relevant when considering the need for whole GM food/feed toxicology studies of the GM stacked event. However, it should be realized that such whole food testing experiments have their limitations, due to limited dose range and complexity of the product. Considering this, the significant differences in expression levels for Cry34Ab1 found between stack and single event in leaves and roots of the stack in question, was not found to be big enough for further analysis of potential toxicity/allergeniciy aspects by the applicant. These differences in expression of the Cry protein should have been analysed further.

In the new and updated bioinformatics search made in 2011, sequence homologies for the new proteins Cry1Ab, mCry3A, PAT, MIR604 PMI and mEPSPS were conducted. They found no new significant similarity matches with known allergens. Also, a potential combinatorial effect of the newly expressed proteins is not considered to be an issue. Although they are considered to be safe on individual basis, they might lead to unforeseen and harmful effects when exposure is in combination. As De Schrijver et al (2007) notes: "Only in case synergistic toxic effects are expected (e.g. toxins with common health effect), it will be relevant to demand additional toxicity studies, the exact nature of which will depend on the data available and the characteristics of the modified crops, transgenes, and anticipated effects". So, if the synergism is not expected by the applicant, such additional studies will not be performed.

Recommendation:

- The potential adjuvancy of Cry proteins should be further addressed since some scientific studies have shown that the Cry1Ac protein is a potent systemic and mucosal adjuvant

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 Bt11x59122xMIR604x1507xGA21. The Applicant should thereby provide the necessary data in order to conduct a thorough assessment on these issues, or the application should be refused.

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 Bt11x59122xMIR604x1507xGA21 and its contribution to sustainable development, in accordance with the Norwegian Gene Technology Act.

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 GMO, 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 issues in relation to the questionable safe use of Bt11x59122xMIR604x1507xGA2 that do not justify a conclusion of safe use, social utility and contribution to sustainable development. 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 Bt11x59122xMIR604x1507xGA21 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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