Vår ref:2017/H_137
Deres ref: 2017/3344

Høringsuttalelse av søknad om markedsføring av genmodifisert mais GA21 x T25

EFSA/GMO/DE/2016/137

Under EU forordning 1829/2003

Sendt til

Miljødirektoratet

av

GenØk-Senter for biosikkerhet
Mai 2017

Vår ref:2017/H_137
Deres ref: 2017/3344

Miljødirektoratet
Postboks 5672 Sluppen
7485 Trondheim
Dato: 08.05.2017

Vedlagt er innspill fra GenØk – Senter for Biosikkerhet på offentlig høring av søknad **EFSA/GMO/DE/2016/137**, genmodifisert, stablet mais linje GA21 x T25, fra Syngenta Crop Protection NV/SA under EU forordning 1829/2003. Søknaden gjelder bruksområdene mat, fòr, import og prosessering.

Vennligst ta kontakt hvis det er noen spørsmål.

Med vennlig hilsen,

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Innhold/Content

Vår ref:2017/H_137
Deres ref: 2017/3344

Høringsuttalelse – genmodifisert, stablet mais GA21 x T25, EFSA/GMO/DE/2016/137, under EU forordning 1829/2003.

Søknad EFSA/GMO/DE/2016/137 omhandler genmodifisert, stablet maislinje til bruksområdene mat, for, import og prosessering.

Den genmodifiserte maisen har toleranse mot herbicider som inneholder glyfosat via det innsatte genet *mepsps* og mot glufosinat ammonium via det innsatte genet *pat*.

Den stablete maislinjen er ikke godkjent for noen av bruksområdene i Norge eller EU. Foreldrelinjene GA21 og T25 er godkjente for bruksområdene i EU.

.

Oppsummering

GenØk–Senter for biosikkerhet, viser til høring av søknad EFSA/GMO/DE/2016/137 om GA21 x T25 mais som omfatter bruksområdet import og prosessering og til bruk i fòr og mat eller inneholdende ingredienser produsert fra denne maisen.

Vi har gjennomgått de dokumenter som vi har fått tilgjengelig, og nevner spesielt følgende punkter vedrørende søknaden:

- Genmodifisert, stablet mais linje GA21 x T25 er ikke godkjent i Norge eller EU for noen av de omsøkte bruksområdene.
- GA21 x T25 er tolerant mot sprøytemidler som inneholder glyfosat og glufosinat - ammonium som har ulike grader av helse-og-miljø fare ved bruk.
- Glufosinat ammonium er ikke tillatt brukt i Norge.
- Søknaden om mais linje GA21 x T25 mangler data og informasjon som er relevant for å kunne vurdere kriterier rundt etisk forsvarlighet, samfunnsnytte og bærekraft.

Summary

GenØk-Centre for biosafety refers to the application EFSA/GMO/DE/2016/137 on GA21 x T25 maize for import, processing, food and feed or ingredients thereof.

We have assessed the documents available, and highlights in particular the following points for the current application:

- The gene modified, stacked maize event GA21 x T25 is not approved for any application in Norway or the EU.
- The stacked maize event GA21 x T25 is tolerant to herbicides containing glyphosate and gluphosinate ammonium that has distinct health and environmental dangers upon use.
- It is not allowed to use gluphosinate ammonium in Norway.
- The application on maize event GA21 x T25 lacks data and information relevant for assessment of criteria on ethically justifiability, social utility and sustainability.

Application on EFSA/GMO/DE/2016/137

The stacked event GA21 x T25 maize contains genes providing herbicide tolerance *(mepsps and pat*).

Previous evaluations

The Norwegian Scientific Committee for Food Safety (VKM) has commented on the application for the parental, single event maize GA21 (EFSA/GMO/UK/2005/19) (1) with the following issues:

- Maize event GA21 is considered "compositionally, agronomically and phenotypically equivalent to its conventional counterpart".
- Molecular characterization data show that there is one locus, containing many copies of the GA21 construct that is inherited as a dominant trait. The analysis performed by the Applicant are considered as adequate.
- There is a concern for spillage of viable maize kernels through accidental release upon handling. However, there is no concern for establishment of maize due to the survival, multiplication and dissemination characteristics it has. There is no natural wild relatives present. Thus, hybridization issues are not relevant.
- Gene flow from GM maize to conventional maize in Norway is considered as negligible.
- The EPSPS protein is most probably not allergenic based on performed studies.

The Norwegian Scientific Committee for Food Safety (VKM) has also commented on the parental, single event T25 (EFSA/GMO/NL/2007/46 and EFSA/GMO/RX/T25) (2) with the following issues:

- The molecular characterization of the introduced genetic elements in T25 indicate that the inserts are intact and present in the indicated number of copies.
- There is a lack in the analysis of nutrients, anti-nutrients and metabolites, as required by the OECD consensus document recommended for maize in 2002 (3). VKM states that this document should be followed when such analysis are performed.
- There are no data providing concern of toxicity for the expressed proteins PAT and mEPSPS.
- Feeding experiments on rats, broiler and milky cows have no indications of damage to health.
- Maize event T25 is considered nutritionally equivalent to conventional maize.
- There is no concern for spread, establishment and invasion of maize line T25 in natural areas or other areas outside agricultural areas with the intended use in Norway.

GenØk has not commented on the parental line T25 previously.

GenØK has previously commented on the parental, single event GA21 in stacked combinations in previous hearings (http://genok.no/radgiving/horingsuttalelser/):

- *EFSA/GMO/DE/2011/103: Bt11 x MIR162 x MIR604 x 1507 x 5307 x **GA21***
- *EFSA/GMO/DE/2010/86: Bt11 x MIR162 x 1507 x **GA21***
- *EFSA/GMO/BE/2011/99: Bt11 x 59122 x MIR604 x 1507 x **GA21***

From these hearings, we highlight the following comments:

- *The regulator is encouraged to ask the Applicant to acknowledge the context of use for the stacked event and its complimentary herbicide technologies and also test for to test for herbicide residues.*
- *The regulator is encouraged to ask the Applicant to submit required information on the social utility of Bt11xMIR162xMIR604x1507x5307xGA21 maize and its contribution to sustainable development, in accordance with the Norwegian Gene Technology Act.*
- *The regulator is encouraged to ask the Applicant whether the inclusion of a glyphosate tolerance trait in this event, and implied glyphosate use, can be considered a sustainable weed control solution, given the spread of glyphosate resistant weeds in many cropping systems.*
- *The Applicant should demonstrate the lack of interactive effects between transgenic proteins in this* ***stacked event*** *through scientific testing and evidence gathering.*
- *The regulator is encouraged to consider the safety of co-products intended to be used with the GM event in the evaluation of safety.*

Social utility and sustainability issues on the stacked maize event GA21 x T25, EFSA/GMO/DE/2016/137

In Norway, an impact assessment follows the Norwegian Gene Technology Act (NGTA) (4) in addition to the EU regulatory framework for GMO assessment. In accordance with the aim of the NGTA, the development, introduction and/or use of a GMO needs to be *ethically justifiable*, demonstrate a *benefit to society* and contribute to *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*" (See section 17 and annex 4 for more detail on the regulation on impact assessment). Recent developments within European legislation on GMOs allow Member States to restrict the cultivation of GMOs on their own territory based on socio-economic impacts, environmental or agricultural policy objectives, or with the aim to avoid the unintended presence of GMOs in other products (Directive 2015/412) (5). Additionally, attention within academic and policy spheres increased in recent years on broadening the scope of the assessment of new and emerging (bio) technologies to include issues that reach beyond human and environmental health (6-11).

To assess the criteria of *ethically justifiable*, *benefit to society* and *sustainability* as in the NGTA, significant dedication is demanded as it covers a wide range of aspects that need to be investigated (e.g. Annex 4 within the NGTA, or 12). Nevertheless, the Applicant has currently not provided any information relevant to enable an assessment of these criteria. Therefore, this section will highlight some areas that are particularly relevant to consider with maize GA21 x T25 and where the Applicant should provide data for in order to conduct a thorough assessment according to the NGTA. Table 1 offers specific questions connected to the sections below.

Sustainability

Maize GA21 x T25 contains a modified *mepsps* gene that confers increased tolerance to herbicides that contain glyphosate. Recent studies have shown negative effects from glyphosate, both on species present in terrestrial and aquatic ecosystems and on animals and cell cultures (for further elaboration and references on this issue see page 18-19) as well as in villages in areas where glyphosate is systematically used as part of the GM crops tolerance to glyphosate (13). Consequently, glyphosate is now increasingly recognized as more toxic to the environment and human health than what it was initially considered to be. This is particularly a concern as the introduction of glyphosate tolerant GM crops has led to an increase in the use of glyphosate (14-16). As maize GA21 x T25 is genetically modified to possess a gene that provides glyphosate tolerance, this crop could potentially further increase the use of glyphosate, as a higher amount of glyphosate will not affect the cultivation of GA21 x T25. An increase in the resistance and use of glyphosate is in contrast to a contribution to sustainable development and therefore an important aspect the Applicant should provide information on, for example by mentioning the current use of glyphosate in the sites of cultivation and what approaches are used to minimize the use of glyphosate.

Herbicide-resistant genes

When an herbicide - such as glyphosate – is used in agriculture, it is important to minimize the potential of weeds becoming resistant. Indeed, when crops are engineered to be herbicide tolerant in order to maintain an agricultural practice that uses herbicide, it is essential to remain attentive to the amount of herbicide used, the potential increase of use and the consequences of this for the area in which the crop is cultivated. The development of management strategies to make sure that this does not create (more) resistant weed is warranted to be able to respond to a potential increase in weed-resistance. Moreover, studies have shown increased levels of herbicide residues in herbicide tolerant GM crops (e.g. 17), which could have health impacts on humans and animals consuming food/feed based on ingredients from this type of GM plants.

The Applicant has not provided information on whether the cultivation of maize GA21 x T25 could affect the emergence of glyphosate resistance in weeds, nor if there are cases of this in the areas intended for cultivation of the variety, which are also important aspect to evaluate the ethical justifiability. Furthermore, this maize is cultivated in Canada and the USA, where glyphosate resistant weeds have increased significantly[1]. Additionally, no information is currently provided by the Applicant that demonstrates reflection on how the monitoring, assessment or evaluation of the GM crop in countries where the crop will potentially be cultivated in the future is assessed, as the Applicant considers information on this not relevant because maize GA21 x T25 will not be cultivated in Europe. However, it remains an important aspect for a sustainability evaluation and thus necessary if the application is to be evaluated according to this criteria in the NGTA.

Impacts of the co-technology: glyphosate

The evaluation of the co-technology, that is, secondary products that are intended to be used in conjunction with the GMO, is also considered important in the risk assessment of a GMO (18). Therefore, considerations of the co-products also warrant an evaluation of safe use and data required for such an assessment is not provided by the Applicant.

Impacts in producer countries

As already stated, the Applicant does not provide data relevant for an environmental risk assessment of maize GA21 x T25 as it is not intended to be cultivated in the EU/Norway. However, this information is necessary in order to assess the sustainability criteria as laid down in the NGTA. This criterion is referring to a global context, including the contribution to sustainable development in the producing countries with a view to the health, environmental and socio-economic effects in other countries, in this case where the maize GA21 x T25 is cultivated.

In addition to a lack of information, there can also be ambiguity about how scientific conclusions may be achieved. For example, it is difficult to extrapolate on hazards or risks taken from data generated under different ecological, biological, genetic and socio-economic contexts as regional growing environments, scales of farm fields, crop management practices, genetic

[1] http://weedscience.org/Summary/Country.aspx Status of Herbicide Resistance in Canada and USA, accessed on 19 April 2017.

background, interactions between cultivated crops, and surrounding biodiversity are all likely to affect the outcomes. It can therefore not be expected that the same effects will apply between different environments and across continents. This is particularly relevant to consider as field trials of the maize have been in the USA, while cultivation will also be in Canada and no information about how this difference may affect the adequacy of the evaluation has been provided, nor what this means for potential cultivation sites of maize GA21 x T25 in other countries in the future.

The Applicant highlights that the appearance of "volunteer" maize in rotational fields following the maize crop from the previous year is rare under European conditions. Still, an evaluation of the occurrence of volunteer plants in the producing countries and suggested control strategies is important for a sustainability assessment. Information about the occurrence of volunteers and which herbicides that will potentially be used for killing volunteers is required to evaluate potential health and environmental impacts of these.

Benefit to society

The criteria of 'benefit to society' in the NGTA should be interpreted on a national level. That means that the import of maize GA21 x T25 needs to demonstrate how it will benefit Norway. However, no information on this part is provided by the Applicant. Indeed, the Applicant state that this maize will replace maize in existing food and feed products. It is therefore important to evaluate how GM crops in general, GM maize in particular, and the use of GM maize in food and feed are valued by Norwegian consumers. This information will contribute to anticipate impacts at an early stage, as well as that it may demonstrate a need to assess the alternative options for import of maize. Although the empirical data available on the attitude of Norwegian citizens towards GM is limited (e.g. 19, 20) and more empirical research on this is warranted to investigate consumers' attitude, demand and acceptance, a report on the perceptions among Norwegian citizens on GMOs describes how about half of the respondents expressed that they were negative for sale of GMO-products in Norwegian grocery stores in the future, and only 15 percent were positive (21). Furthermore, it should be noted that 29 % of the global maize production is GM. It is therefore not a problem for Norway to import GM free maize and therefore no need to replace current imports. The GM maize in question does also not contain any beneficial characteristics for consumers that would prioritize this maize over non-GM maize.

Assessing alternatives

When a new (bio-) technology is developed, it is important to reflect on what problem it aims to solve and to investigate whether alternative options may achieve the same outcomes in a safer and / or a more ethically justifiable way. After all, when a crop is genetically modified to tolerate a particular herbicide, it means that the crop is developed for a particular cultivation practice in which these herbicides are to be used. What is meant with alternatives, and what would benefit from being assessed could include alternative varieties (e.g. conventional or organic maize) for import, alternative sources to satisfy the demand, alternative ways of agriculture, or even explore alternative life visions. In fact, this corresponds with the increased trend within research and policy of science and innovation to anticipate impacts, assess alternatives, reveal underlying values, assumptions, norms and beliefs (9, 22) as a way to reflect on what kind of society we want, and assess how certain (biotechnological) developments may or may not contribute to shaping a desired future. Thus, in order to evaluate whether maize GA21 x T25 contributes to social utility, it is important to investigate current and future demands and acceptance of this in Norway and if there are alternatives sources for maize that could be cultivated elsewhere that may satisfy this demand, or are more desirable.

Ethical considerations: socio-economic impacts

As known, GM crops have been, and still are, a hot topic for debate. A significant amount of this debate focuses on the safety of GMOs and currently no scientific consensus on this topic has been achieved (23). Nevertheless, another substantial part of the debate is around the socio-economic impacts of GM productions and many questions for evaluating the above mentioned criteria in the NGTA are based on an assessment of the socio-economic impacts. These impacts can vary and range from seed choice for farmers, co-existence of different agricultural practices, impacts among poor and/or small-scale farmers in developing countries, share of the benefits among sectors of the society, changing power dynamics among stakeholders, autonomy of farmers, intellectual property right on seeds, benefit sharing, the decreasing space for regional and local policy, and more organisational work and higher costs for non-GM farmers (e.g. for cleaning of sowing machines or transport equipment to avoid contamination). Although the examples of socio-economic impacts clearly indicate the complexity and extensive list of concerns beyond safety aspects, little empirical investigation on these kind of aspects has been done. For example a study performed by Fischer et al. (24) concerning social implications from cultivating GM crops found that from 2004 – 2015 there has only been 15 studies corning socio-economic implications of cultivating Bt-maize. The study demonstrates that published literature is dominated by studies of economic impact and conclude that very few studies take a comprehensive view of social impacts associated with GM crops in agriculture. The amount of research performed in this case and the minimal focus on social impacts strongly indicate a high need for further investigation on how the cultivation of GM crops affects different parties involved. It is therefore striking that no information on any of the above mentioned points is discussed by the Applicant.

Co-existence

The cultivation of GM plants in general is causing problems with regard to co-existence, an important socio-economic impact. For instance, Binimelis (25) has investigated consequences on co-existence of Bt maize in Spain among small-scale farmer and has found that co-existence is very difficult and that farmers in some areas have given up growing non-GM maize. Even though the cultivation of maize GA21 x T25 is not planned in Europe/Norway, it is important to obtain information about the strategies adopted to ensure co-existence with conventional and organic maize production and information about consequences for co-existence in the countries intended for cultivation of maize GA21 x T25 and minimize the likelihood for gene flow to wild relatives, or contamination during transport or processing. Legal information and clarity could provide evaluators a more comprehensive understanding of governance strategies and possibilities to ensure co-existence, although it has been noted that this may not suffice as co-existence has become an arena of opposed values and future vision of agriculture, including the role of GM crops within these visions (26). Indeed, although a framework for maintaining co-existence in Europe was established in 2003 (27) this effectively meant technical measurements and recommendations (e.g. cleaning of sowing machines and transport vehicles) and remains challenging in practice (28, 29). Moreover, this framework arguably reduced the significance of the issue of co-existence to questions concerning economic aspects for individuals (e.g. farmers), rather than recognizing that agricultural practices are interwoven in dynamic social, economic and political systems (30, 31). For the criteria in the NGTA, information on co-existence is required to enable a coherent analysis.

The ethical issue of glufosinate-ammonium

A significant ethical issue arises as maize GA21 x T25 is meant to be resistant to gluphosinate-ammonium, a class of herbicide that is banned in Norway (except a limited use on apples) due to the risks to human health and the environment. It seems ethically ambiguous and inconsistent to import a plant that is resistant to this herbicide, thereby allowing the use and development of a harmful herbicide in other countries, while considering the herbicide as too harmful to be used in Norway. Additionally, this troubles the fulfilment of the criteria of *sustainable development*, as this criteria is meant to be considered in a global context. Information on how this can be ethically justified is therefore highly warranted.

Summary

In order to meet the requirements for the NGTA, the regulator is encouraged to ask the Applicant to submit information relevant for the assessment of the criteria of ethically justifiable, benefit to society and sustainability assessment. An important part that is lacking is information about the consequences of the cultivation of maize GA21 x T25 for the producing country.

The information provided by the Applicant must be relevant for the specific agricultural context of this country and should also stress the need for information on integrated weed management strategies in those countries (32).

Moreover, the information should contain issues such as changes in herbicide use, development of herbicide resistant weed, potential for gene flow and possible socio-economic impacts such as poor and/or small-scale farmers in producing countries, share of the benefits among sectors of the society and as explained, effects of co-existence of different agricultural systems.

Furthermore, maize GA21 x T25 is tolerant to gluphosinate-ammonium which is banned for use in Norway. Banning the use of gluphosinate-ammonium based herbicides domestically due to health and environmental concerns, while indirectly supporting its use in other countries would be ethically ambiguous and goes against the criteria of sustainable development.

Additionally, the Applicant does not attempt to demonstrate a benefit to society, a reference of the consumers' attitude on GM maize, or the demand within Norway for maize GA21 x T25 and does therefore not provide sufficient information as required by the NGTA.

Table 1: Questions to the Applicant

Sustainability	*How does the cultivation of GA21 x T25 affect the use of glyphosate?*
	How is the current use of glyphosate in the sites of cultivation and what approaches are used to minimize the use of glyphosate?
Herbicide-resistant weed	*What kind of management strategies are taken to prevent the increase of herbicide-resistant weed?*
	Who will be affected if the amount of resistant weeds increases?
	How is the burden of increase of resistant weeds distributed and what strategies are in place to compensate this?
Benefit to society	*Is GA21 x T25 available for further breeding and research? If so, under which circumstances?*
	Is there a demand for GA21 x T25 in Norway?
	Does GA21 x T25 contribute to business development and value creation in Norway, including new job opportunities?
Assessing alternatives	*Will GA21 x T25 benefit Norwegian consumers more than the other alternatives available from conventional or organic agricultural practices? If so, how?*
Ethically justifiable	*What are the different public values and visions on the development, introduction or use of GA21 x T25 within Norway and how does the development of GA21 x T25 relates to these?*
	Does the development, introduction or use of GA21 x T25 contradict ideas about solidarity and equality between people, such as the particular consideration of vulnerable groups in the population?
Socio-economic impacts	*Does GA21 x T25 affect the seed choice of farmers?*
	Which parties will be affected by the development, introduction or use of GA21 x T25 and how does this change their autonomy, practice and position compared to other stakeholders?
	Does GA21 x T25 change the power dynamic among stakeholders? If so, how?
	Can the development, introduction or use of GA21 x T25 create significant ruptures or ecological relationships?
Co-existence	*Does the cultivation of GA21 x T25 affect other types of agricultural practices in the nearby areas? If so, how?*
	Is there a system in place for keeping GMO and non-GMO crops separate in the production and transport line? If so, who pays for this system?

Environmental risk issues in a Norwegian context

The level of maize production is very low in Norway and only some varieties can grow in the southern part due to climate conditions. There are also no wild populations of maize in Norway.

These limitations lead to minimal possibilities for establishment of maize outside agricultural practices. Loss of gene modified maize seed through storage or transport would therefore not involve great risk for spread into the wild or spread of transgenes to wild relatives.

Molecular characterization, expressed proteins and herbicide use - special issues to consider in the present application

Stacked events

The stacked maize event GA21 x T25 contains two inserted transgenes providing herbicide tolerance towards two different herbicides. Stacks should be regarded as new events, even if no new modifications have been introduced, as the combination itself in the stack is unique for that event. The combinations of the gene-cassettes are 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 within stacked traits cannot be excluded and whether or not the expressed proteins in the plant can give specific immunological effects or adjuvant effects in mammals has been discussed previously (33, 34).

Molecular characterization

The present application concerns a stacked GM maize developed by crossing two parental lines – one with event GA21 and one with T25. The resulting GM maize contains both parental GM lines expressing the genes *mepsps* and *pat*.

Comments to the data provided in the molecular characterization:

- The pUC sequences in T25 include a β-lactamase *(bla*) gene and a bacterial origin of replication. The Applicant claims that the *bla* gene has regulatory signals recognized in bacteria but is not functional in plant cells. Functional antibiotic resistance genes carry a risk of horizontal gene spread to bacteria via DNA uptake mechanisms (transformation, transduction, conjugation). The genes are still present in the DNA of imported maize kernels and not only in the plants, and as such poses a hazard for HGT also in Norway through waste and disposal of maize kernels used in feed and food.
- The illustration in Figure 1.2-2 shows that the *bla* gene has a duplication of the P35s promoter upstream. P35S is a strong promoter that works in plants and partial duplications should be screened for potential downstream gene activations.
- The Applicant referenced the comparative analyses of T25 and GA21 of the hybrid cross (T25 x GA21) to appendix 1.2-2 and 1.2-4. According to the Applicant, these analyses shows that no changes has occurred in the DNA of the insertions in the hybrid, when compared to parental strains. We were, however, unable to locate these analyses.
- The Applicant claims that "Expression data for specific herbicide treatments linked to the herbicide tolerance traits are not considered necessary for GA21 x T25 maize, because the data obtained from the respective single events, GA21 and T25 maize, have not indicated any potential safety concern that could be due to the effects on the expression levels caused by the treatment with the intended herbicides glyphosate or

gluphosinate ammonium. The treatment with the intended herbicides will, therefore, not have any biologically significant effects on the protein expression levels in GA21 x T25 maize". This is assumes that the gene expression of the traits 1) is solely important for herbicide tolerance and 2) that the combination of GM proteins in a stack is not affected by the new genetic context and that the effects of one herbicide is not influenced by application of the other.

- Southern blots: In the section on GA21 x T25 stack being digested with RE *HindIII, the* upper bands, which corresponds to undigested DNA of GA21 is lower in intensity than for the stack itself (GA21xT25). However, the lower bands are not. This suggests that the amount of undigested DNA potentially is higher in the hybrid than in the parental line, and may indicate fewer copies of *mEPSPS* in the hybrid than the parent, lower affinity of the probe or incomplete digestion. Lower probe affinity is an indication of sequence variability within the probe binding site. This is impossible to evaluate if the sequences are not provided, preferably as chromatograms.

Comments relevant for the assessment of the current application

CaMV promoter in maize event GA21 x T25

The 35S cauliflower mosaic virus (CaMV) promoter is commonly used to drive transgene expression in the genetically engineered (GE) crop plants that have been commercialized so far (35-37). Safety questions related to the use of the Cauliflower Mosaic Virus 35S promoter (P35S) in GM plants has recently been discussed in an article from Podevin and Du Jardin (38). In the article, the authors state that some P35S variants contain open reading frames (ORFs) that when expressed could lead to "unintended phenotypic changes". Gene VI encodes the multifunctional P6 protein that can be divided into four domains (39). Functions of P6 include nuclear targeting (40), viral particle binding and assembly (41), si- and ds-RNA interference and interference suppression (42) and transcriptional transactivation (43, 44). The main debate when it comes to the use of this promoter is that it may not only be active in plants, but may confer activity with respect to gene expression in lower and higher vertebrates such as mammals and fish. Today there are reports that conclude that the 35S CaMV promoter is active in several eukaryotic cell lines after transfection (35, 37), as well as that the promoter is able to drive expression of a transgene in fish as demonstrated recently by Seternes et al (36). The potential risk when it comes to GM food/feed that contains the CaMV promoter may be unlikely but cannot be excluded.

Protein expression and characterization of the newly expressed protein(s)

Maize tissues (leaf, root, kernel, pollen and whole plant) were analyzed using enzyme-linked immune-sorbent assay (ELISA). Tissues were isolated from the stack T25 x GA21, the corresponding single events and a conventional maize line.
The measured concentrations of proteins PAT and mEPSPS were comparable to those of the single parental lines. Levels in pollen were beneath level of quantification.

The double-mutated 5-enolpyruvylshikimate-3-phosphate synthase (mEPSPS) and phosphinothricin acetyltransferase (PAT) proteins produced in GA21 x T25 maize are identical to the mEPSPS protein produced in GA21 maize and the PAT protein produced in T25 maize based on the characteristics analysis performed.

Toxicity and allergenicity

Toxicity

PAT and mEPSPS proteins have previously been assessed by EFSA to be safe based on the criteria of analysis of homology to other proteins known to be toxic, rapid degradation in digestion assays (*in vitro*), no sequence similariy to known toxins and not acute oral toxicity found in previous analysis of the proteins.
Some 90 day feeding trials have been performed with the single parental as well as the stacked event GA21 x T25 maize.
No toxic effects on body weights, food consumption, the analysed clinical conditions or any of the analyzed parameters were detected.

Allergenicity

Proteins 2mEPSPS and PAT have been tested for their allergenic potential through the weight of evidence approach.
According to the Applicant, the proteins produced in GA21 x T25 are not likely to be allergenic due to this.

Potential interactions between newly expressed proteins

Not relevant according to the Applicant.

Hazard identification

Based on the analysis performed on toxicity and allergenicity, the Applicant conclude that the stacked maize event GA21 x T25 is comparable to conventional maize, and do not have any adverse effect on animal or human health.

Summary:

- The *bla* gene originating from the pUC plasmid is present in the stacked maize plant.
- The P35S promoter seem duplicated in front of the *bla* gene
- Experimental data for herbicide treated stack GA21 x T25 is lacking.
- Explanation for differences in band intensities on Southern blot after *HindIII* digestion of stack GA21 x T25 is lacking.

Herbicides

Herbicide use on GM plants

Herbicide tolerant (HT) plants are sprayed with one or more of the relevant herbicide(s), which will kill weeds without harming the HT GM plant with the inserted transgenes. The use of HT GM plants may cause negative effects on ecosystem as well as animal/human health. Of particular concern are: 1) increased use of, and exposure to, toxic herbicides; 2) accelerated resistance evolution in weeds; 3) accumulation of herbicides in the plants since they are sprayed in the growing season; 4) combinatorial effects of co-exposure to several herbicides at the same time (relevant for plants with pyramided HT genes); and 5) points 1-4 indicate that the agricultural practice of growing HT GM plants, fails to fulfill the criteria for a sustainable agriculture.

Total use of herbicides

HT GM plants are documented to be a strong driver of increased use of glyphosate-based herbicides (the dominant herbicide tolerance trait until now). From 1995 to 2014 the global agricultural use of glyphosate rose 14.6 fold, from 51 million kg to 747 million kg and HT GM crops have been a major driver for this change. Moreover, by 2016, about 56 % of the global use of glyphosate was related to the use of HT GM crops (16).

Increased use and resistance evolution

Specific for the HT GM plants is that herbicides can be sprayed in higher doses than before, and repeatedly during the growth season of the plants. The increased use must be linked to resistance evolution in weeds. At present, 36 species of weeds are documented to be glyphosate resistant on a global scale (45). Such development may lead to a ‘treadmill’ where resistance triggers more applications/higher doses, which leads to stronger selection pressure for resistance, etc. and eventually the use of additional herbicides like atrazine, 2,4-D or others (46). Crop and herbicide monoculture makes the agroecosystem more vulnerable to further resistance development (47).

For glufosinate-ammonium, six species of weeds are shown to be resistant and 50 % of these were discovered after 2015 (45).

Sustainability

For the farmers, resistant weeds are a difficult obstacle to handle. However, evolution of resistance is the process by which it develops. Therefore, more research should be performed on the plurality of responses that can be done with integrated pest management, not only to delay resistance but to promote alternative and preferably non-toxic pest control systems (UN). Chemical treatment coupled with the unavoidable resistance development are major blocking factors to a sustainable agriculture. The accelerated use seen for glyphosate used on glyphosate tolerant GM plants can be expected to happen for *any* herbicide used as co-technology for HT GM plants, indicating that HT GM plants are not sustainable.

Environmental effects of herbicides

The use of herbicides like glyphosate also has the potential to affect ecosystem, animal and human health. The massive use of glyphosate, totaling 852 million kg globally by 2014 (16), which directly or indirectly will expose non-target biodiversity in terrestrial, soil and aquatic communities (48), represent a major source of environmental pollution.

Accumulating herbicide residues and health effects

Glyphosate accumulates in HT soybeans, more when the plant is sprayed later in the season (32). This may bring significant amounts of glyphosate into the food and feed chain. Bøhn and colleagues measured on average 9.0 mg of glyphosate in HT GM soybeans grown in Iowa (49).

Clearly HT GM plants with tolerance to 2,4-D, glufosinate ammonium or other herbicides may serve as a vector for these chemicals into the global food and feed chains.

The increased awareness of glyphosate toxicity, coupled with the increased volume used, should lead to stronger restrictions, for example lower acceptance level for glyphosate residues in food and feed (50). But the opposite has happened, the maximum residue level (MRL) for glyphosate has been raised 200-fold from 0.1 to 20 mg/kg in Europe,, and to 40 mg/kg in the US (51). This set of events has been termed "The Glyphosate Paradox" (50). The WHO/IARC categorization of glyphosate as *probably carcinogenic to humans (52)*, although disputed by EFSA (53), is underlining the significance of the controversy around the glyphosate-based herbicides.

Studies in Daphnia

In *Daphnia magna*, the LC50/EC50 acute toxicity is shown in the range 144 – 248 mg/L for 24 h, and 25 mg/L for 48 h, respectively (54, 55).
However, the issue on accumulation of herbicides in the HT plants, including metabolites, are not regularly tested as part of the risk assessment of HT plants. Bøhn et al. (49) documented high levels of glyphosate residues in HT GM soybeans grown in the USA, and the same research group have published papers showing that such residues have the potential for negatively to affect the feed quality of HT GM soybeans (51, 56). It is important to look at the potential metabolites of the herbicides in use and if these are documented to have a negative effect on health and environment.

Glyphosate tolerance

The *mepsps* gene present in GA21 x T25 maize confers tolerance to herbicides containing glyphosate.

Glyphosate kills plants by inhibiting the enzyme 5-enolpyruvoyl-shikimate-3-phosphate synthase (EPSPS), necessary for production of important amino acids. There are also some microorganisms that have a version of EPSPS that is resistant to glyphosate inhibition.

Glyphosate has previously been announced as an herbicide with low toxicity for users and consumers as well as the environment surrounding agricultural fields (32, 57). However, glyphosate has recently received more risk-related attention due to its potential for negative effects on both aquatic and terrestrial ecosystems (58), as well as from studies in animals and cell cultures that have indicated possible negative health effects in rodents, fish and humans (59-61).

It has also been shown that agriculture of GM plants is associated with greater overall usage of pesticides than the conventional agriculture (62).

A number of publications indicate unwanted effects of glyphosate on health (61, 63), aquatic (64) and terrestric (58, 65) organisms and ecosystems. Also, a study of Roundup (containing glyphosate as the active ingredient) effects on the first cell divisions of sea urchins (66) is of particular interest to human health. The experiments demonstrated dysfunctions of cell division at the level of CDK1/Cyclin B activation (these proteins are involved in mitosis). Considering the universality among species of the CDK1/Cyclin B cell regulator, these results question the safety of glyphosate and Roundup on human health. In another study (59) it was demonstrated a negative effect of glyphosate, as well as a number of other organophosphate pesticides, on nerve-cell differentiation. Surprisingly, in human placental cells, Roundup was always more toxic than its active ingredient. The effects of glyphosate and Roundup were tested at lower non-toxic concentrations on aromatase, the enzyme responsible for estrogen synthesis (67). The glyphosate-based herbicide disrupts aromatase activity and mRNA levels and interacts with the active site of the purified enzyme, but the effects of glyphosate are facilitated by the Roundup formulation. The authors conclude that the endocrine and toxic effects of Roundup, not just glyphosate, can be observed in mammals. They suggest that the presence of Roundup adjuvants enhances glyphosate bioavailability and/or bioaccumulation.

Additionally, the International Agency for Reseach on caner (IARC) released a report where glyphosate was considered as “probably carcinogenic to humans”(68), an issue which is under debate.

Gluphosinate ammonioum tolerance

The stacked maize event GA21 x T25 contain the *pat* gene from *Streptomyces viridochromogenes* that confers tolerance to herbicides containing gluphosinate-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. Gluphosinate 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 gluphosinate ammonium is used (69-72) EFSA has concluded on the risk of gluphosinate ammonium, as especially harmful to mammals (73).

Summary:

- Two herbicide genes are inserted into stacked maize GA21 x T25.
- Gluphosinate ammonium is banned due to health and environmental issues.
- Glyphosate has and increased focus due to potential health related effects.

Main summary

Maize event GA21 x T25 is tolerant to herbicides containing glyphosate and gluphosinate ammonium that has different degrees of health and environmental dangers upon use.
Thus, the issue on accumulation should be considered for GM plants to be used in food and feed.
In addition, gluphosinate ammonium is banned for use in Norway.
The applicant should provide data relevant for assessment of social utility and sustainable development according to the NGTA (4).

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