Vår ref:2017/H_RX_008
Deres ref: 2017/5156

Høringsuttalelse av fornyelsessøknad om markedsføring av genmodifisert mais 1507 x NK603

EFSA/GMO/RX/008

Under EU forordning 1829/2003

Sendt til

Miljødirektoratet

av

GenØk-Senter for biosikkerhet
Juli 2017

Vår ref:2017/H_RX_008
Deres ref: 2017/5156

Miljødirektoratet
Postboks 5672 Sluppen
7485 Trondheim
Dato: 05.07.2017

Vedlagt er innspill fra GenØk – Senter for biosikkerhet på offentlig høring av fornyelsessøknad **EFSA/GMO/RX/008**, genmodifisert, stablet mais 1507 x NK603, fra Pioneer Hi-Bred International, Inc., under EU forordning 1829/2003 med høringsfrist 07.08.2017. Fornyelsessøknaden gjelder fornyet godkjenning for bruksområdene mat, fòr, import og prosessering.

Vennligst ta kontakt hvis det er noen spørsmål.

Med vennlig hilsen,

Idun Merete Grønsberg
Forsker II
GenØk – Senter for biosikkerhet
idun.gronsberg@genok.no

Bidragsyter(e):

Lillian van Hove
Forsker III
GenØk-Senter for biosikkerhet

Innhold/Content

Vår ref:2017/H_RX_008
Deres ref: 2017/5156

Høringsuttalelse – genmodifisert, stablet mais 1507 x NK603 (EFSA/GMO/RX/008) under EU forordning 1829/2003.

Fornyelsessøknad EFSA/GMO/RX/008 omhandler genmodifisert, stablet mais til bruksområdene mat, for, import og prosessering.

Den genmodifiserte maisen har toleranse mot herbicider som inneholder glyfosat via det innsatte genet *cp4 epsps*, mot glufosinat ammonium gjennom det innsatte genet *pat* og mot enkelte insekter i Lepidoptera ordenen via det innsatte genet *Cry1F*.

Den stablete mais linjen 1507 x NK603 er ikke godkjent for noen av bruksområdene i Norge.

Import av levende maislinje 1507 ble forbudt av Regjeringen pr 2.Juni 2017. Maislinje 1507 er en av foreldrelinjene i den omsøkte fornyelsessøknaden.

Oppsummering

GenØk–Senter for biosikkerhet, viser til høring av fornyelsessøknad EFSA/GMO/RX/008 om 1507 x NK603 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 fornyelsessøknaden:

- Genmodifisert mais 1507 x NK603 er ikke godkjent i Norge for noen av de omsøkte bruksområdene.
- Det er forbudt å importere levende 1507 til Norge .
- Genmodifisert mais 1507 x NK603 er tolerant mot sprøytemidler som inneholder glyfosat og glufosinat-ammonium som har ulike grader av helse-og-miljø fare ved bruk, samt resistens mot insekter i Lepidoptera ordenen via det innsatte genet *Cry1F*.
- Glufosinat-ammonium er forbudt i Norge.
- Fornyelsessøknaden om mais linje 1507 x NK603 mangler data og informasjon som er relevant for å kunne ytterligere vurdere kriterier rundt etisk forsvarlighet, samfunnsnytte og bærekraft.

Summary

GenØk-Centre for biosafety refers to the reapplication EFSA/GMO/RX/008 on 1507 x NK603 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 reapplication:

- The gene modified maize event 1507 x NK603 is not approved for any application in Norway.
- It is not allowed to import living maize 1507 to Norway.
- Maize event 1507 x NK603 is tolerant to herbicides containing glyphosate and glufosinate-ammonium that has distinct health and environmental dangers upon use, and resistance towards Lepidoptera insects through the inserted gene *Cry1F*.
- Glufosinate-ammonium is not allowed in Norway.
- The reapplication on maize event 1507 x NK603 lacks data and information relevant for additional assessment of criteria on ethically justifiability, social utility and sustainability.

Reapplication on EFSA/GMO/RX/008

The stacked event 1507 x NK603 maize contains genes providing herbicide tolerance *(cp4 epsps* and *pat*) as well as a *Cry1F* gene providing resistance against insects in the Lepidoptera order

Previous evaluations

Below are some evaluations of parental lines or the stack 1507 x NK603:

EFSA evaluated the parental line NK603 in 2004 (1) for food and feed concluding that this event was as safe as conventional maize.

The Norwegian Scientific Committee for Food Safety (VKM) published a risk assessment on parental line NK603 on food and feed uses in 2013 (2) with the following conclusion:

"*Based on current knowledge, the VKM GMO Panel concludes that maize NK603 is nutritionally equivalent to conventional maize varieties, and that it is unlikely that the CP4 EPSPS protein will introduce a toxic or allergenic potential in food derived from maize NK603 compared to conventional maize. The VKM GMO Panel likewise concludes that maize NK603, based on current knowledge, is comparable to conventional maize varieties concerning environmental risk in Norway with the intended usage*".

The Norwegian Scientific Committee for Food Safety (VKM) published a final food/feed and environmental risk assessment on parental event 1507 in 2014 (3) with the following comments/conclusions:

- Maize event 1507 is nutritionally equivalent to conventional maize, based on the present knowledge.
- The expressed proteins PAT and Cry1F are not likely to be toxic or allergenic when present in food and feed.
- Cultivation of 1507 will most probably not have negative effects on environment or agriculture in Norway.

The Scientific Panel of EFSA evaluated the stack 1507 x NK603 in 2006 (4), concluding that it was as safe as conventional maize and that there were no hazards or adverse effects documented on human or animal health or on the environment with the intended uses at that time.

Norwegian Scientific Committee for Food Safety (VKM) made a food/feed and environmental risk assessment of 1507 x NK603 in 2013 (5) with the following conclusion:

"The VKM GMO Panel has not identified toxic or altered nutritional properties in maize 1507 x NK603 or its processed products compared to conventional maize. Based on current knowledge, it is also unlikely that the Cry1F protein will increase the allergenic potential of food and feed derived from maize 1507 x NK603 compared to conventional maize varieties. The

VKM GMO Panel likewise concludes that maize 1507 x NK603, based on current knowledge, is comparable to conventional maize varieties concerning environmental risk in Norway with the intended usage".

The Norwegian Biotechnology Advisory Board published a statement regarding maize event 1507 in 2016 (6) as a response to the evaluation made by the Norwegian Environmental Agency (7) where they recommended that this event was not prohibited for import based on their evaluation of the event and its contribution to the criteria of the NGTA (8). In the statement by the Norwegian Biotechnology Advisory Board they commented the following:

- Maize event 1507 is made to be tolerant to an herbicide that is banned in Norway and is about to be phased out of EU due to health and environmental risk issues. In the evaluation of sustainability, the perspective must be global and longterm. Based on this, glufosinate ammonium is not contributing to the demands of sustainability in the NGTA.

GenØk has not evaluated this particular stack of maize event 1507 x NK603 before, but has evaluated the parental events (alone or in combinations) in other stacks, as:

- *2010: MON89034 x **NK603** x **1507** (H65), EFSA/GMO/NL/2009/65)*
- *2010: MON89034 x **NK603** (H72), EFSA/GMO/NL72009/72)*
- *2012: **1507** x 59122 x MON810 **x NK603** (H92), EFSA/GMO/NL/2011/92)*
- *2015: MON87427 x MON89034 x **NK603** (H117), EFSA/GMO/BE/2013/117)*
- *2015: **1507** (RX001), EFSA/GMO/RX001*
- *2016: MON84722 x MON89034 x MIR162 x **NK603** (H131), EFSA/GMO/NL/2016/131)*
- *2016: **1507** x MIR162 x MON810 **x NK603** (H127), EFSA/GMO/N/2015/127)*
- *2017: MON87427 x MON87460 x MON89034 x MIR162 x **NK603** (H134), EFSA/GMO/NL72016/134)*
- *2017: MON89034 x **1507** x **NK603** x DAS-40278-9 (H112), EFSA/GMO/NL/2013/112)*

From these, the reapplication of parental event 1507 in 2015 we put forward the following comments:

- *The regulator is encouraged to perform a re-evaluation of the maize event 1507, which includes glufosinate–herbicide applications.*
- *The regulator is encouraged to ask the applicant for assessment of potential adverse effects of glufosinate-ammonium and changes in weed management.*
- *The regulator is encouraged to ask the applicant to address the potential of non-target effects of Bt toxins.*
- *The applicant should include a full evaluation of the actual use of glufosinate-ammonium with maize event 1507 with a particular focus on the level of accumulation of herbicides in the plants, particularly the parts used in food and feed production, and whether or not these levels of exposure could cause acute and/or chronic health issues. This needs to be tested in animal and feeding studies, separating the effects of the plant and the herbicide(s) by using both sprayed and unsprayed plant samples.*

- *The applicant should include a section on the potential environmental implications for farm workers exposed to the herbicide and toxicity assessment for the farmers.*
- *The regulator is encouraged to ask the applicant to include a section on the potential environmental effects of the herbicide i.e. monitoring changes in use, potential drift into the surrounding area and ecosystems including water systems and wildlife.*
- *The regulator is encouraged to ask the applicant to further elaborate and investigate the increase and spread of resistance towards Cry1F and development of cross-resistance.*
- *The regulators are encouraged to ask the applicant to provide a full ERA of the life cycle of maize event 1507, i.e. from being planted in the field and through the cultivation process, harvesting, transportation, processing, and as waste.*
- *The applicant should include proper analysis of chromosomal locations of the actual inserts and effect on endogenously expressed genes.*
- *We also encourage the applicant to specify if they use microbial or plant derived proteins for their analysis of toxicology and allergenicity studies in the risk assessment of maize event 1507.*
- *We encourage the applicant to perform and go through newer studies on toxicology and allergy with the relevant transgenic proteins.*

The Norwegian Authorities have, through a Royal Resolution dated on the 2nd of June, 2017 (9) pointed the following regarding maize event 1507:

- Ministry of Climate and Environment (KLD) propose that maize event 1507 is prohibited to be traded in Norway under the Gene Technology Act (8). This applies to living maize only (dead and processed 1507 is not covered by this prohibition)
- This prohibition applies for the approved areas of use after directive 2001/18/EC (http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32001L0018&from=EN), feed and industrial processes.
- The Ministry base its conclusion on the following: “the use is ethically problematic” and emphasizes that based on the use of glufosinate ammonium where the maize is produced and that Norway has a ban on this herbicide, import of 1507 is evaluated as ethically problematic and not sustainable by consumer organisations in Norway. This is because the cultivation of the maize depends on the use of glufosinate ammonium, a herbicide that is banned in Norway.
- Maize event 1507 have no traits evaluated as useful for Norwegian consumers/users since it is not allowed to use the herbicide that the maize is modified to tolerate.

See also https://www.regjeringen.no/no/aktuelt/regjeringen-sier-nei-til-genmodifiserte-planter/id2555387/

The Norwegian Authorities are at present considering several other GMOs (https://www.regjeringen.no/no/aktuelt/Rettslig-status-for-genmodifiserte-produkter/id2342458/).

Social utility and sustainability issues on the stacked maize event 1507 x NK603, EFSA/GMO/RX/008

In Norway, an impact assessment follows the Norwegian Gene Technology Act (NGTA) (8) in addition to the EU regulatory framework for GMO assessment. In accordance with 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 regulation 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) (10). 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 (11-17).

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 (18)). 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 1507 X NK603 and where the Applicant should provide data for in order to conduct a thorough assessment according to the NGTA.

The ban on maize 1507

Norwegian authorities have banned the release of living maize 1507 in Norway. The Norwegian Scientific Committee for Food Safety concluded that this maize is as safe as conventional maize. However, the Norwegian Biotechnology Advisory Board concluded in their assessment that this maize should not be allowed in Norway as it was ethically problematic and does not contribute to sustainable development. Maize 1507 is developed to be resistant to glufosinate-ammonium. This is 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. The NBAB concluded that 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. This also troubles the fulfilment of the criteria of *sustainable development*, as this criteria is meant to be considered in a global context. This problem has been previously identified by the Norwegian Biotechnology Advisory Board (19) and GenØk has addressed it multiple times when an applicant seeks approval of a product containing maize 1507 (e.g. 20, 21). Although the Norwegian Environmental Agency recommended approval of maize 1507, the Ministry of Climate and Environment was oppose to this approval. In the Royal Resolution of June 2nd 2017, a final decision was made and living maize 1507 is prohibited to be traded in Norway. This is the first GM crop to be prohibited based on ethical considerations only.

As the current application includes maize 1507 and this event is now prohibited in Norway, we consider this application as opposing the aim of the criteria in the NGTA. Approving this application would be against the Royal resolution. Unless the applicant is able to demonstrate how the combination of maize 1507 with NK603 contains a benefit that could outweigh this decision, we consider a reference to this resolution as sufficient and therefore consider a further elaboration on the evaluation of maize 1507 x NK603 according to the NGTA as superfluous.

Short summary of previous evaluations

In previous hearings with the events maize 1507 and/or NK603, we have pointed out that information was lacking to enable a fruitful evaluation of the criteria in the NGTA. More information is required on the following key issues:

- *Herbicide resistant genes*; when crops are engineered to be herbicide tolerant (such as maize 1507 x NK603) in order to maintain an agricultural practice that uses herbicide, information is warranted on the amount of herbicide used, the potential increase of use and what management strategies are in place to avoid weed resistant.
- *Impact in producer countries*; some products may not directly affect Norway, but will have a (potential negative) impact in producer countries. Currently, this and previous applicants provide no information on this as the product will not be cultivated in Norway. However, to be able to evaluate the criteria of 'sustainable development' and 'ethically justifiable', information on the effect of cultivation on producing countries is warranted. The ground on which maize 1507 is now prohibited in Norway is a suiting example of this.
- *Co-existence*; the cultivation of GM plants in general is causing problems with regard to co-existence. It is important to obtain information about the strategies adopted to ensure co-existence with conventional and organic maize production and the applicant should provide information on this to enable an accurate evaluation of the criteria in the NGTA.

Environmental risk issues in a Norwegian context

The level of maize production is quite 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 1507 x NK603 contains three distinct, inserted transgenes providing herbicide tolerance and insect (Lepidoptera) resistance.

Stacks are combinations of several, single parental events and should be regarded as new events, as the combination itself in the stack is unique. 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. The potential for synergistic effects of transgenic proteins has also been described by Kramer et al (22) where they look at new approaches for risk assessment of stacked events.

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 (23, 24). There has also been investigations of whether stacking have effects on the maize proteome (25). Here, results indicate that the levels of transcripts were affected by the stacking per se (seemingly), with changes in protein profiles that needs further investigation.

Cry genes and proteins

This stack contains one Cry gene, namely *Cry1F*. The Cry genes encode a class of proteins called Cry toxins or Bt-toxins. The insertion of Cry genes in transgenic plants are widely used for pest management (*Lepidoptera* related insects), leading to a selection pressure resulting in increased resistance development during the years (26-28).
According to Yang et al (29), field resistance to Cry1F have been documented in several countries already.

The development of cross resistance to other related Cry proteins when using Cry1F is also an important issue. In a publication by Velez et al in 2013 (30) this issue was investigated and compared to other Cry toxins. Here they found that there was no significant cross resistance to certain Cry toxins, although some resistance alleles were found in some US populations. Thus, by using plants expressing this toxin, awareness to this issue is important.

Non-target effects

In relation to non-target and environmental effects, two meta-analyses on published studies on non-target effects of Bt proteins in insects (31) documented that 30% of studies on predators and 57% of studies on parasitoids display potentially negative effects by Cry1Ab transgenic insecticidal proteins.

Another quantitative review by Marvier et al. (32) 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 (33)*, and caddisflies (34). 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 (35) have previously presented 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.

Adjuvancy effects

The potential adjuvancy of Cry proteins has previously been addressed by the GMO Panel of the Norwegian Scientific Committee for Food Safety (36). Scientific studies have shown that the Cry1Ac protein is highly immunogenic and has systemic and mucosal adjuvant effects (37). In the evaluation of another 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. The Panel continues:

"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" (38).

The GMO Panel of the Norwegian Scientific Committee for Food Safety (36) also writes that:

"There are many knowledge gaps related to assessment of adjuvants. Most of the immunologic adjuvant experiments have been performed using Cry1Ac. Whether the other Cry proteins have similar adjuvant properties is unknown".

And;

"The possibility that Cry proteins might increase the permeability of the intestinal epithelium and thereby lead to "bystander" sensitization to strong allergens in the diet of genetically susceptible individuals cannot be completely excluded."

We also agree with these concerns and highlight them for the maize event 1507 x NK603.

Summary*:*

- Cry proteins might have potential for non-target effects.
- Some Cry proteins have adjuvant effects. It is unclear from the available and published data if Cry1F also has that.
- Cross-resistance development is an issue that needs awareness for maize event 1507 x NK603

Molecular characterization

Maize event 1507 x NK603 is a stacked event produced from the single-events 1507 and NK603 by traditional maize breeding.

According to EFSA (39): *"For GM plants containing stacked events the primary concern for risk assessment is to establish that the combination of events is stable and that no interactions between the stacked events, that may raise safety concerns compared to the single events, occur … In order to allow for the assessment of and conclusions on interactions between multiple events, the applicant is asked to include in the application, either in the Part II or as a separate appendix, a table comprising compositional data (combined site results) including mean values and ranges for all materials analysed for all single events stacked in the GM plant, the GM plant containing stacked events and all controls. If the events were not included in the same set of field trials, the applicant is asked to include indications on the origin of the data on the single events [references to previous applications and e.g. number of field sites, season(s), location(s), number(s) of replicates]"*.

CaMV promoter

The parental event NK603 contains a 35S promoter. We refer to the published literature surrounding this issue (40) for further elaboration by the applicant of the presence of potential ORFs.

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

ELISA

ELISAs were used as a method to investigate the expression levels of the CP4 EPSPS and Cry1Ab proteins in the NK603 x Mon810 maize hybrid. The test substance was forage and grain collected from three sites in France (dossier p.35).

As a capture antibody for the protein Cry1Ab, a purified polyclonal rabbit antibody raised against the tryptic core of the protein was used. In the application it is not clear from where the capturing antibody originate. Due to potential differences in post translational modifications, the protein that is actually expressed in the GM plant should be used (41, 42).

The expression levels of expressed, transgenic proteins CP4 EPSPS and Cry1Ab is not available for the reapplication. Data available are from the original technical dossier from 2005/2006. No new analysis are performed according to the summary of the reapplication.

Toxicity and allergenicity

Updated bioinformatics searched of expressed proteins in 1507 x NK603 maize were performed. No data concerning risk of toxicity or allergenicity were detected by the methods used (BLASTp).

Protein sequence databases were used in the search for potential toxic of allergenic proteins (p.25 in technical dossier of reapplication). Here, homology with 3 known allergens were detected for two reading frames, where these were evaluated as "two likely false positive hits" by referring to previous information to EFSA and that these reading frames were not biologically relevant and thus had no safety concerns according to the applicant.

Hazard identification

According to the applicant, they have monitored "*for new, per-reviewed scientific publications confirming that no adverse effects on human or animal health or the environment have arisen from the import of 1507 x NK603 into the EU…". ""No articles or reports detailing any adverse effects to human or animal health or the environment arising from 1507 x NK603 maize have been noted during the current reporting period"* (section 2.3.2.6 in technical dossier).

Summary:

- One of the parental events, NK603, has a 35S CaMV promoter driving expression of one of the transgenes. This promoter is shown active in plant as well as mammalian cells and that some variants have ORFs.
- Two ORFs were detected but evaluated as two likely false positives.

Any other new information which has become available with regard to the evaluation of safety in the use of the food and feed and the risks of the food and feed to the consumer, animal or the environment (section 3, techincal dossier).

Updated literature search (p.22)

Systematic review of literature through two selected databases (Scopus[1] and CAB Direct[2]). Here, only one publication was identified after the criteria set by the applicant. This publication was by EFSA (43).

No information from this publication raise any concerns regarding human or animal health or the environment.

[1] http://www.scopus.com/
[2] http://www.cabdirect.org/

Bioinformatic analysis (p.25)

Up-to date databases (according to the applicant), were used for analysis of the flanking regions for each of the parental events.

Data show that no genes are interrupted upon transformation, and no unintended modifications are detected by the analysis performed.

Comment:

- For parental event 1507: it is not clear if the sequences analyzed are from an old or new DNA isolation.
- For parental event NK603: It is not clear if the sequences analyzed are from old or new DNA isolations.

Herbicides used on 1507 x NK603

The use of herbicides on GM plants

Gene modified (GM) herbicide tolerant (HT) plants can be sprayed with the herbicides that are relevant according to the inserted transgenes.

There are however several issues to consider when plants are sprayed with herbicides when it comes to the potential for negative effects on environment, as well as humans and animals.

Some of these issues could be:

1. Increased exposure to herbicides
2. Potential for development of weeds that are herbicide resistant
3. Potential for accumulation of herbicides inside plants
4. Combinatorial effects of several herbicides used on one plant/crop at the same time

Total use of herbicides

The commercialization of GM-HT crops have led to an increased use of certain herbicides in agriculture (44). Especially glyphosate, but also the use of other herbicides connected to this has increased the last decades and by 2016, about 56 % of the global use of glyphosate was related to the use of HT GM crops (44).

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 can be connected to resistance evolution in weeds. At present, 36 species of weeds are documented to be glyphosate resistant on a global scale (45).
For glufosinate-ammonium, six species of weeds are shown to be resistant and 50 % of these were discovered after 2015 (45).

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 (44), which directly or indirectly will expose non-target biodiversity in terrestrial, soil and aquatic communities (46), represent a major source of environmental pollution.

Accumulating herbicide residues and health effects

Through the introduction of GM-HT plants, the use of certain herbicides are increasing. The issue on accumulation and potential of health effects are thus issues of major importance when it comes to plants being used as food and feed.

Glyphosate

The *cp4 epsps* gene present in 1507 x NK603 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 (47, 48). However, glyphosate has recently received more risk-related attention due to its potential for negative effects on both aquatic and terrestrial ecosystems (49), as well as from studies in animals and cell cultures that have indicated possible negative health effects in rodents, fish and humans (50-52).

A number of publications indicate unwanted effects of glyphosate on health (52, 53), aquatic (54) and terrestric (49, 55) organisms and ecosystems. Also, a study of Roundup (containing glyphosate as the active ingredient) effects on the first cell divisions of sea urchins (56) is of particular interest to human health.

Glufosinate ammonioum

Maize event 1507 x NK603 contains a *pat* gene that confers resistance 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. Glufosinate 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 (57-60). EFSA has concluded on the risk of glufosinate ammonium, as especially harmful to mammals (61).

Summary:

- Maize event 1507 x NK603 is tolerant to glyphosate, a herbicide that is potentially damaging to health and environment in different ways.
- Maize event 1507 x NK603 is also tolerant to glufosinate ammonium, which is banned in Norway due to effects on health and environment.
- Potential for accumulation of the herbicides should be considered in GM plants used in food and feed.

Main summary

Maize event 1507 x NK603 is tolerant to herbicides containing glyphosate and glufosinate ammonium with distinct implications related to health and environment. The issue on accumulation should be considered for GM plants to be used in food and feed.
Glufosinate ammonium is banned for use in Norway.
Living maize 1507, which is one of the parental events, is prohibited for import to Norway.
The applicant should provide data relevant for further assessment of social utility and sustainable development according to the NGTA if needed (8).

References.

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