Vår ref:2017/H_112
Deres ref: 2016/11192

Høringsuttalelse av søknad om markedsføring av genmodifisert mais

MON89034 x 1507 x NK603 x DAS-40278-9

EFSA/GMO/NL/2013/112

Under EU forordning 1829/2003

Sendt til

Miljødirektoratet

av

GenØk-Senter for biosikkerhet
Februar 2017

GenØk – Senter for biosikkerhet
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Vår ref:2017/H_112
Deres ref: 2016/11192

Miljødirektoratet
Postboks 5672 Sluppen
7485 Trondheim
Dato: 06.02.2017

Vedlagt er innspill fra GenØk – Senter for Biosikkerhet på offentlig høring av søknad **EFSA/GMO/NL/2013/112**, genmodifisert mais MON89034 x 1507 x NK603 x DAS-40278-9, fra Dow AgroSciences LLC, 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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Vår ref:2017/H_112
Deres ref: 2016/11192

Høringsuttalelse – genmodifisert mais linje MON89034 x 1507 x NK603 x DAS-40278-9, EFSA/GMO/NL//2013/112/ under EU forordning 1829/2003.

Søknad EFSA/GMO/NL/2013/112 omhandler genmodifisert mais til bruksområdene mat, for, import og prosessering.

Den genmodifiserte maisen har toleranse mot herbicider som inneholder glyfosat, glufosinat ammonium, 2.4D og aryloksyfenoksypropionater via de innsatte genene *cp4 epsps*, *cp4 epsps l214p*, *pat* og *aad-1* og er en såkalt «stack» eller «stablet» genmodifisert mais.

I tillegg er det satt inn gener som gir maisen resistens mot larver fra insekter i *Lepidoptera* ordenen.

Maisen er ikke godkjent for noen av bruksområdene i Norge eller EU.

Av foreldrelinjene er søknaden til maislinje DAS-40278-9 under behandling i EU og 1507 gjennomgår en behandling av fornyelssesøknad.

Den genmodifiserte maislinjen MON89034 x 1507 x NK603 x DAS-40278-9 er godkjent for dyrking i Brasil og Canada.

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OPPSUMMERING

GenØk–Senter for biosikkerhet, viser til høring av søknad EFSA/GMO/NL/112 om MON89034 x 1507 x NK603 x DAS-40278-9 mais som omfatter bruksområdet import og prosessering og til bruk i fôr 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 søknad om fornyelse:

- MON89034 x 1507 x NK603 x DAS-40278-9 er ikke godkjent i Norge for noen bruksområder, og foreldrelinjene 1507 (fornyelsessøknad) og DAS-40278-9 er fremdeles under behandling i EU.
- Vitenskapskomiteen for mattrygghet (VKM) har kommentert at foreldre linjene MON89034, 1507, NK603 og DAS-40278-9 er like trygge som ikke genmodifisert mais til bruk i fôr og næringsmidler (1-4).
- Maisen er tolerant mot glyfosat, glufosinate- ammonium og 2.4D sprøytemidler som har ulik grad av helse-og-miljø fare ved bruk.

SUMMARY

GenØk-Centre for biosafety refers to the application EFSA/GMO/NL/112 on MON89034 x 1507 x NK603 x DAS-40278-9 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 for MON89034 x 1507 x NK603 x DAS-40278-9 maize:

- MON89034 x 1507 x NK603 x DAS-40278-9 is not approved for any application in Norway. Maize event DAS-40278-9 is under assessment in EU, as is the reapplication for maize event 1507.
- The Norwegian Food Safety Authority has commented that the parental events MON89034, 1507, NK603 and DAS-40278-9 are as safe as non-modified oilseed rape for use in feed and foodstuffs (1-4).
- This maize event is tolerant to glyphosate, gluphosinate ammonium and 2.4D herbicides that has different degrees of health and environmental dangers upon use.

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Application on EFSA/GMO/NL/2013/112

Previous evaluations of parental events
The parental events of the stacked event MON89034 x 1507 x NK603 x DAS40278-9 has been evaluated by the Norwegian Scientific Committee for Food Safety (vkm.no).

The parental event MON89034 went through a health and environmental risk assessment in 2014 (4) where it was concluded that maize event MON89034 is unlikely to have a allergenic of toxic potential through the introduced protein Cry1A.105 and Cry2Ab2. The environmental risk was assessed to be comparable to conventional maize "based on current knowledge".

The parental event 1507 went through a risk assessment for cultivation, import, processing, food and feed uses in 2014 (5) where the Panel on Genetically Modified Organisms concluded that maize event 1507 is nutritionally equivalent to convetional varieties of maize. They also concluded that the cry protein (Cry1F) and Pat did not pose any risk related to toxicity of allergy, and that the environmental risk was comparable to that of conventional maize. Meaning, no harm to environment or agriculture in Norway.

The parental event NK603 went through a food and environmental risk assessment in 2013 (2) concluding that this gene modified maize event is nutritionally equivalent to conventional maize and is comparable to other maize varieties concerning environmental risk in Norway. Also, there is no evidence that CP4 EPSPS will introduce any toxic or allergenic potential.

Parental event DAS40278-9 was preliminary assessed by the Norwegian Scientific Committee for Food Safety in 2011 (1) concluding that there is a low probability that this event will establish in Norway and spread, and that there is low probability of risk related to health regarding the inserted *aad-1* gene encoding tolerance to 2.4D and aryloxyphenoxypropionate containing herbicides.

The Norwegian Biotechnology Advisory Board has also assessed all single, parental events in this stack, except DAS-40278-9. In 2013 (6) they published a summary document with the completion of several gene modified events assessed for food, feed, import and processing.

In this document, they list 27 applications on maize where they recommend that the Norwegian authorities reject all. Amongst these, MON89034, 1507 and NK603 are present with their inserted genes and introduced traits.

The Norwegian Biotechnology Advisory Board rejects all these applications based on the following grounds:

- Weed that develop resistance towards herbicides faster than with alternative production methods
- Seems to be an increase in the use of herbicides in the big GMO-producing countries.

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- Herbicides containing gluphosinate-ammonium have documented health and environmental damage.
- Plant produced pesticides can harm non-target organisms.
- Pests can develop resistance quicker than if using alternative production methods.
- Science based data indicate that there might be a potential health related risk from these GMOs and this must be investigated further.

These are important points that need further consideration.

The Norwegian Biotechnology Advisory Board has assessed maize event 1507 on several occasions (2003, 2004 and 2004), as mentioned in the letter to the Environmental Agency of Norway in 2006 (7). The majority of the board wanted to prohibit maize event 1507 due to lack of immunological studies of one of the Cry toxins expressed (Cry1F) and lack of information on the demands in the Gene technology Act (8) on sustainability and social utility.

The Norwegian Environment Agency has also made a final evaluation of on maize event 1507 concluding that there is no risk to health or environment and that there is no information available on sustainability or social utility issues that should lead to prohibiton or restriction on 1507 in Norway (9).

Maize event NK603 has been evaluated as as safe as conventional maize by EFSA (10). And the Norwegian Environment Agency has also evaluated this maize event as safe.

We have also assessed parental single events or combinations of these in the following:

- EFSA/GMO/NL/2009/65: **MON89034 x 1507 x NK603**
- EFSA/GMO/BE/2011/90: **MON89034**
- EFSA/GMO/BE/2013/117: MON87427 x **MON89034 x NK603**
- EFSA/GMO/BE/2013/118: MON87427 x **MON89034 x 1507** x MON88017 x 59122
- EFSA/GMO/NL/2016/131: MON87427 x **MON89034** x MIR162 x **NK603**

Social utility and sustainability issues on maize event MON 89034 x 1507 x NK603 x DAS-40278-9, EFSA/GMO/NL/2013/112

In addition to the EU regulatory framework for GMO assessment, an impact assessment in Norway follows the Norwegian Gene Technology Act (NGTA) (11). In accordance with the aim of the NGTA, production and use of the GMO needs to be *ethically justifiable*, *benefit 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 regulations 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) (12). Additionally, in recent years, attention increased within academic as well as policy spheres to include broader aspects in the assessment of new and emerging (bio) technologies that reach beyond human and environmental health. These broader aspects are in line with the criteria in the NGTA, such as sustainability, benefit for society and ethical considerations (13-18).
The assessment of these three criteria in the NGTA demands significant dedication as it covers a wide range of aspects that needs to be investigated (e.g. Annex 4 within the NGTA, or 19). Nevertheless, the applicant has currently not provided any information relevant to demonstrate a benefit to society, the contribution of maize MON89034 x 1507 x NK603 x DAS-40278-9 to sustainable development, nor provide information on the ethical justifiability. Therefore, this part will highlight some areas that are particularly relevant to consider with maize MON89034 x 1507 x NK603 x DAS-40278-9 and where the applicant should either provide data for in order to conduct a thorough assessment according to the NGTA, or the application should be refused.

Impacts in producer countries

As already stated, the Applicant does not provide data relevant for an environmental risk assessment of maize MON89034 x 1507 x NK603 x DAS-40278-9, 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 which is referring to a global context, including the contribution to sustainable development in the producing countries. Importantly, 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 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. Hence, a proper evaluation of potential impacts that are relevant for sustainability is lacking, and sufficient information relevant for the ERA and socio-economic impacts in these agricultural contexts needs to be provided. This should include information from an ERA concerning impacts on cultivation, management and harvesting stages, as well as the post-market environmental monitoring in the producing country.

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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 MON89034 x 1507 x NK603 x DAS-40278-9 needs to demonstrate how it will benefit Norway but no information on this part is provided by the applicant. In addition, it is also important to evaluate whether there is any demand from the consumer for this product and what the attitude of Norwegian consumers are toward GM crops. However, the limited amount of empirical data on this is for Norway (e.g. 20, 21) is outdated and more empirical research on this is needed to investigate consumer attitude, demand and acceptance.

Assessing alternatives
When a new variety (biotechnological) 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 ethically justified way. What is meant with alternatives, and what would benefit from being assessed could include alternative varieties (e.g. non-GM) 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 and reflect on underlying values, assumptions, norms and beliefs (16, 22) 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 MON89034 x 1507 x NK603 x DAS-40278-9 contributes to social utility, it is important to investigate current and future demands for this product in Norway and if there are alternatives sources that could be cultivated in Norway that may satisfy this demand.

Ethical considerations
Maize MON89034 x 1507 x NK603 x DAS-40278-9 is meant to be resistant to gluphosinate-ammonium, an herbicide that is banned in Norway due to the risks to human health and the environment. It seems ethically ambiguous and inconsistent to develop or even import a plant that is resistant to this herbicide, thereby allowing the use of a harmful herbicide in other countries, while considering the herbicide as too harmful to be used in Norway. Information on how this can be ethically justified – if possible at all – is wanted.
Additionally, it is worth noting that the stack of maize MON89034 x 1507 x NK603 x DAS-40278-9 contains the event MON 89034 that is already a stack. Currently, the applicant does not provide any information about the possible risks related to stacking with 'stacked-event' and is treating this stacked-event in the same way as a 'single event'. Clarification and transparency is wanted about the (lack of) information available on stacking with stacked-events. Furthermore, it should be noted that the applicant create a stack with the event DAS-40278-9, which is in itself an application that is still under evaluation, as well as 1507, an event that still does not have an approval for its renewal.

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 ERA and socio-economic

impacts of maize MON89034 x 1507 x NK603 x DAS-40278-9 and its contribution to sustainable development. The information provided by the Applicant must be relevant for the agricultural context in the producing country/countries. The information should also include issues such as: changes in pesticide use, development of pest resistance in target populations, impacts on non-target organisms, potential for gene flow and possible impacts among poor and/or small-scale farmers in producing countries and share of the benefits among sectors of the society. Furthermore, maize MON89034 x 1507 x NK603 x DAS-40278-9 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 supporting its use in other countries would be ethically ambiguous, as is the use of an event that is currently still under evaluation. Moreover, the applicant does not attempt to demonstrate a benefit to the community or any reference on the consumer attitude and demand within Norway for maize MON89034 x 1507 x NK603 x DAS-40278-9 and does therefore not provide sufficient information as required by the NGTA.

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 is 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.

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

The event MON89034 x 1507 x NK603 x DAS-40278-9 is a stacked maize containing several inserted genes expressing distinct classes of proteins.

Molecular characterization

All inserted genes in the stacked maize event MON89034 x 1507 x NK603 x DAS-40278-9 has been thoroughly described before. Here is a short description of their source and actions:

- The *pat* gene (source: *Streptomyces viridohromogenes*) encode the enzyme phosphinothricin N-acetyltransferase that removed activity of gluphosinate containing herbicides by acetylation[1].

[1] http://www.isaaa.org/gmapprovaldatabase/event/default.asp?EventID=349

- The *CP4 epsps* genes (source: *Agrobacterium tumefaciens*) encode a herbicide tolerant form of 5-enolpyruvulshikimate-3-phosphate synthase enzyme that confer resistance to glyphosate containing herbicides by decreasing binding affinitiy to it.

- The *aad-1* gene encodes a aryloxyalkanoate dioxygenase 1 protein that" detoxifies 2,4-D herbicide by side-chain degradation and degrades the R-enantiomers of aryloxyphenoxypropionate herbicides".

- The *Cry1A.105, Cry2Ab2 and Cry1F* genes confers resistance to lepidopteran insects by damaging the midgut of them.

CaMV promoter in maize event NK603

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 (23-25). 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 (26). 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 (27). Functions of P6 include nuclear targeting (28), viral particle binding and assembly (29), si- and ds-RNA interference and interference suppression (30) and transcriptional transactivation (31, 32). 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 (23, 25), as well as that the promoter is able to drive expression of a transgene in fish as demonstrated recently by Seternes et al (24). The potential risk when it comes to GM food/feed that contains the CaMV promoter may be unlikely but cannot be excluded.

Characterization of the newly expressed protein(s)

Cry proteins

The stacked event MON89034 x 1507 x NK603 x DAS40278-9 maize combines three Cry-proteins named Cry1F, Cry2Ab2 and Cry1A.105. These proteins, also called Bt-toxins work by giving the gene modified maize plants protection against certain Coleoptera insects. However, Bt-toxins also have the potential of non-target effects, and alternative modes of action for Cry toxins have been addressed previously (33-36).

Studies performed on non-target insects of Bt-toxins have documented that 30% of studies on predators and 57% of studies on parasitoids display negative effects to Cry1Ab transgenic insecticidal proteins (37). Further, Cry toxins and proteinase inhibitors have shown non-neutral effects on natural enemies, and seemingly more often negative than positive effects (38). A

review by Hilbeck and Schmidt (36) on Bt-plants, found that half of the studies documented negative effects on tested invertebrates.

In addition, a review by van Frankenhuyzen (39) indicated that several Cry proteins exhibit activity outside of their target orders. This study also found that many Cry proteins had been tested with a very limited number of organisms: thus, activity outside of the target organisms of many Cry proteins may be undocumented because testing has not included sensitive organisms.

A quantitative review analysis based on 42 field experiments with GM plants showed that unsprayed fields of Bt-maize plants have significantly higher abundance of terrestrial non-target invertebrates than sprayed conventional fields (40). Thus, Bt-plants with a single Bt-gene inserted may represent an improvement for non-target organisms in the environment. However, an indication of some negative effects of the Cry1Ab toxin itself, or the Cry1Ab maize plant, on non-target abundance was shown in the same meta-analysis: when conventional (non-GM) fields were not sprayed, the non-target abundance was significantly higher than in the Bt-fields (40).

Research on aquatic environments investigating potential impact of Bt-crops on aquatic invertebrates including *Daphnia magna* (33) and caddisflies (41) has also been performed. Douville et al. (42) presented data of the persistence of the *cry1Ab* transgene in aquatic environments: it persisted more than 21 days in surface waters, and 40 days in sediments. A follow-up on this study in 2009 indicated possible horizontal gene transfer of transgenic DNA fragments to aquatic bacteria (43). Impacts on soil microflora and fauna, including earthworms (44) , mychorizzal fungi (45) and microarthropods in response to Cry endotoxins have also been reported (46-48). The significance of tri-trophic effects of accumulation, particularly of insecticidal Cry toxins (49, 50) is, however, yet to be firmly established.

In an experiment using broccoli plants containing Cry1Ac, Cry1C or both to investigate resistance development in a population of diamondback moths (*Plutella xylostella*), they found that when using stacked, similar Cry proteins, the resistance development in this population increased to both traits (51). Another group (52) later commented this on; suggesting that gene stacking might not be a solution to the development of resistance towards Cry proteins.

It has also been shown that the combination of two (or maybe more) insecticidal proteins against the same pest as target, is a tactic used to delay the resistance development towards either protein in the combination (53).

A study in mice showed that exposure to purified Cry1Ab resulted in specific anti-Cry1Ab IgG1 and IgE production, indicating inherent immunogenicity and allergenicity. Further, mice exposed to leaf extracts from both MON810 and unmodified maize demonstrated influx of lymphocytes and eosinophils in the broncho-alveolar lavage, and increased cytokine release in mediastinal lymph node cells (54). We suggest that further studies should also include animals with immune-deficiencies and/or animals exposed to other stress agents simultaneously.

Adjuvancy effects

The potential adjuvancy of Cry proteins has previously been addressed by the GMO Panel of the Norwegian Scientific Committee for Food Safety (55). Scientific studies have shown that the Cry1Ac protein is highly immunogenic and has systemic and mucosal adjuvant effects (56). 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" (57).

The GMO Panel of the Norwegian Scientific Committee for Food Safety (55) 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 MON89034 x 1507 x NK603 x DAS-40278-9.

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.
- Cry proteins might have potential for non-target effects.
- Pyramiding of Cry genes can delay resistance development of either of the proteins in the pyramide.
- As some Cry proteins have adjuvant effects, it can not be excluded that other Cry proteins have that also. This should be investigated.

Herbicides

The stacked maize event MON89034 x 1507 x NK603 x DAS40278-9 contains a PAT gene providing gluphosinate ammonium tolerance, CP4 epsps providing glyophosate tolerance and aad-1 provoding tolerance towards 2.4 D and aryloxyphenoxypropionate containing herbicides.

Herbicide use on GM plants

The combination of Bt-toxins and herbicide tolerance (HT) gene is the most used combination of inserted genes when it comes to GM plants. In this case, maize event MON89034 x 1507 x NK603 x DAS40278-9 is tolerant to the herbicides gluphosinate ammonium, glyphosate, 2.4D, aryloxyphenoxypropionates as well as expressing three Bt-toxins.

HT plants are sprayed with the actual herbicide(s), leaving the weed to die whereas the plant with the inserted genes will survive. However, the issue on accumulation of herbicides in the HT plants, including metabolic pathways and metabolites of these, are often not tested as part of the risk assessment of HT plants. Bøhn et al. (58) 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 (59, 60). 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.

Another issue is the development of resistance towards the herbicides (61) in use that is a relevant issue, but not discussed further here.

Glufosinate ammonium tolerance

The stacked event MON89034 x 1507 x NK603 x DAS40278-9 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. 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 gluphosinate ammonium is used (62-65) EFSA has concluded on the risk of gluphosinate ammonium, as especially harmful to mammals (66).

Glyphosate tolerance

The *cp4 epsps* and *cp4 epsps L214P* genes present in MON89034 x 1507 x NK603 x DAS40278-9 maize confers tolerance to herbicide products containing glyphosate.

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

Glyphosate has been announced as an ideal herbicide with low toxicity for operators, consumers and the environment surrounding agriculture fields (67, 68). However, it has received more risk-related attention due to its potential for negative effects on both aquatic and terrestrial ecosystems (69), as well as in studies in animals and cell cultures that have indicated possible negative health effects in rodents, fish and humans (70-72).

Recent studies indicate that agriculture of GM plants is associated with greater overall usage of pesticides than the conventional agriculture (73).

A restricted number of recent publications indicate unwanted effects of glyphosate on health (72, 74), aquatic (75) and terrestric (69, 76) organisms and ecosystems.
A study of Roundup effects on the first cell divisions of sea urchins (77) is of particular interest to human health. The experiments demonstrated cell division dysfunctions at the level of CDK1/Cyclin B activation. 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 (70) 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 is 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 (78). 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 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 concluding that glyphosate is “probably carcinogenic to humans”(79).

2.4D tolerance
The *aad-1* gene provides 2.4D (dichlorophenoxy) and arylphenoxypropionate tolerance in the maize stack MON89034 x 1507 x NK603 x DAS-40278-9.
This herbicide has negative effects on the endocrine and immune system,and is thought to might have a role in cancer as well as affecting reproductively (http://www.pesticideinfo.org/Detail_Chemical.jsp).

From the homepage of the Norwegian government (https://www.regjeringen.no/no/sub/eos-notatbasen/notatene/2015/okt/plantevernmiddel---24-d/id2469257/) the following is noted:

“Commission Implementing Regulation (EU) 2015/2033 of 13 November 2015 renewing the approval of the active substance 2,4-D in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending the Annex to Commission Implementing Regulation (EU) No 540/2011”.
Thus, 2.4D is approved for use in Norway.

Summary:

- Maize event MON89034 x 1507 x NK603 x DAS-40278-9 is tolerant to glyphosate, gluphosinate ammonium, 2.4D and aryloxyohenoxypropionates. These herbicides are damaging to health and environment.
- Potential for accumulation of the herbicides should be considered in GM plants used in food and feed.

Stacked events

Today there is a clear trend towards combining many transgenic traits through conventional breeding of the single, parental transgenic parental events. Studies on how these GM stacked events should be assessed is limited, and assessment data for each single GM events is taken into account to prove the safety of the whole food/feed.

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 (80, 81). Then (82) 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.

MON89034 x 1507 x NK603 x DAS-40278-9 maize combines several classes of Bt proteins active against insects pest like Lepidoptera. It is well known that synergistic and additive effects both between Bt toxins and other compounds do occur (82). This article 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. However, it has been suggested that risk assessments for gene-modified plants with stacked genes could be less carefully investigated than the assessments of the single events (83). The basis for this suggestion is that there is no additional recombinant DNA introduced by conventional breeding and interaction in the plant is not expected when the transgene product are not part of, or interact with, common metabolic pathways.

Allergenicity and toxicity issues

Toxicological assessment

Toxicological studies were performed on the proteins Cry1A.105, Cr2Ab2, Cry1F, PAT, CP4 EPSPS, CP4 EPSPSl214P and AAD-1according to OECD guidelines (84) and other described

practices (technical dossier p.149), in previous applications for authorisations of the single, parental events MON89034, 1507, NK603 and DAS-40278-9.

Data from these assessments are the basis for the conclusion on safety based on the history of safe use, no structural similarity to known toxins, proteins do not exert any acute toxicity to mammals, they are in low concentration and are rapidly digested in simulated gastric fluids (SGFs).

Cry1A1.105 does however have 93.6% aminoacid sequence similarity with the Cry1Ac proteins, thus the issue on adjuvancy on page 12 is relevant.

Allergenicity

Potential interactions between newly expressed proteins
Mode of action, molecular analysis of the corresponding genes, activity and response to combined administration to target organisms was assessed based on previous data from applications on the single, parental events of the maize stack MON89034 x 1507 x NK603 x DAS-40278-9.
This data made the basis for the conclusion made by the applicant; that "no interactions that could possibly affect human and animal health would be reasonably expected from consumption"…and..." "we expect these conclusions to be transferable to all subcombinations of MON89034 x 1507 x NK603 x DAS-40278-9"…

Hazard identification
According to the applicant, it is unlikely that the proteins expressed from the gene modified maize stack will be hazardous non-target organisms.

Main summary

Maize event MON89034 x 1507 x NK603 x DAS-40278-9 is tolerant to herbicides containing glyphosate, gluphosinate ammonium, 2.4D and aryloxyphenoxypropionates that has distinct 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(11).

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