Vår ref:2017/H_133
Deres ref: 2017/1003

Høringsuttalelse av søknad om markedsføring av genmodifisert mais MZHG0JG

EFSA/GMO/DE/2016/133

Under EU forordning 1829/2003

Sendt til

Miljødirektoratet

av

GenØk-Senter for biosikkerhet
Mars 2017

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Miljødirektoratet
Postboks 5672 Sluppen
7485 Trondheim
Dato: 15.03.2017

Vedlagt er innspill fra GenØk – Senter for Biosikkerhet på offentlig høring av søknad **EFSA/GMO/DE/2016/133**, genmodifisert mais MZHG0JG, 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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Vår ref:2017/H_133
Deres ref: 2017/1003

Høringsuttalelse – genmodifisert mais linje MZHG0JG, EFSA/GMO/DE/2016/133 under EU forordning 1829/2003.

Søknad EFSA/GMO/DE/2016/133 omhandler genmodifisert mais til bruksområdene mat, for, import og prosessering.

Den genmodifiserte maisen har toleranse mot herbicider som inneholder glyfosat og glufosinat ammonium via de innsatte genene *mepsps-02 og pat-09.*

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

Den genmodifiserte maislinjen MZHG0JG er godkjent for dyrking i USA og Canada, og elles for import til Australia, New Zealand og Sør-Afrika.

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OPPSUMMERING

GenØk–Senter for biosikkerhet, viser til høring av søknad EFSA/GMO/DE/2016/133 om MZHG0JG 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 mais linje MZHG0JG er ikke godkjent i Norge eller EU for noen av de omsøkte bruksområdene.
- MZHG0JG er tolerant mot sprøytemidler som inneholder glyfosat og glufosinate-ammonium som har ulike grader av helse-og-miljø fare ved bruk.
- Søknaden om mais linje MZHG0JG 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/2016/133 on MZHG0JG 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 maize event MZHG0JG is not approved for any application in Norway or the EU.
- Maize event MGHZ0JG is tolerant to herbicides containing glyphosate and gluphosinate ammonium that has distinct health and environmental dangers upon use.
- The application on maize event MZHG0JG lacks data and information relevant for assessment of criteria on ethically justifiability, social utility and sustainability.

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Application on EFSA/GMO/DE/2016/133

Maize event MZHG0JG contains the genes *mepsps-02* and *pat-09* providing tolerance to herbicides containing glyphosate and gluphosinate ammonium.

Previous evaluations

EU has not assessed maize event MZHG0JG before. However Food Standards Australia New Zealand (FSANZ) has evaluated the herbicide tolerant maize event MZHG0JG (1, 2) and have concluded that there are no health and safety concerns based on the data provided by the Applicant.

GenØk has not accessed maize event MZHG0JG in any combinations previously, neither the genes pat-09 or mepsps-02.

However, other epsps and pat proteins have been assessed in other applications, from other genetic variants.

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Social utility and sustainability issues on maize event MZHG0JG, EFSA/GMO/DE/2016/133

In addition to the EU regulatory framework for GMO assessment, an impact assessment in Norway follows the Norwegian Gene Technology Act (NGTA) (3).

In accordance with the aim of the NGTA, production and use of the 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 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) (4). Additionally, in recent years, attention increased within academic and policy spheres to broaden the assessment of new and emerging (bio) technologies to include issues that reach beyond human and environmental health. (5-10).

With the assessment of *ethically justifiability, 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 11). 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 event MZHG0JG and where the applicant should provide data for in order to conduct a thorough assessment according to the NGTA.

Sustainability

The maize event MZHG0JG confers tolerance to herbicides that contain glyphosate and gluphosinate ammonium.
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 section on Herbicides). Consequently, glyphosate is now increasingly recognized as more toxic to the environment and human health than what it initially was considered to be.

This is particularly a concern as the introduction of glyphosate tolerant GM plants has led to an increase in the use of glyphosate (12, 13).

As maize MZHG0JG is genetically modified to possess genes that provide glyphosate and gluphosinate ammonium tolerance, it is likely to assume that this GM crop is tolerant to higher doses of herbicides and could potentially further increase the use of these.

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Impacts of the co-technology: herbicides (glyphosate and gluphosinate ammonium)
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 (14). 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 MZHG0JG 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 criteria 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 MZHG0JG is cultivated.

When herbicides are 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 agriculture practice that uses herbicides, it is essential to remain attentive to:

- the amount of herbicide used,
- the potential consequences of this use for the area in which the crop is cultivated, and
- develop management strategies to make sure that this does not create (more) resistant weed.

The Applicant has not provided information on whether the cultivation of maize MZHG0JG could affect the emergence of glyphosate resistance in weeds, nor if there are already cases of this in the areas intended for cultivation of the variety. Indeed, this is an important aspect to evaluate the ethical justifiability as well. Furthermore, the cultivation of this maize is,, among others, in the USA, where a significant amount of glyphosate-resistant weeds have already appeared in different States (15). Additionally, no information is currently provided that demonstrates reflection on how the monitoring, assessment or evaluation of the GM crop in countries where the crop will potentially be cultivated is assessed, as the applicant considers information on this ‘not relevant’ because maize MZHG0JG 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.

The ethical issue of gluphosinate-ammonium
A significant ethical issue arises due to the fact that maize MZHG0JG is meant to be tolerant to gluphosinate-ammonium, a herbicide that is banned in Norway 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. This thereby troubles to fulfil the criteria to contribute to *sustainable development*, the criteria that

is meant to be considered in a global context. Information on how this can be ethically justified is therefore highly warranted.

In addition to the 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 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 this sustainability criteria is lacking, and sufficient information in this agricultural context 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.

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 MZHG0JG 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 what the attitude of Norwegian consumers are toward GM maize and GM crops in general. 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. However, the limited amount of empirical data on the attitude towards GM in Norway available (e.g. 16, 17) is outdated and more empirical research on this is warranted to investigate consumers' attitude, demand and acceptance.

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 ethically justified 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. 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, reveal underlying values, assumptions, norms and beliefs (8, 18) in order 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 MZHG0JG 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 (19). 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, changing power dynamics among stakeholders, new dependencies 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. (20) concerning social implications from cultivating GM crops found that from 2004 – 2015 there has only been 15 studies corning social 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. Although this study focused on Bt-maize, 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.

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 justifiability, benefit to society and sustainability assessment. 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 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 and share of the benefits among sectors of the society. It is also important to stress the need for (information on) integrated weed management strategies in those countries (21). Furthermore, maize event MZHG0JG 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. 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 MZHG0JG 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 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.

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

The event MZHG0JG maize contains two inserted transgenes expressing two distinct classes of proteins from a mepsps-02 and a pat-09 expression cassette driven by different promoters, where one of them is a 35S CaMV promoter.

Molecular characterization

According to the Applicant, all inserted genes in maize event MZHG0JG has been thoroughly described before. However, in this application, these genes have been modified on the molecular level to provide enhanced tolerance to the herbicides in question.

Here is a short description of their source and actions:

- The *pat-09* gene (source: *Streptomyces viridohromogenes*) encode the enzyme phosphinothricin N-acetyltransferase that removed activity of gluphosinate containing herbicides by acetylation.

The change made to the *pat-09* gene as compared to the native *pat*-gene provides increased tolerance to gluphosinate ammonium containing herbicides. According to the Applicant, the PAT protein was used as a selectable marker during development of the GM maize. However, as the gene is present in the regenerated plants used for propagation, it must be assumed that gluphosinate ammonium can be used as a herbicide later on in agricultural practices as well.

- The *mepsps-02* gene (source: *Agrobacterium tumefaciens*) is a double mutant form of 5-enolpyruvulshikimate-3-phosphate synthase enzyme that confer resistance to glyphosate containing herbicides by decreasing binding affinitiy to it.

The changes made to the *mepsps-02* gene as compared to the native *mepsps* gene is a double mutation providing lower affinity to the herbicides containing glyphosate.

Neither *pat-09* or *mepsps-02* are not considered as synthetic molecules[1] by Biosafety Clearing-House. However, the dossier refers to the *pat-09* (p.23) gene as " The synthetic *pat* gene was obtained from AgrEvo, Germany.. accession nr…The gene *pat-09* enocode the same amino acid sequence as *pat* from AgroEvo, but several nucleotide changes were made to remove cryptic splice site[2], restriction site and unintended ORFs…"

[1] http://bch.cbd.int/database/record.shtml?documentid=110613
[2] Cryptic splice site: disadvantageous sites or dormant sites less frequently used but potentially very active by mutation 22. Kapustin Y, Chan E, Sarkar R, Wong F, Vorechovsky I, Winston RM, et al. Cryptic splice sites and split genes. Nucleic acids research. 2011;39(14):5837-44.

It is unclear to what extent removal of cryptic splice sites affects expression of *pat* or other genes.

CaMV promoter in maize event MZHG0JG
The 35S cauliflower mosaic virus (CaMV) promoter is commonly used to drive transgene expression in many of the genetically engineered (GE) crop plants that have been commercialized so far (23-25). In maize event MZHG0JG it drives the expression of the *pat-09* expression cassette, providing tolerance to gluphosinate ammonium containing herbicides. The sequence used in maize event MZHG0JG is called 35s-19.

An other CaMV sequence is used as an enchancer in the mepsps-02 expression cassette (35s-05 enhancer).

Safety questions related to the use of the Cauliflower Mosaic Virus 35S promoter (P35S) in GM plants has been discussed in an article from Podevin and Du Jardin (26). In this article, the authors comment 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). This promoter is however not only active in plants, but may confer activity with respect to gene expression in lower and higher vertebrates such as mammals and fish. There are published literature that has found the 35S CaMV promoter to be active in several eukaryotic cell lines after transfection (23, 25), as well being able to drive expression of a transgene in fish as demonstrated 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.

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

EPSPS protein
The EPSPS protein encoded from the modified maize *mepsps-02* gene provides glyphosate tolerance. According to the Applicant, the gene encode transgenic protein mEPSPS.

PAT protein
The PAT protein encoded from the *pat-09* gene provides gluphosinate ammonium tolerance. According to the Applicant, the gene encode the transgenic protein PAT.

For both proteins, key plant tissues (leaves, roots, whole plants, kernels, pollen) were analysed by Enzyme-linked immunosorbent assay (ELISA) at different sampling times and places. Conventional counterparts were also analysed for comparison. Pollen did not have protein concentrations above limit of quantification (Tables 1.2-5 and 1.2-6, p.40-41 in Technical dossier of maize event MZHG0JG).

To perform the safety analysis/assessments of the proteins expressed, microbially derived proteins were used (source: *E. coli*). Plant derived and microbially produced proteins were compared (molecular weight, immunereactivity, peptide mass mapping, N-and C-terminal amino acid sequence analysis, glycosylation status and enzymatic activity) prior to assessments and found equal.

Summary:

- *The pat-09 gene is used as a selectable marker.*
- *The mepsps-02 gene has a double mutation.*
- *The pat-09 gene has undergone some nucleotide changes to remove cryptic splice sites.*
- *Microbial versions of PAT and EPSPS proteins are used for the safety assessments.*

Herbicides

The maize event MZHG0JG contains a PAT-09 gene providing gluphosinate ammonium tolerance and mEPSPS-02 gene providing glyphosate tolerance.

Herbicide use on GM plants

Herbicide tolerant (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. (33) 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 (34, 35). 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 (36) in use that is a relevant issue, but not discussed further here.

Gluphosinate ammonium tolerance

The maize event MZHG0JG contain the *pat-09* gene from *Streptomyces viridochromogenes* that confers tolerance to herbicides containing gluphosinate-ammonium, a class of herbicides that where withdrawn from the market in Norway in 2008 due to both acute and chronic effects on mammals including humans. This herbicide is also about to be phased out in EU this year (2017). 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 (37-40). EFSA has concluded on the risk of gluphosinate ammonium, as especially harmful to mammals (41).

Glyphosate tolerance

The m*epsps-02* gene present in MZHG0JG 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 (21, 42). However, it has received more risk-related attention due to its potential for negative effects on both aquatic and terrestrial ecosystems (43), as well as in studies in animals and cell cultures that have indicated possible negative health effects in rodents, fish and humans (44-46).

Studies indicate that agriculture of GM plants is associated with greater overall usage of pesticides than the conventional agriculture (47).

A restricted number of publications indicate unwanted effects of glyphosate on health (46, 48), aquatic (49) and terrestric (43, 50) organisms and ecosystems.

A study of Roundup effects on the first cell divisions of sea urchins (51) 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 (44) 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 (52). 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”(53).

Summary:

- Maize event MZHG0JG is tolerant to glyphosate and gluphosinate ammonium containing herbicides that are are potentially damaging to health and environment.
- Potential for accumulation of the herbicides should be considered in GM plants used in food and feed.

Allergenicity and toxicity issues

Both EPSPS and PAT proteins have been evaluated by EFSA in several applications previously and considered to be safe.

The maize event MZHG0JG also expressed these two proteins, from two modified genes, *mepsps-02* and *pat-09*.

Toxicological assessment

According to the applicant, the proteins mEPSPS and PAT are identical to the ones expressed in maize events GA21 and Bt11. Both of these have been assessed by EFSA previously.
The mEPSPS in GA21 has to induced point mutations.

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). In addition, previous data on molecular and biochemical characterization, stability under processing and toxicity studies, as well as no indications of protein interactions indicate that these proteins are safe in light of these criteria.

In addition, a 90-day feeding study was performed according to EU regulation 503/2013 (54) on rodents with whole maize grain, showing no detected effects on body weight, food consumption or clinical conditions.

Allergenicity

Due to expected biochemical characteristics of the two proteins, and their equivalence to corresponding proteins produced in microbial hosts showing that molecular weight, glycosylation pattern, amino acid sequences and enzyme activity are comparable, the applicant has no concern regarding allergenicity of the two proteins expressed in the maize event MZHG0JG. In addition, the proteins are rapidly degraded in simulated gastric fluids and inactivated by heating, criteria that are used to assess allergenicity of proteins. The bioinformatics studies that are performed also show that there is no similarity to known toxins or allergens present.

Potential interactions between newly expressed proteins

Mode of action, molecular analysis of the corresponding genes and activity of proteins of maize event MZHG0JG made the basis for the conclusion made by the applicant that there are no indications of potential interactions of safety concern between the traits expressed.

Hazard identification

According to the applicant, it is unlikely that the proteins expressed from the gene modified maize event will be hazardous.

Main summary

Maize event MZHG0JG is tolerant to herbicides containing glyphosate and gluphosinate ammonium 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(3).

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