Vår ref:2017/H_RX_007
Deres ref: 2017/4375

Høringsuttalelse av fornyelsessøknad om markedsføring av genmodifisert mais NK603 x MON810

EFSA/GMO/RX/007

Under EU forordning 1829/2003

Sendt til

Miljødirektoratet

av

GenØk-Senter for biosikkerhet
Juni 2017

Vår ref:2017/H_RX_007
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Miljødirektoratet
Postboks 5672 Sluppen
7485 Trondheim
Dato: 12.06.2017

Vedlagt er innspill fra GenØk – Senter for biosikkerhet på offentlig høring av fornyelsessøknad **EFSA/GMO/RX/007**, genmodifisert, stablet mais NK603 x MON810, fra Monsanto Europe S.A/N.V., under EU forordning 1829/2003. Fornyelsessøknaden gjelder fornyet godkjenning for bruksområdene mat, fòr, import og prosessering.

Vennligst ta kontakt hvis det er noen spørsmål.

Med vennlig hilsen,

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Innhold/Content

Høringsuttalelse – genmodifisert, stablet mais NK603 x MON810 (EFSA/GMO/RX/007) under EU forordning 1829/2003.

Søknad EFSA/GMO/RX/007 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* og mot enkelte insekter i Lepidoptera ordenen via det innsatte genet *Cry1Ab*.

Den stablete mais linjen NK603 x MON810 er ikke godkjent for noen av bruksområdene i Norge.

Oppsummering

GenØk–Senter for biosikkerhet, viser til høring av fornyelsessøknad EFSA/GMO/RX/007 om NK603 x MON810 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 NK603 x MON810 er ikke godkjent i Norge for noen av de omsøkte bruksområdene.
- Genmodifisert mais NK603 x MON810 er tolerant mot sprøytemidler som inneholder glyfosat som har ulike grader av helse-og-miljø fare ved bruk, samt resistens mot insekter i Lepidoptera ordenen via det innsatte genet *Cry1Ab*.
- Søknaden om mais linje NK603 x MON810 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 reapplication EFSA/GMO/RX/007 on NK603 x MON810 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 NK603 x MON810 is not approved for any application in Norway.
- Maize event NK603 x MON810 is tolerant to herbicides containing glyphosate that has distinct health and environmental dangers upon use, and resistance towards Lepidoptera insects through the inserted gene *Cry1Ab*.
- The reapplication on maize event NK603 x MON810 lacks data and information relevant for assessment of criteria on ethically justifiability, social utility and sustainability.

Application on EFSA/GMO/RX/007

The stacked event NK603 x MON810 maize contains a gene providing herbicide tolerance (*cp4 epsps*) as well as a Cry1Ab gene providing resistance against insects in the Lepidoptera order

Previous evaluations

Below are some evaluations of parental lines or the stack NK603 x MON810:

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 Environmental Agency made a full evaluation and recommendation in 2014 of parental event MON810 (3), with the following comments/conclusion:

- Based on the present knowledge, there is no risk for health or environment, or information related to social utility, sustainability or ethical justifiability that should provide basis for limitation or ban of import of MON810 for import, processing or feed.
- The insecurity related to effect on non-target organisms is emphasized for the situation of cultivation due to exposure to the environment. The potential social costs and that the introduced trait can not be utilized, in addition to ethical considerations in parts of the population, points to a prohibition of cultivation of MON810 in Norway. Thus, it is recommended to prohibit cultivation of MON810 in Norway.

Norwegian Scientific Committee for Food Safety (VKM) made a food/feed and environmental risk assessment of NK603 x MON810 in 2014 (4) with the following conclusion:

"Based on current knowledge, the VKM GMO Panel concludes that maize NK603 x MON810 is nutritionally equivalent to conventional maize varieties. It is unlikely that the CP4 EPSPS and Cry1Ab proteins will introduce a toxic or allergenic potential in food or feed based on maize NK603 x MON810 compared to conventional maize. The VKM GMO Panel likewise concludes that maize NK603 x MON810, based on current knowledge, is comparable to conventional maize varieties concerning environmental risk in Norway with the intended usage.»

GenØk has not evaluated this particular stack of maize event NK603 x MON810 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)*
- *2012: MON810 pollen (H107), EFSA/GMO/NL/2002/107*
- *2015: MON87427 x MON89034 x **NK603** (H117), EFSA/GMO/BE/2013/117)*
- *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)*

Social utility and sustainability issues on the stacked maize event NK603 x MON810, EFSA/GMO/RX/007

In Norway, an impact assessment follows the Norwegian Gene Technology Act (NGTA) (5) in addition to the EU regulatory framework for GMO assessment. In accordance with the aim of the NGTA, the development, introduction and/or use of a GMO needs to be *ethically justifiable*, demonstrate a *benefit to society* and contribute to *sustainable development*. This is further elaborated in section 10 of the Act (approval), where it is stated that: "*significant emphasis shall also be placed on whether the deliberate release represent a benefit to the community and a contribution to sustainable development*" (See section 17 and annex 4 for more detail on the regulation on impact assessment). Recent developments within European legislation on GMOs allow Member States to restrict the cultivation of GMOs on their own territory based on socio-economic impacts, environmental or agricultural policy objectives, or with the aim to avoid the unintended presence of GMOs in other products (Directive 2015/412) (6). 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 (7-12).

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 (13). 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 NK603 X MON810 and where the Applicant should provide data for in order to conduct a thorough assessment according to the NGTA. Table 1 offers specific questions connected to the sections below.

Sustainability

Maize NK603 X MON810 contains a modified *epsps* gene that confers increased tolerance to herbicides that contain glyphosate. Recent studies have shown negative effects from glyphosate, both on species present in terrestrial and aquatic ecosystems and on animals and cell cultures (for further elaboration and references on this issue see pages 15-16 and onwards) as well as in villages in areas where glyphosate is systematically used as part of the GM crops tolerance to glyphosate (14). Consequently, glyphosate is now increasingly recognized as more toxic to the environment and human health than what it was initially considered to be. This is particularly a concern as the introduction of glyphosate tolerant GM crops has led to an increase in the use of glyphosate (15-17). As maize NK603 X MON810 is genetically modified to possess a gene that provides glyphosate tolerance, this crop could potentially further increase the use of glyphosate as a higher amount of glyphosate will not affect the cultivation of NK603 X MON810. An increase in the resistance and use of glyphosate is in contrast to a contribution to sustainable development and therefore an important aspect the Applicant should provide information on, for example by mentioning the current use of glyphosate in the sites of cultivation and what approaches are used to minimize the use of glyphosate.

Herbicide-resistant genes

When an herbicide - such as glyphosate – is used in agriculture, it is important to minimize the potential of weeds becoming resistant. Indeed, when crops are engineered to be herbicide tolerant in order to maintain an agricultural practice that uses herbicide, it is essential to remain attentive to the amount of herbicide used, the potential increase of use and the consequences of this for the area in which the crop is cultivated. The development of management strategies to make sure that this does not create (more) resistant weed is warranted to be able to respond to a potential increase in weed-resistance. Moreover, studies have shown increased levels of herbicide residues in herbicide tolerant GM crops (e.g. 18), which could have health impacts on humans and animals consuming food/feed based on ingredients from this type of GM plants. The Applicant has not provided information on whether the cultivation of maize NK603 X MON810 could affect the emergence of glyphosate resistance in weeds, nor if there are cases of this in the areas of cultivation, which are also important aspect to evaluate the ethical justifiability. Furthermore, this maize is cultivated in Argentina, Brazil, Canada, Colombia, the Philippines, Japan, Uruguay, South Africa. In all these countries, glyphosate resistant weeds has been located and in most of them the amount of glyphosate resistant weeds has increased significantly[1].

Based on the available data for us to evaluate this applicant, there is no information provided on how the location of field trials provide a variety of environmental conditions. Additionally, no information is currently provided by the Applicant that demonstrates reflection on how the monitoring, assessment or evaluation of the GM crop in countries where the crop will be cultivated in the future is assessed. However, it remains an important aspect for a sustainability evaluation and thus necessary if the application is to be evaluated according to this criteria in the NGTA.

Impacts of the Bt-toxin on target and non-target organisms in the producer country

The maize NK603 X MON810 confers resistance to certain lepidopteran pests. A growing number of studies and reviews indicate potential harm to a range of non-target organisms (19-21). Both impacts on non-target organisms and resistance development among target pests of Bt maize have been documented (22, 23). Evaluation of resistance development within the target pest population and strategies suggested to halt this development are warranted, as impacts on non-target organisms is crucial in a sustainability assessment.

Impacts of the co-technology: glyphosate

The evaluation of the co-technology, that is, secondary products that are intended to be used in conjunction with the GMO, is also considered important in the risk assessment of a GMO (24). 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

To perform an accurate assessment of the sustainability criteria as laid down in the NGTA, more information is needed to evaluate the impact that this GMO has on the producing

[1] http://weedscience.org/Summary/Country.aspx Status of Herbicide Resistance, accessed on 26 May 2017.

countries. The sustainability 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 maize NK603 X MON810 is cultivated.

Even if a large set of information is provided, that does not necessarily mean that the same conclusions will be drawn. Within science, there can also be ambiguity about how 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. This is particularly relevant to consider in relation to the field trials. The difference between the field trials and the sites of cultivation can affect the adequacy of the evaluation of NK603 X MON810. It is therefore important that the Applicant provides information on how the difference between the site of field trials and of cultivation sites may affect the evaluation of NK603 X MON810.

Moreover, to perform an adequate sustainability assessment, it remains important to have an evaluation of the occurrence of volunteer plants in the producing countries and suggested control strategies. Information about the occurrence of volunteers and which herbicides may be used for killing volunteers is required to evaluate potential health and environmental impacts of these.

Benefit to society

The criteria of 'benefit to society' in the NGTA should be interpreted on a national level. That means that the import of maize NK603 X MON810 needs to demonstrate how it will benefit Norway. However, no information on this part is provided by the Applicant. It is important to evaluate how GM crops in general, GM maize in particular, and the use of GM maize in food and feed are valued by Norwegian consumers. This information will contribute to anticipate impacts at an early stage, as well as that it may demonstrate a need to assess the alternative options for import of maize. Although the empirical data available on the attitude of Norwegian citizens towards GM is limited (e.g. 25, 26) and more empirical research on this is warranted to investigate consumers' attitude, demand and acceptance, a report on the perceptions among Norwegian citizens on GMOs describes how about half of the respondents expressed that they were negative for sale of GMO-products in Norwegian grocery stores in the future, and only 15 percent were positive (27). Furthermore, it should be noted that 29 % of the global maize production is GM. It is therefore not a problem for Norway to import GM free maize and therefore no need to replace current imports. The GM maize in question does also not contain any beneficial characteristics for consumers that would prioritize this maize over non-GM maize.

Assessing alternatives

When a new (bio-)technology is developed, it is important to reflect on what problem it aims to solve and to investigate whether alternative options may achieve the same outcomes in a safer and / or a more ethically justifiable way. After all, when a crop is genetically modified to tolerate a particular herbicide, it means that the crop is developed for a particular cultivation practice in which these herbicides are to be used. What is meant with alternatives, and what would benefit from being assessed could include alternative varieties (e.g. conventional or organic maize) for import, alternative sources to satisfy the demand, alternative ways of agriculture, or even explore alternative life visions. In fact, this corresponds with the increased trend within research and policy of science and innovation to anticipate impacts, assess alternatives, reveal underlying values, assumptions, norms and beliefs (10, 28) as a way to reflect on what kind of society we want, and assess how certain (biotechnological) developments may or may not contribute to shaping a desired future. Thus, in order to evaluate whether maize NK603 X MON810 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 (29). Nevertheless, another substantial part of the debate is around the socio-economic impacts of GM productions and many questions for evaluating the above mentioned criteria in the NGTA are based on an assessment of the socio-economic impacts. These impacts can vary and range from seed choice for farmers, co-existence of different agricultural practices, impacts among poor and/or small-scale farmers in developing countries, share of the benefits among sectors of the society, changing power dynamics among stakeholders, autonomy of farmers, intellectual property right on seeds, benefit sharing, the decreasing space for regional and local policy, and more organisational work and higher costs for non-GM farmers (e.g. for cleaning of sowing machines or transport equipment to avoid contamination). Although the examples of socio-economic impacts clearly indicate the complexity and extensive list of concerns beyond safety aspects, little empirical investigation on these kind of aspects has been done. For example a study performed by Fischer et al. (30) concerning social implications from cultivating GM crops found that from 2004 – 2015 there has only been 15 studies corning socio-economic implications of cultivating Bt-maize. The study demonstrates that published literature is dominated by studies of economic impact and conclude that very few studies take a comprehensive view of social impacts associated with GM crops in agriculture. The amount of research performed in this case and the minimal focus on social impacts strongly indicate a high need for further investigation on how the cultivation of GM crops affects different parties involved. It is therefore striking that no information on any of the above mentioned points is discussed by the Applicant.

Co-existence

The cultivation of GM plants in general is causing problems with regard to co-existence, an important socio-economic impact. For instance, Binimelis (31) has investigated consequences on co-existence of Bt maize in Spain among small-scale farmer and has found that co-existence is very difficult. Farmers in some areas even have given up growing non-GM maize. Even though this application is not about cultivation of maize NK603 X MON810 in Europe/Norway, it is important to obtain information about the strategies adopted to ensure co-existence with conventional and organic maize production. Information about consequences for co-existence in the countries where maize NK603 X MON810 is cultivated should be provided. This information should demonstrate how the Applicant aims to minimize the likelihood for gene flow to wild relatives, or contamination during transport or processing.

Legal information and clarity could provide evaluators a more comprehensive understanding of governance strategies and possibilities to ensure co-existence, although it has been noted that this may not suffice as co-existence has become an arena of opposed values and future vision of agriculture, including the role of GM crops within these visions (32). Indeed, although a framework for maintaining co-existence in Europe was established in 2003 (33) this effectively meant technical measurements and recommendations (e.g. cleaning of sowing machines and transport vehicles) and remains challenging in practice (34, 35). Moreover, this framework arguably reduced the significance of the issue of co-existence to questions concerning economic aspects for individuals (e.g. farmers), rather than recognizing that agricultural practices are interwoven in dynamic social, economic and political systems (36, 37). For the criteria in the NGTA, information on co-existence is required to enable a coherent analysis.

Summary

In order to meet the requirements for the NGTA, the regulator is encouraged to ask the Applicant to submit information relevant for the assessment of the criteria of ethically justifiable, benefit to society and sustainability assessment. An important part that is lacking is information about the consequences of the cultivation of maize NK603 X MON810 for the producing countries. The information provided by the Applicant must be relevant for the specific agricultural context of this country and should also stress the need for information on integrated weed management strategies in those countries (38). Moreover, the information should contain issues such as changes in herbicide use, development of herbicide resistant weed, potential for gene flow and possible socio-economic impacts such as poor and/or small-scale farmers in producing countries, share of the benefits among sectors of the society and as explained, effects of co-existence of different agricultural systems. Additionally, the Applicant does not attempt to demonstrate a benefit to society, a reference of the consumers' attitude on GM maize, or the demand within Norway for maize NK603 X MON810 and does therefore not provide sufficient information as required by the NGTA.

Table 1: Questions to the Applicant

Sustainability	*How does the cultivation of NK603 X MON810 affect the use of glyphosate?*
	How is the current use of glyphosate in the sites of cultivation and what approaches are used to minimize the use of glyphosate?
Herbicide-resistant weed	*What kind of management strategies are taken to prevent the increase of herbicide-resistant weed?*
	Who will be affected if the amount of resistant weeds increases?
	How is the burden of increase of resistant weeds distributed and what strategies are in place to compensate this?

Benefit to society	*Is NK603 X MON810 available for further breeding and research? If so, under which circumstances?*
	Is there a demand for NK603 X MON810 in Norway?
	Does NK603 X MON810 contribute to business development and value creation in Norway, including new job opportunities?
Assessing alternatives	*Will NK603 X MON810 benefit Norwegian consumers more than the other alternatives available from conventional or organic agricultural practices? If so, how?*
Ethically justifiable	*What are the different public values and visions on the development, introduction or use of NK603 X MON810 within Norway and how does the development of NK603 X MON810 relates to these?*
	Does the development, introduction or use of NK603 X MON810 contradict ideas about solidarity and equality between people, such as the particular consideration of vulnerable groups in the population?
Socio-economic impacts	*Does NK603 X MON810 affect the seed choice of farmers?*
	Which parties will be affected by the development, introduction or use of NK603 X MON810 and how does this change their autonomy, practice and position compared to other stakeholders?
	Does NK603 X MON810 change the power dynamic among stakeholders? If so, how?
	Can the development, introduction or use of NK603 X MON810 create significant ruptures or ecological relationships?
Co-existence	*Does the cultivation of NK603 X MON810 affect other types of agricultural practices in the nearby areas? If so, how?*
	Is there a system in place for keeping GMO and non-GMO crops separate in the production and transport line? If so, who pays for this system?

Environmental risk issues in a Norwegian context

The level of maize production is 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 NK603 x MON810 contains two distinct, inserted transgenes providing herbicide tolerance and insect (Lepidoptera) resistance. This stack with the specific combination of transgenes should be regarded as a new event, even if no "new" modifications have been introduced, as the combination itself in the stack is unique for that event. The combinations of gene-cassettes are new and unique and only minor conclusions could be drawn from the assessment of the parental lines, since unexpected effects (e.g. synergistic effects of the newly introduced proteins) cannot automatically be excluded. Stacked events should in general be considered as potentially more complex than their single, parental lines, 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 (39, 40).

Safety of Cry genes

As already mentioned, NK603 x MON810 maize expresses a Bt protein called Cry1Ab. This protein belongs to a class of proteins called Bt-toxins. These toxins are claimed and believed to be safe, but the potential of non-target effects of Bt toxins concerning mode of action have been addressed (41-43). A review by Hilbeck and Schmidt (43) on all Bt-plants at that time, found that 50% of the studies documented negative effects on tested invertebrates.

In relation to non-target and environmental effects, two meta-analyses on published studies on non-target effects of Bt proteins in insects (44) 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. (20) 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 (45)*, and caddisflies (21). 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 (46) 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.

In relation to health impacts, a publication by Dona and Arvanitoyannis (47) have reviewed the potential health implications of GM foods for humans and animals, including incidences and effects of increased immunogenicity, amounts of anti-nutrients, possible pleiotropic and epigenetic effects, including possible reproductive and developmental toxicity. They concluded that while there is strong evidence for health concerns on many fronts, exposure duration many have not been long enough to uncover important effects. These studies should however also include subjects with immunodeficiency or subjects exposed to other stress agents.

Indications of harm to non-target organisms in the environment, and possible impacts to human and animal health prompted the Austrian Authorities to invoke a safeguard clause to ban the use of Cry1Ab-containing maize event MON810 (48). We refer to this report as a detailed analysis of potential adverse effects from a Cry1Ab-producing GMO.

Adjuvancy effects

The potential adjuvancy of Cry proteins has previously been addressed by the GMO Panel of the Norwegian Scientific Committee for Food Safety (49). Scientific studies have shown that the Cry1Ac protein is highly immunogenic and has systemic and mucosal adjuvant effects (50). 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" (51).

The GMO Panel of the Norwegian Scientific Committee for Food Safety (49) 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 NK603 x MON810.

Summary:

- Cry proteins might have potential for non-target effects.
- As some Cry proteins have adjuvant effects, it can not be excluded that other Cry proteins have that also. This should be investigated.

Molecular characterization

NK603 x MON810 is a stacked event produced from the single-event NK603 and MON 810 by traditional maize breeding.
The risk assessment is based on assessment of the single parental events NK603 and MON810. Original application was launched in 2005.

According to EFSA: *"A stacked event has to be regarded as a new event, even if no new modifications have been introduced. The gene-cassette combination is new and only minor conclusions could be drawn from the assessment of the parental lines, since unexpected effects (e.g. synergistic effects of the newly introduced proteins) cannot be excluded. "*

Most of the information submitted in this application is derived from previous findings from the single events and it is referred to the approved application for NK603 (2005) and MON 810 (1995). Assumption-based reasoning with single-events should however not replace scientific testing of hypothesis regarding interactions. This is also part of the EFSA guidelines (52) stating that " For GM plants containing stacked events, the main objective of the analysis is to assess the potential of any interactions between the events".

The presentation of rawdata are from the previous application and they are presented in variable degree throughout the reapplication. Some methods are described very well, but the results from these are not highlighted to the same extent.
Methods like PCR, gel electrophoresis, sequencing etc have little or no description, and there are no figures or presentation of the data from these in the literature that we have available.

Many of the analyses and results of these are more than 10 years old. There seem to be no documented analysis after 2005. In addition, no new methods looking at for instance synergic effects, allergies, genetic instability etc. are present in the reapplication.
As this is a reapplication, the use of newer analytical methods to look at these issues is suggested.

Southern blots

Southern blot analysis were performed to confirm the information about the number and structure upon the transgenic insert (p.22 in dossier). For NK603, a probe of 1560 bp was used to detect the ctp2-cpsps coding sequence, and for MON 810, a 900 bp probe for cry1Ab coding sequence. Number of inserts were confirmed by this analysis. The size of the probes used in the Southern blots could be too large in order to detect point mutations, small deletions and rearrangements in the DNA sequence.

In addition to the southern blot method, a supplementary and more sensitive method should have been used, for example sequencing of the insert and flanking regions (53) or (54).
The Applicant is also suggested to ensure that the probe restriction enzyme combinations used are sufficient to prove intactness and stability of the insert and including the flanking regions (55).

CaMV promoter

The parental event NK603 contains a 35S promoter. We refer to the published literature surrounding this issue (56) 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 (57, 58).

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

Toxicity

No new data on toxicity is present in the reapplication of maize event NK603 x MON810. It is not clear if the “updated bioinformatics analysis” performed (according to point 2.3, p.3 in the reapplication) is for allergenicity or toxicity analysis.

Allergenicity

No new data on alleregenicity is presented. It is not clear if the “updated bioinformatics analysis” performed (according to point 2.3, p.3 in the reapplication) is for allergenicity or toxicity analysis.

Potential interactions between newly expressed proteins

The inserted genes *cp4 epsps* and *Cry1Ab* and their gene products have a history of safe use according to the Applicant. This is based on the many reviews and assessments that these proteins have undergone through the years since their first approval.
Based on the present criteria, no interaction among the proteins expressed from the transgenes and negative synergistic effects are expected by the Applicant. This is also based on their distinct differences in mode of action.

Hazard identification

According to the Applicant, there is no evidence for maize stack NK603 x MON810 to be hazardous to humans or animals.

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.
- No new bioinformatic approaches is performed on the sequence data available for analysis of potential allergens or toxins, or even ORFs.

Herbicides

Herbicide use on GM plants

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

Total use of herbicides

HT GM plants are documented to be a strong driver of increased use of glyphosate-based herbicides (the dominant herbicide tolerance trait until now). From 1995 to 2014 the global agricultural use of glyphosate rose 14.6 fold, from 51 million kg to 747 million kg. Moreover, by 2016, about 56 % of the global use of glyphosate was related to the use of HT GM crops (17).

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 (59).

Sustainability

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

Environmental effects of herbicides

The use of herbicides like glyphosate also has the potential to affect ecosystem, animal and human health. The massive use of glyphosate, totaling 852 million kg globally by 2014 (17), which directly or indirectly will expose non-target biodiversity in terrestrial, soil and aquatic communities (60), represent a major source of environmental pollution.

Accumulating herbicide residues and health effects

Glyphosate accumulates in HT soybeans, more when the plant is sprayed later in the season (38). This may bring significant amounts of glyphosate into the food and feed chain. Bøhn and colleagues measured on average 9.0 mg of glyphosate in HT GM soybeans grown in Iowa (61).

The increased awareness of the potential toxicity of glyphosate, coupled with the increased volume used, should give more attention to the accumulation of herbicide residues in food and feed.

However, the maximum residue level (MRL) for glyphosate has been raised 200-fold from 0.1 to 20 mg/kg in Europe, and to 40 mg/kg in the US (62). This set of events has been termed "The Glyphosate Paradox" (63). The WHO/IARC categorization of glyphosate as *probably carcinogenic to humans (64)*, although disputed by EFSA (65), is underlining the significance of the controversy around the glyphosate-based herbicides.

Modeling studies have shown that long-term implications of large scale bioenergy crops can surpass toxicity thresholds for fish (bluegill) and humans in significant parts of relevant watersheds, particularly because of glyphosate, and thus negatively impact aquatic life and drinking water (66).

Glyphosate tolerance

The *cp4 epsps* gene present in NK603xMON810 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 (38, 67). However, glyphosate has recently received more risk-related attention due to its potential for negative effects on both aquatic and terrestrial ecosystems (68), as well as from studies in animals and cell cultures that have indicated possible negative health effects in rodents, fish and humans (69-71).

It has also been shown that agriculture of GM plants is associated with greater overall usage of pesticides than the conventional agriculture (72).

A number of publications indicate unwanted effects of glyphosate on health (71, 73), aquatic (74) and terrestric (68, 75) organisms and ecosystems. Also, a study of Roundup (containing glyphosate as the active ingredient) effects on the first cell divisions of sea urchins (76) is of particular interest to human health. The experiments demonstrated dysfunctions of cell division at the level of CDK1/Cyclin B activation (these proteins are involved in mitosis). Considering the universality among species of the CDK1/Cyclin B cell regulator, these results question the safety of glyphosate and Roundup on human health. In another study (69) it was demonstrated a negative effect of glyphosate, as well as a number of other organophosphate pesticides, on nerve-cell differentiation. Surprisingly, in human placental cells, Roundup was always more toxic than its active ingredient. The effects of glyphosate and Roundup were tested at lower non-toxic concentrations on aromatase, the enzyme responsible for estrogen synthesis (77). The glyphosate-based herbicide disrupts aromatase activity and mRNA levels and interacts with the active site of the purified enzyme, but the effects of glyphosate are facilitated by the Roundup formulation. The authors conclude that the endocrine and toxic effects of Roundup, not just glyphosate, can be observed in mammals. They suggest that the presence of Roundup adjuvants enhances glyphosate bioavailability and/or bioaccumulation.

Summary:

- Maize event NK603xMON810 is tolerant to glyphosate,a herbicide that is pontentially damaging to health and environment in different ways.
- Potential for accumulation of the herbicides should be considered in GM plants used in food and feed.

Main summary

Maize event NK603xMON810 is tolerant to herbicides containing glyphosate that is debated as to whether it has health and environmental dangers upon use. Thus the issue on accumulation should be considered for GM plants to be used in food and feed.

The applicant should provide data relevant for assessment of social utility and sustainable development according to the NGTA(5).

References.

1. European Food Safety A. Opinion of the Scientific Panel on genetically modified organisms [GMO] on a request from the Commission related to the safety of foods and food ingredients derived from herbicide-tolerant genetically modified maize NK603, for which a request for placing on the market was submitted under Article 4 of the Novel Food Regulation (EC) No 258/97 by Monsanto. EFSA Journal. 2004;2(3):9-n/a.
2. Safety NSCfF. Food and environmental risk assessment of herbicide-tolerant genetically modified maize NK603 for food uses, import and processing under Directive 2001/18 /EC (Notification C/ES/00/01). Norwegian Scientific Comittee for Food Safety, Organisms PoGM; 2013 2013/10/18. Report No.: 13/320.
3. Miljødirektoratet. Genmodifisert mais MON810 Helhetlig vurdering og anbefaling til vedtak. Miljødirektoratet; 2014. Report No.: M-272.
4. (VKM) NSCfFS. Food/feed and environmental risk assessment of herbicide-tolerant and insect-resistant genetically modified maize NK603 x MON810 for import, processing, food and feed uses under Regulation (EC) No 1829/2003 (EFSA/GMO/UK/2004/01). Risk assessment. VKM, organisms Pogm; 2014 2014/10/03. Report No.: 14/304-final.
5. Gene Technology Act, NGTA(1993).
6. Directive (EU) 2015/412 of the European Parliament and of the Council of 11 March 2015 amending Directive 2001/18/EC as regards the possibility for the Member States to restrict or prohibit the cultivation of genetically modified organisms (GMOs) in their territory Text with EEA relevance, (2015).
7. European Commission. Responsible Research and Innovation. Europe’s Ability to Respond to Societal Challenges. KI-31-12-921-EN-C: Available from: ec.europe.eu; 2012.
8. Hoven Jvd. Options for strengthening Responsible Research and Innovation. Report of the Expert Group in the State of the Art in Europe on Responsible Research and Innovation. KI-NA-25-766-EN-C: Available from: ec.europe.eu; 2013.
9. Strand R, Spaapen J, Bauer M, Hogan E, Revuelta G, Stagl S, et al. Indicators for promoting and monitoring Responsible Research and Innovation. Report from the Expert Group on Policy Indicators for Responsible Research and Innovation. KI-NA-26-866-EN-N: Available from: ec.europe.eu; 2015.
10. Hartley S, Gillund F, van Hove L, Wickson F. Essential Features of Responsible Governance of Agricultural Biotechnology. PLoS Biol. 2016;14(5):e1002453.
11. Pavone V, Goven J, Guarino R. From risk assessment to in-context trajectory evaluation-GMOs and their social implications. Environmental Sciences Europe. 2011;23(1):1.
12. Binimelis R, Myhr AI. Inclusion and Implementation of Socio-Economic Considerations in GMO Regulations: Needs and Recommendations. Sustainability. 2016;8(1):62.
13. Bioteknologirådet. Herbicide-resistant genetically modified plants and sustainability. Oslo, Norway: Bioteknologirådet; 2014.
14. Vazquez MA, Maturano E, Etchegoyen A, Difilippo FS, Maclean B. Association between Cancer and Environmental Exposure to Glyphosate. International Journal of Clinical Medicine. 2017;8(02):73.

15. Dill GM, Sammons RD, Feng PCC, Kohn F, Kretzmer K, Mehrsheikh A, et al. Glyphosate: Discovery, Development, Applications, and Properties. Glyphosate Resistance in Crops and Weeds: John Wiley & Sons, Inc.; 2010. p. 1-33.
16. Benbrook CM. Impacts of genetically engineered crops on pesticide use in the US - the first sixteen years. Environmental Sciences Europe. 2012;24(1):24.
17. Benbrook CM. Trends in glyphosate herbicide use in the United States and globally. Environmental Sciences Europe. 2016;28(1):1-15.
18. Bøhn T, Cuhra M, Traavik T, Sanden M, Fagan J, Primicerio R. Compositional differences in soybeans on the market: glyphosate accumulates in Roundup Ready GM soybeans. Food chemistry. 2014;153:207-15.
19. Holderbaum DF, Cuhra M, Wickson F, Orth AI, Nodari RO, Bohn T. Chronic Responses of Daphnia magna Under Dietary Exposure to Leaves of a Transgenic (Event MON810) Bt-Maize Hybrid and its Conventional Near-Isoline. Journal of toxicology and environmental health Part A. 2015;78(15):993-1007.
20. Marvier M, McCreedy C, Regetz J, Kareiva P. A meta-analysis of effects of Bt cotton and maize on nontarget invertebrates. Science (New York, NY). 2007;316(5830):1475-7.
21. Rosi-Marshall EJ, Tank JL, Royer TV, Whiles MR, Evans-White M, Chambers C, et al. Toxins in transgenic crop byproducts may affect headwater stream ecosystems. Proceedings of the National Academy of Sciences of the United States of America. 2007;104(41):16204-8.
22. Van den Berg J. Evolution in Action: Field-Evolved Resistance of African Stem Borer to BT Maize. Outlooks on Pest Management. 2013;24(5):236-9.
23. Van den Berg J, Hilbeck A, Bøhn T. Pest resistance to Cry1Ab Bt maize: Field resistance, contributing factors and lessons from South Africa. Crop Protection. 2013;54:154-60.
24. Dolezel M MM, Eckerstorfer M, Hilbeck A, Heissenberger A, Gaugitsch H. Standardising the Environmental Risk Assessment of Genetically Modified Plants in the EU. Final report. Bonn, Germany: Umweltsbundesamt GmbH, regulation B-G; 2009 April 2009.
25. Chern WS, Rickertsen K, Tsuboi N, Fu T-T. Consumer acceptance and willingness to pay for genetically modified vegetable oil and salmon: A multiple-country assessment. 2003.
26. Grimsrud KM, McCluskey JJ, Loureiro ML, Wahl TI. Consumer attitudes to genetically modified food in Norway. Journal of Agricultural Economics. 2004;55(1):75-90.
27. Bugge AB, Rosenberg TG. Fremtidens matproduksjon. Forbrukernes syn på genmodifisert mat: GMO-mat eller ikke? Oslo: Forbruksforskningsinstituttet SIFO; 2017.
28. Stilgoe J, Owen R, Macnaghten P. Developing a framework for responsible innovation. Research Policy. 2013;42(9):1568-80.
29. Hilbeck A, Binimelis R, Defarge N, Steinbrecher R, Székács A, Wickson F, et al. No scientific consensus on GMO safety. Environmental Sciences Europe. 2015;27(1):4.
30. Fischer K, Ekener-Petersen E, Rydhmer L, Björnberg K. Social Impacts of GM Crops in Agriculture: A Systematic Literature Review. Sustainability. 2015;7(7):8598.
31. Binimelis R. Coexistence of Plants and Coexistence of Farmers: Is an Individual Choice Possible? Journal of Agricultural and Environmental Ethics. 2008;21(5):437-57.
32. Devos Y, Demont M, Dillen K, Reheul D, Kaiser M, Sanvido O. Coexistence of genetically modified (GM) and non-GM crops in the European Union. A review. Agronomy for Sustainable Development. 2009;29(1):11-30.

33. European Commission. Commission addresses GM crop co-existence. Brussels: Press Release, IP/03/314; 2003.
34. Purnhagen K, Wesseler J. The Principle (s) of Co-existence in the Market for GMOs in Europe: Social, Economic and Legal Avenues. The Coexistence of Genetically Modified, Organic and Conventional Foods: Springer; 2016. p. 71-85.
35. Herrero A, Binimelis R, Wickson F. Just existing is resisting: The everyday struggle against the expansion of GM crops in Spain. Sociologia Ruralis. 2017.
36. Binimelis R, Wickson F, Herrero A. Agricultural Coexistence. 2016.
37. Herrero A, Wickson F, Binimelis R. Seeing gmos from a systems perspective: The need for comparative cartographies of agri/cultures for sustainability assessment. Sustainability. 2015;7(8):11321-44.
38. Duke SO, Powles SB. Glyphosate: a once-in-a-century herbicide. Pest Management Science. 2008;64(4):319-25.
39. De Schrijver A, Devos Y, Van den Bulcke M, Cadot P, De Loose M, Reheul D, et al. Risk assessment of GM stacked events obtained from crosses between GM events. Trends in Food Science & Technology. 2007;18(2):101-9.
40. Halpin C. Gene stacking in transgenic plants--the challenge for 21st century plant biotechnology. Plant biotechnology journal. 2005;3(2):141-55.
41. Crickmore N. Using worms to better understand how Bacillus thuringiensis kills insects. Trends in microbiology. 2005;13(8):347-50.
42. Gilliland A, Chambers CE, Bone EJ, Ellar DJ. Role of Bacillus thuringiensis Cry1 delta endotoxin binding in determining potency during lepidopteran larval development. Applied and environmental microbiology. 2002;68(4):1509-15.
43. Hilbeck A, J.E.U S. Another view on Bt-proteins-how specific are they and what else might they do? Biopesticides International. 2006;2(1):1-50.
44. Lövei GL, Arpaia S. The impact of transgenic plants on natural enemies: a critical review of laboratory studies. Entomologia Experimentalis et Applicata. 2005;114(1):1-14.
45. Bohn T, Primicerio R, Hessen DO, Traavik T. Reduced fitness of Daphnia magna fed a Bt-transgenic maize variety. Archives of environmental contamination and toxicology. 2008;55(4):584-92.
46. Douville M, Gagne F, Blaise C, Andre C. Occurrence and persistence of Bacillus thuringiensis (Bt) and transgenic Bt corn cry1Ab gene from an aquatic environment. Ecotoxicology and environmental safety. 2007;66(2):195-203.
47. Dona A, Arvanitoyannis IS. Health risks of genetically modified foods. Critical reviews in food science and nutrition. 2009;49(2):164-75.
48. Eckerstorfer M, Heissenberger A, Gaugitsch H. Supplementary Risk Assessment for GM Maize MON 810 with regard to the conclusions of the WTOPanel in the case „EC Biotech“ on Austrian safeguard measures for GM maize. Report. Wien: Bundesministerium für Gesundheit, Familie und Jugend; 2007 Dezember 2007. Report No.: 4.
49. (VKM) NSCfFS. Summary of the health risk assessment of the adjuvant effects of Cry proteins from genetically modified plants used in food and fodder. In: Mikalsen A, Aasma Finne M, Haraldsen T, editors. Opinion of the Panel on Genetically Modified Organism of the Norwegian Scientific Committee for Food Safety. Oslo: Vitenskapskomitteen for Mattrygghet; 2012. p. 29.

50. Moreno-Fierros L, Ruiz-Medina EJ, Esquivel R, Lopez-Revilla R, Pina-Cruz S. Intranasal Cry1Ac protoxin is an effective mucosal and systemic carrier and adjuvant of Streptococcus pneumoniae polysaccharides in mice. Scandinavian journal of immunology. 2003;57(1):45-55.
51. Food/feed and environmental risk assessment of insect-resistant and herbicide-tolerant genetically modified maize MIR604 x GA21 in the European Union under Regulation (EC) No 1829/2003 (EFSA/GMO/UK/2007/48): Hearing before the VKM(2014/01/21, 2014).
52. European Food Safety A. EFSA guidance on the submission of applications for authorisation of genetically modified food and feed and genetically modified plants for food or feed uses under Regulation (EC) No 1829/2003. EFSA Journal. 2011;9(7):2311-n/a.
53. Heinemann JA, Kurenbach B, Quist D. Molecular profiling--a tool for addressing emerging gaps in the comparative risk assessment of GMOs. Environment international. 2011;37(7):1285-93.
54. Glowacka K, Kromdijk J, Leonelli L, Niyogi KK, Clemente TE, Long SP. An evaluation of new and established methods to determine T-DNA copy number and homozygosity in transgenic plants. Plant Cell Environ. 2016;39(4):908-17.
55. European Food Safety A. Guidance Document for the risk assessment of genetically modified plants containing stacked transformation events by the Scientific Panel on Genetically Modified Organisms (GMO). EFSA Journal. 2007;5(7):512-n/a.
56. Podevin N, du Jardin P. Possible consequences of the overlap between the CaMV 35S promoter regions in plant transformation vectors used and the viral gene VI in transgenic plants. GM crops & food. 2012;3(4):296-300.
57. Gomord V, Chamberlain P, Jefferis R, Faye L. Biopharmaceutical production in plants: problems, solutions and opportunities. Trends in biotechnology. 2005;23(11):559-65.
58. Kuster B, Krogh TN, Mortz E, Harvey DJ. Glycosylation analysis of gel-separated proteins. Proteomics. 2001;1(2):350-61.
59. Heap I. The International Survey of Herbicide Resistant Weeds Weedscience.org: Weedscience.org; 2017 [cited 2017 14.March]. Available from: http://www.weedscience.org/.
60. Venter HJ, Bøhn T. Interactions between Bt crops and aquatic ecosystems: A review. Environmental Toxicology and Chemistry. 2016:n/a-n/a.
61. Bohn T, Cuhra M, Traavik T, Sanden M, Fagan J, Primicerio R. Compositional differences in soybeans on the market: glyphosate accumulates in Roundup Ready GM soybeans. Food chemistry. 2014;153:207-15.
62. Cuhra M, Traavik T, Dando Ml, Primicerio R, Holderbaum DF, B?hn T. Glyphosate-Residues in Roundup-Ready Soybean Impair Daphnia magna Life-Cycle. Journal of Agricultural Chemistry and Environment. 2015;Vol.04No.01:13.
63. Cuhra M, Bøhn T, Cuhra P. Glyphosate: Too Much of a Good Thing? Frontiers in Environmental Science. 2016;4(28).
64. Guyton KZ, Loomis D, Grosse Y, El Ghissassi F, Benbrahim-Tallaa L, Guha N, et al. Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. The Lancet Oncology. 2015;16(5):490-1.
65. European Food Safety A. Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate. EFSA Journal. 2015;13(11):4302-n/a.

66. Love BJ, Einheuser MD, Nejadhashemi AP. Effects on aquatic and human health due to large scale bioenergy crop expansion. Science of The Total Environment. 2011;409(17):3215-29.
67. Giesy JP, Dobson S, Solomon KR. Ecotoxicological Risk Assessment for Roundup® Herbicide. In: Ware GW, editor. Reviews of Environmental Contamination and Toxicology: Continuation of Residue Reviews. New York, NY: Springer New York; 2000. p. 35-120.
68. Blackburn LG, Boutin C. Subtle effects of herbicide use in the context of genetically modified crops: a case study with glyphosate (Roundup). Ecotoxicology (London, England). 2003;12(1-4):271-85.
69. Axelrad JC, Howard CV, McLean WG. The effects of acute pesticide exposure on neuroblastoma cells chronically exposed to diazinon. Toxicology. 2003;185(1-2):67-78.
70. Benachour N, Sipahutar H, Moslemi S, Gasnier C, Travert C, Seralini GE. Time- and dose-dependent effects of roundup on human embryonic and placental cells. Archives of environmental contamination and toxicology. 2007;53(1):126-33.
71. Dallegrave E, Mantese FD, Coelho RS, Pereira JD, Dalsenter PR, Langeloh A. The teratogenic potential of the herbicide glyphosate-Roundup in Wistar rats. Toxicology letters. 2003;142(1-2):45-52.
72. Benbrook C. Impacts of Genetically Engineered Crops on Pesticide Use in the United States: The First Thirteen Years. The Organic Center: The Organic Center; 2009.
73. Malatesta M, Caporaloni C, Gavaudan S, Rocchi MB, Serafini S, Tiberi C, et al. Ultrastructural morphometrical and immunocytochemical analyses of hepatocyte nuclei from mice fed on genetically modified soybean. Cell structure and function. 2002;27(4):173-80.
74. Solomon KR, Thompson DG. Ecological risk assessment for aquatic organisms from over-water uses of glyphosate. Journal of toxicology and environmental health Part B, Critical reviews. 2003;6(3):289-324.
75. Ono MA, Itano EN, Mizuno LT, Mizuno EH, Camargo ZP. Inhibition of Paracoccidioides brasiliensis by pesticides: is this a partial explanation for the difficulty in isolating this fungus from the soil? Medical mycology. 2002;40(5):493-9.
76. Marc J, Mulner-Lorillon O, Boulben S, Hureau D, Durand G, Belle R. Pesticide Roundup provokes cell division dysfunction at the level of CDK1/cyclin B activation. Chemical research in toxicology. 2002;15(3):326-31.
77. Richard S, Moslemi S, Sipahutar H, Benachour N, Seralini G-E. Differential Effects of Glyphosate and Roundup on Human Placental Cells and Aromatase. Environmental Health Perspectives. 2005;113(6):716-20.