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Testbiotech comment on EFSA GMO Panel Scientific Opinion on application (EFSAGMO-BE-2011-101) for the placing on the market of herbicide-tolerant genetically modified oilseed rape MON 88302 for food and feed uses, import and processing under Regulation (EC) No 1829/2003 from Monsanto

SHORT VERSION

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Summary

MON88303 is a genetically modified herbicide-resistant oilseed rape developed by Monsanto, which is designed to withstand even higher dosages and even more frequent applications of herbicides. Monsanto filed an application for import licensing in the EU. If authorisation is granted, viable whole kernels would be allowed for import into the EU, thereby risking the uncontrolled spread of the plants in the environment.

The risk assessment prepared by EFSA has considerable shortcomings:

- Only a superficial analysis of the effects of the genetic intervention on the genome and the ingredients of the plants was carried out.
- No stress-tests were carried out to test the plants' reactions to different environmental conditions – as a consequence, these reactions cannot be evaluated.
- No investigations were performed (such as feeding studies or cell culture tests) with regard to possible health effects.
- Possible health risks related to the residues of spraying with herbicides were not assessed, even though MON88302 is especially designed to withstand higher dosages and more frequent applications of glyphosate (brands like Roundup).
- Evident unintentional changes in the plants such as a significant delay in days-to-first-flowering were not examined for their causes.
- The likelihood of an uncontrolled spread into the environment has been systematically played down.
- Although the data presented by Monsanto were scientifically useless with regard to the risk for persistence and invasiveness, EFSA did not require any further investigation.
- Important publications were not considered in the assessment of long-term effects and the risks for gene flow to native plant populations.

The manner in which the MOB88302 risk assessment was carried out by EFSA is nothing less than a systematic attempt to avoid detailed investigations as far as possible. This approach might suit the interests of the industry, but falls short of legal requirements. The EU legislation as formulated in the regulations 18929/2003 and 178/20012 and in the directive 2001/18 requires a high level of

protection for both humans and the environment with due regard to the precautionary principle. Instead of respecting the nature of the legislation, EFSA is following a "don't look – don't find" approach and claims that the product's safety has been proven, even though crucial data are missing. Consequently, EFSA's opinion must be rejected and the import of MON88302 cannot be permitted.

Introduction

MON88302 is a genetically engineered, herbicide-tolerant (glyphosate) oilseed rape. According to Monsanto´s application the plants are "designed to provide growers with improved weed control through tolerance to higher rates of glyphosate and greater flexibility for glyphosate herbicide application."

MON88302 is part of Monsanto´s tailored strategy to combat herbicide resistant weeds that occur in many fields where glyphosate resistant plants are grown. Farmers who plant MON88302 oilseed rape will be able to apply higher dosages of glyphosate more frequently as required. Consequently, the environment will be exposed to even higher amounts of the herbicide and the plants will have higher levels of residue, which will subsequently be present in any food or feed derived thereof. At the same time Monsanto will be able to sell more of the herbicide and its patented genetically engineered seeds.

Investigation of the genome, plant composition and agronomic characteristics

The data as presented by Monsanto are not conclusive. No investigation was carried out to see whether the insertion of the additional DNA has changed plant gene activity and to identify unintended gene products.

The compositional analysis revealed many statistically significant differences between oilseed rape MON88302 and its conventional counterparts. 14 of 52 parameters were identified (carbohydrates, ash and total fat, amino acid lysine, several fatty acids, mineral calcium and vitamin E). These differences can indicate unintended effects in the plants caused by the process of genetic engineering, and should have been assessed in detail.

The kernels were the only part of the plant to be investigated. EFSA argues that other parts of the plants are not relevant since the company only applied for the import of the kernels. However, this lack of compositional analysis data from all other parts of the plants makes it more likely that unintended effects that are relevant for the safety of any derived food and feed will be overlooked.

Furthermore, although MON88302 is designed to enable late and repeated spraying (after the first flowering) with glyphosate, the plants tested for the market application were only sprayed once and at an early stage of the vegetation period. It is known that the dosage and the frequency of spraying with herbicides can impact plant composition as well as agronomic characteristics. EFSA deliberately ignored the specific purpose for which the plants were developed. Consequently, the whole of the risk assessment is fundamentally flawed throughout.

To assesses unintended changes in gene activity, composition an agronomic characteristics, the plants should have been subjected to a much broader range of defined stress conditions such as drought, heat and pest infestations. It is known that genetically engineered plants often show unintended reactions to stress, different to those from conventional breeding. This also can impact composition and safety of the plants.

In regard to agronomic and phenotypic characteristics, MON88302 showed a significant delay in days-to-first flowering. This was explicitly confirmed in the EFSA risk assessment. Significant differences were also observed in seed maturity and lodging, but these were set aside as being not of biological relevance and no further assessment was carried out. None of the changes observed in agronomic and phenotypical characteristics were not investigated in regard to underlying causes and possible implications. This gives reason to assume that the EFSA risk assessment is not sufficiently based on empirical findings and has an underlying bias aimed at avoiding more thorough investigations.

In the application as filed by Monsanto, it is stated that

> "MON 88302 is not different in composition, nutritional and agronomic characteristics relative to the conventional counterpart, except for the introduced tolerance to glyphosate..."

Apparently this statement is an assumption that is not based on scientific facts and can be considered wrong. This view is also endorsed by several experts from Member States. Nevertheless, EFSA more or less comes to a very similar conclusion as Monsanto. These conclusions are decisive for all the other parts of the MON88302 risk assessment: If comparative analysis does not reveal relevant differences, EFSA does not request further detailed testing for toxicology, allergenicity and nutritional effects. The plants are generally regarded as safe as their conventional counterparts. In reality, the plants are only subjected to a quick inspection, but not to detailed empirical studies.

Toxicology

As EFSA states in response to comments from experts from the Members States:

> "No hazard was identified in the molecular characterization and comparative analysis. In line with the EFSA guidance, no animal feeding study is necessary."

In consequence, not a single feeding study or *in vitro* study (such as using cell cultures) with the whole plants or parts derived thereof was requested. Neither were residues from spraying assessed. Since MON88302 allows a higher dosage and/ or higher frequency of spraying, it would be necessary to run detailed investigations into residues, metabolites and possible interactions.

Environmental risk assessment

Oilseed rape (Brassica napus) can spread via pollen and seeds. Similarly to Mexico, which is the centre of origin for maize, Europe is the center of origin and genetic diversity for the group of Brassica plants to which oilseed rape belongs. Some native plant populations such as Brassica rapa (turnip) can hybridise with oilseed rape. Brassic napus itself occurs mainly as a cultivated plant, but still maintains significant characteristics of a wild plant. Disturbed soil promotes the establishment of Brassica napus beyond the fields whereas dense vegetation will hinder establishment. However, wild growing Brassica napus is found primarily in habitats where wild relatives of the Brassica genus and related genera grow. In addition, many related species can hybridise with oilseed rape. Consequently, gene flow to wild relatives is possible and likely to happen.

The plants are mostly pollinated by insects such as flies, honey bees and butterflies which can also carry the pollen over many kilometers. Wind is also relevant for pollen drift: The farthest pollen-mediated outcrossing distance measured to date is 26 kilometres. Further, the seed remains viable in the soil for more than ten years (seed dormancy) so that oilseed rape has a high potential for volunteer plants even many years after the first sowing.

EFSA is fully aware of the inevitability of MON88302 escaping into the environment during transport and processing. However, EFSA is of the opinion that the dispersal of the plants (which they summarise as genetically modified herbicide tolerant – GMHT - oilseed rape) does not cause environmental risks or hazards because the plants do not show a higher fitness compared to other oilseed rape plants:

> "The EFSA GMO Panel confirms that feral GMHT oilseed rape plants are likely to occur wherever GMHT oilseed rape is transported. However, there is no evidence that the herbicide tolerance trait results in enhanced fitness, persistence or invasiveness of oilseed rape MON 88302, or hybridising wild relatives, unless these plants are exposed to glyphosate-based herbicides. Escaped oilseed rape plants and genes introgressed into other cross-compatible plants would therefore not create any additional agronomic or environmental impacts."

Consequently, EFSA believes that gene flow to crops in the field or to native plant population is not a cause for concern. It further assumes that the overall likelihood of MON88302 spillage is low. According to EFSA, even where glyphosate has been applied to the plants and rendered an advantage to MON88302 and its hybrids, there is no need for concern. However, these statements are largely misleading and not based on scientific facts.

(1) Does MON88302 show enhanced fitness?

The assessment of higher fitness which can lead to higher persistence and invasiveness of MON88302 is a crucial aspect of EFSA´s risk assessment. Therefore, data on the duration of flowering, pollen production, pollen viability as well as seed dormancy (which shows how long the seed can remain in the soil and still germinate; also called seed bank) are very relevant parameters that should have been investigated. Changes in these agronomic and phenotypical characteristics can impact the general fitness of the plants and their potential to persist in the environment or become invasive. However, no reliable data were made available. Kernels and the pollen were subjected to various temperatures to assess seed dormancy and pollen viability. But - as confirmed by EFSA - these experiments did not provide the data that was needed because the methods that Monsanto used were simply inadequate. Despite this observation, EFSA did not request any data on seed dormancy, duration of flowering, number of pollen, viability of pollen. Further, it did not assess in detail the impact of the delay in flowering and possible outcrosses to wild relatives of the plant. No crossing experiments with MON88302 were performed to investigate the effects of the transgenes in plants with other genetic backgrounds. It is therefore not possible to predict fitness, persistence or the invasiveness of hybrids from crossing with oilseed rape MON 88302. In conclusion, there are no sufficiently reliable data to assess fitness, persistence or invasiveness of oilseed rape MON 88302. Again, the EFSA risk assessment process appears not to be governed by real scientific findings, but rather a fundamental bias to presuppose safety, mostly based on the absence of relevant data.

EFSA overlooked publications that indicate unexpected changes in the fitness of transgenic plants that is unrelated to the intended trait. For example, according to research from Japan, the properties of feral transgenic oilseed rape plants might have changed under the influence of climatic conditions and showed that some of the plants found were larger than normal. These plants have also become perennial. This is a major change in the biology of the plants, as oilseed rape and all other Brassica species cultivated in Japan are annual. Perennial plants could have a higher probability of spreading their genes because they persist for a longer period. This could be seen as a factor supporting a higher fitness. Also other publications show unexpected higher fitness in transgenic plants that are not related to the specificity of the trait.

(2) Is the occurrence of feral MON88303 oilseed rape and further gene flow likely to be low?

The assumption of EFSA that occurrence of feral MON88032 oilseed rape resulting from seed import spills is likely to be low is not based on facts. Japan is especially relevant in this context because even though transgenic oilseed rape is not commercially cultivated in this country, genetically engineered oilseed rape has been found growing and attributed to imports. The first studies on the presence of transgenic oilseed rape in Japan were published in 2005. Plants that proved to be resistant to glyphosate or glufosinate were found in the proximity of many ports as well as along transportation routes to industry plants where oilseed rape is processed. Follow-up studies (2009-2011) found ruderal populations along further transportation routes and in areas close to all other major ports. Further, experts came to the conclusion that oilseed rape populations are able to self-sustain over time. Obviously, the percentage of transgenic oilseed rape in ruderal populations is constantly growing. In 2008, 90 percent of all tested plants in the proximity of Yokkaichi port proved to be genetically engineered. It was also shown that transgenic hybrid plants between B. napus and B. rapa do occur as well as herbicide tolerant transgenic oilseed rape plants that had hybridised with each other and were thus tolerant to glyphosate and glufosinate herbicides.

There are clearly major gaps in EFSA risk assessment, and it further ignores relevant findings regarding the frequency of gene flow and indications for unintended effects rendering higher fitness to transgenic oilseed rape and its hybrids.

(3) What about cross-contamination of fields?

EFSA does not believe that cross contamination with conventional oilseed rape grown on the fields is a matter for concern, because transport routes will be too far away. Such assumptions ignore facts about the biology of oilseed rape. For example, honey bees are known to transport pollen for several kilometers thereby enabling gene flow to fields much further away. Some animal species such as deer are also known to transport the seed. A large portion of the oilseed rape kernels remain viable after passage through the intestines of these animals. This might also be the case in other animals which have not so far been investigated. This issue not only raises economic problems, but also ecological concerns, since transgenic volunteers in the fields can become a source of enhanced gene flow to the environment. Together with feral oilseed rape populations these volunteers can open up many opportunities for genetic recombination, stacking of genes, and the evolution of genotypes that could lead to not only an increase in the cost of weed control in the future, but also to phenotypes with new environmental risks such as enhanced invasiveness. For example, new combinations of herbicide resistant traits can emerge such as crossings with Clearfield oilseed rape which is grown in the EU and was made resistant by mutagenesis to an ALS-inhibitor herbicide called Imazamox. Oilseed rape could become a multi-resistant weed with a much higher fitness (at least under current agricultural practices) compared to other oilseed rape plants.

(4) What impact should we expect from applications with glyphosate?

Application of glyphosate has steadily increased within last decade. Glyphosate is the most used herbicide worldwide with an upward trend in demand including the European market (see Monsanto´s annual reports). According to recent estimates, globally around one million tons of glyphosate are sprayed every year. Applications are not restricted to agriculture but are also used on non-cultivated areas, for example areas along transport routes. Thus, the likelihood that feral MON88302 and its hybrids will repeatedly come into contact with the herbicide is very high - and with current practice being what it is - MON88302 and its hybrids will definitely have an advantage to persist and spread into the environment. EFSA is trying to give the impression that this is only a minor problem by saying that spillage will be a rare event. However, as the example of Japan shows, this cannot not be assumed in general. The frequency of spillage is likely to increase with a higher volume of imports. Demands for import that might vary over the years are driven by various markets, not only for usage in food and feed but also for energy production.

(5) What kind of long term effects have to be considered?

As mentioned, in its risk assessment, EFSA admits that feral MON88302 plants are likely to occur wherever this oilseed rape is transported. In its application Monsanto gives the impression that it would be easy to control the uncontrolled spread of MON83302. But looking at existing experience, such as from the spread of transgenic oilseed rape along the transport routes in Japan and in other parts of the world, there is a high likelihood that spillage, gene flow and introgression into fields and the environment can result in a loss of spatio-temporal control of these plants – at least in the long-term. There is a considerable and partly irreducible uncertainty about potential environmental concern and potential damage which could be caused by an uncontrolled spread of transgenes. Some risks are obvious:

- The control of weedy species can become more complicated with the proliferation of genetically engineered plants with herbicide tolerance. This could increase the pesticide use in the environment and the shift to more toxic substances. It can lead to higher workload for farmers and to an increase in operational costs.
- Genetically engineered organisms, which are no longer allowed on the market for economic or ecological reasons, cannot be removed efficiently if they proliferate in the environment. They can also contaminate harvests and cause substantial economic damage.
- The biodiversity in the centres of diversity are an important genetic resource for plant breeding. Future plant breeding might be hampered substantially if transgenes spread into these resources.

In general, the overall long-term impact on ecosystems is hard to predict. In this regard, transgenic plants can be compared to alien species. Even if the biological characteristics of a species are known, its potential to persist or invade under new environmental conditions very often cannot be predicted. Some of the alien species only persist in distinct local regions and do not spread substantially over a longer period of time (i.e. lag-phase) but even after many years they may still become invasive. It is also difficult to predict the ecological impacts of invasiveness. The fact that climate change and disturbed ecological systems can foster invasiveness could cause even further uncertainty.

The comparison between the spread of genetically engineered organisms and the invasive potential of alien species also shows major differences. In the case of MON88302, one must consider both the adaption and spread of a new species within an ecosystem and the spread of technically inserted genetic information within the pool of genes of Brassica plants in the field and in the environment that are already adapted to the environment. The dynamics of proliferation within established species can be different from the pattern of the ecological potential of alien species within a new environment.

In the context of genetic engineering, specific attention should be given to the genetic stability and functionality of the inserted DNA. Unlike alien species, genetically engineered crops contain technical DNA constructs, very often composed from elements such as promotors and stop codons, that are not subject to the natural self-regulation of gene expression in the plant cells. Under the influence of climate change or in their interaction with other stress factors, this can have unexpected effects in the crops as shown in several publications that may also imply new risks for the environment. This issue was completely ignored by risk assessment of EFSA.

Consequently, it is very difficult to predict the long-term ecological impact of transgenes that escape spatio-temporal control, and it may be exacerbated by genetic re-arrangements and newly occurring mutations in combination with environmental changes. Therefore, risk assessment must take evolutionary dimensions into account. Evolutionary processes make it possible to turn events with a low probability of ever happening into events that may feasibly happen.

For example, outcrossing into wild species could be enhanced by climate or other environmental change. There are cases published showing that especially hybrids of cultivated species with wild species develop a higher fitness under stress. A higher amount of gene flow for oilseed rape under extreme climatic conditions was reported. The study shows there was a change in the time for flowering resulting in matching of flowering between species.

Where there are uncertainties, the precautionary principle provides a rational management strategy for the admission of transgenes. In the EU, the precautionary principle is part of the regulatory system. It has to be taken into account before decisions on experimental release or commercial cultivation are made (EU Directive 2001/18).

In this context, it is important to understand that environmental risk assessment in the EU is an iterative process. If new information on the genetically engineered plants and their effects on human health or the environment becomes available, the risk assessment may need to be re-addressed in order to determine whether the risk characterisation has changed and whether it is necessary to amend the risk management. The EU Directive 2001/18 foresees the monitoring of environmental impact (Article 20) and the admission of a specific GMO has to be renewed after ten years. Its outcome should indicate whether the genetically engineered organism can remain on the market or whether the authorisation should expire (Article 17). Article 8 and 23 cover cases where stopping the release of a genetically engineered plant may be deemed a matter of urgency immediately after new information about risks becomes available.

In conclusion, the EU can allow the import, release and commercial growing of plants inheriting transgenes. However, there is a caveat. If new information becomes available, the authorisation can be revoked. Then the release of the transgenes must be terminated.

The release of genetically engineered organisms which cannot be controlled in spatio-temporal dispersal conflicts with these provisions. The precautionary principle as established in Directive 2001/18 is operational only if efficient measures exist that can assure the removal of the genetically engineered organism from the environment is feasible if required becomes a matter of urgency. Therefore, spatio-temporal control is a prerequisite for implementing precaution. There is no doubt that under current EU regulation this principle also has to be applied for applications filed under EU Regulation 1829/2003. Therefore, market authorisation for the import of viable kernels of MON88302 would be in conflict with EU regulations since a substantial risk of permanent uncontrolled gene flow to the environment cannot be ruled out.

Monitoring

EFSA agrees with Monsanto that no targeted case specific monitoring of the uncontrolled spread of MON88302 and related gene flow is necessary if import is allowed. Monsanto and other members of the industry lobby EuropaBio would be the ones to oversee the import and report potential unanticipated adverse effects. The duration of this monitoring would be restricted to the duration of the authorisation. But as the case of transgenic oilseed rape in the EU produced by Bayer shows, contamination with transgenes are likely to occur even many years after the authorisation has expired, if once established.

Several experts from EU Member States voiced concerns that this is not a sufficiently robust approach. They state that there is a need for much more targeted case specific monitoring of factual gene flow. According to some experts from Member States, this monitoring should also include the health risks emerging from residues in the plants sprayed with glyphosate herbicides.

Conclusions:

The process as performed by EFSA is nothing more than a system to avoid more detailed risk assessment, and thus might be in line with the interests of industry. However, it contravenes legal requirements. EU regulations such as 18929/2003, 178/20012 and Directive 2001/18 all request a high level of protection for human health and the environment, based on a precautionary approach. Instead EFSA is following a “don´t look don´t find” approach claiming evidence of safety based on the absence of reliable data. Thus the opinion of EFSA has to be rejected due to major flaws and substantial gaps and the import of MON88302 cannot be allowed.

References: see full version at www.testbiotech.org/node/1079