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Testbiotech comment on the Scientific Opinion on an application (EFSA-GMO-BE-2011-98) for the placing on the market of herbicide-tolerant genetically modified soybean FG72 for food and feed uses, import and processing under Regulation (EC) No 1829/2003 from Bayer CropScience

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Introduction

Soybean FG72 was produced using a genetic construct that confers resistance to two groups of herbicides: Glyphosate and isoxaflutole. The EU application for FG72 is for food and feed, import and processing. This is the first time that it will be possible to apply a combination of the two herbicides, isoxaflutole and glyphosate, to soybean cultivated commercially. These plants are a consequence of problems with the increasing number of herbicide resistant weeds in countries where genetically engineered plants are cultivated. The degradation of glyphosate leaves residues such as AMPA (aminomethylphosphonic acid) in the plants which is under suspect to be carcinogenic (IARC 2015). The residues from isoxaflutole are already classified as "likely to be a human carcinogen". Despite these risks, EFSA did not ask for risk assessment of the combinatorial effects of these residues that are likely to occur in the harvest which is supposed to be imported as food & feed into the EU.

Molecular characterisation

The plants were produced using a ballistic method. There are several copies of the additional DNA inserted in the plants´ genome, showing defragmentations and other unintended characteristics in the size and orientation of the copies.

The emergence of new variations, combinations and concentrations of unintended small, biological active RNA molecules such as microRNA was not assessed. Small biologically active RNA molecules can be passed from the plant to humans or animals at the consumption stage. Potential biological effects will depend on similarities between the cell regulation in mammals and plants (see, for example, Zhang et al., 2011; Lukasik & Zielenkiewicz, 2014). These molecules are likely to emerge as unintended side products at the insertion sites of the additional DNA. Their concentration, structure and potential biological effects should be assessed before any conclusion is drawn upon safety of the plants.

Both the expression of the enzyme that confers herbicide resistance and the concentration of small biologically active RNA molecules should have been tested under a wide range of defined environmental conditions, taking into account stressful conditions that, for example, emerge under ongoing climate change. It is known that under stress conditions, genetically engineered plants can show reactions that are not obvious under normal agricultural conditions and can be very different

from those of plants stemming from conventional breeding. For example, environmental stress can cause unexpected patterns of expression of the newly introduced DNA (Trtikova et al., 2015). In this case, the expression data stem from another plant variety than that used in the final field trials. It seems to be unclear if these data are comparable to other plant varieties.

Comparative analysis (for compositional analysis and agronomic traits and the phenotype)
Significant differences were found for several compounds during the comparative assessment, especially in field trials conducted in 2008 / 2009. These results were not taken into account by EFSA. Instead, the basis for risk assessment was confined to field trials from 2011 that were carried out with another genetic background (other plant variety) than that used in the previous field trials.

The results from all field trials should be assessed in detail, investigating specific interaction between the additional DNA and the genetic background of the different plant varieties as well as interaction between the environment and the genome.

Toxicology
The applicant failed to provide a 90-day feeding study of sufficient quality. EFSA should have requested a new study, using material that was sprayed with the complementary herbicides.

Since the feeding study was rejected, health risks stemming from feeding whole food and feed cannot be assessed. This is especially relevant for assessing potential health effects from the combination of the residues from spraying with glyphosate and isoxaflutole. According to the International Agency for Research on Cancer (IARC), a body of the World Health Organisation (WHO), glyphosate can be regarded as having carcinogenic potential (IARC 2015). The US EPA found that isoxaflutole “induced liver and thyroid tumors in rats and liver tumors in mice. Isoxaflutole was therefore classified as "likely to be a human carcinogen”.”[1] According to the draft Renewal Assessment Report prepared by Italy, liver tumours were observed in rats and mice, and thyroid tumours were seen in male rats (Directorate General for Hygiene, Food Safety and Nutrition, 2015).

The plants will contain residues from both herbicides, none of which have been tested for specific combined toxicity. Thus, the residues in combination should have been assessed as relevant plant constituents.

Further, commercially traded herbicide mixtures such as Roundup are considered to be much more toxic than the active ingredient alone (Mesnage et al., 2013). Even though the carcinogenic potential of glyphosate is still under discussion, these two herbicides applied in combination (and as mixtures with further adjuvant ingredients) should trigger very detailed and in-depth risk assessment before any conclusion is drawn upon the safety of this event.

In general, risk assessment as performed by EFSA lacks sufficient interplay between the pesticide assessment and the GMO risk assessment. EFSA carries out the risk assessment of herbicide resistant genetically engineered plants without taking into account the specific risks that emerge from the residues from spraying with the complementary herbicides. These risks are only partially assessed as part of EU pesticide regulation. However, if commercially traded herbicides formulas are applied in specific combinations to herbicide resistant plants, there are specific patterns of residues that need to be assessed. In this case - according to the comments from Member States - the enzymes that confer resistance to isoxaflutole can also render tolerance to other groups of

[1] http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2010-0845-0004

herbicides. Thus, all possible combinations and dosages needs to be taken into account in risk assessment. But no such studies were conducted.

Herbicide resistance in weeds is increasingly becoming a problem in areas where genetically engineered plants are cultivated. In response, several other genetically engineered plants with tolerance to various herbicides have been developed and are pending for market authorisation in the EU, or have already been authorised. This is making it necessary to develop a new systematic approach to deal with new patterns of exposure, interactions between the substances and the accumulated impact on human and animal health.

Allergenicity

Most relevant for health risk assessment in this context are the naturally occurring allergens present in soybeans. A change in the plant composition might also lead to a higher concentration of the endogenic plant allergens. Further, it is known that toxicants, if applied together with the allergens, can have an adjuvant effects, triggering a stronger immune reaction to the proteins. This is a specific risk that needs to be addressed in the context of residues from spraying with the complementary herbicides.

Bayer presented data intended to show that the concentration of the endogenic proteins in the plants was not enhanced. However, soybeans are known to have a substantial variation in their natural concentrations, depending on specific varieties and on interaction with the environment. Bayer failed to show that the level of endogenic allergens in specific varieties and/ or under specific environmental conditions is not increased. For this purpose, further crossing with other varieties should have been performed as well as subjecting the soybeans to suitable stress tests. Further, the risk assessment completely failed to take into account potential interactions between the residues from spraying and the immune reactions to the soybean allergens.

Some additional testing was performed with blood samples from people known to be sensitive to soybean allergens to find out if they had a changed reaction to the genetically engineered soybeans. However, the number of samples used for testing was too small to get reliable results.

No analysis was undertaken of the risks for individuals with an impaired immune system such as the elderly or infants, as requested by the EFSA guidance (EFSA, 2010).

Monitoring

As a legal dossier compiled by Professor Ludwig Kraemer (Kraemer, 2012) shows, EU regulations require the monitoring of effects on health at the stage of consumption in cases where there are uncertainties. Thus, for example, there must be a requirement for the monitoring of health effects that takes residues from spraying with herbicides into account. Epidemiological parameters that are suitable to detect relevant health effects have to be defined.

Further, any spillage from the kernels has to be monitored closely.

Conclusions and recommendations

Based on the data presented and assessed, risk assessment cannot be concluded. Consequently, the application should be rejected.

References:

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