TESTBIOTECH Background 21 – 12 – 2017

Checking the facts: Genetically engineered soybeans from Bayer and Dow with triple resistance to herbicides

Final version

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Summary

Bayer and Dow AgroSciences want the EU to allow import of genetically engineered soybeans "Balance Bean" (company Bayer, also known as FG72 x A5547-127) and „Enlist" (Company Dow, also known as DAS-44406-6). These crops are the first genetically engineered soybeans that are resistant not only to one or two herbicides, but which inherit triple resistance. "Balance Bean" is made resistant to slyphosate, glufosinate and isoxaflutole, „Enlist" to glyphosate, glufosinate and 2,4-D.

These herbicides are known or suspected to be hazardous including glyphosate that is under discussion to be "probably carcinogenic"; glufosinate which, according to an EFSA evaluation, is officially classified as showing reproductive toxicity; isoxaflutole, which officially is classified as a "suspected human carcinogen". In the case of 2,4-D, recent publications suggest that carcinogenic metabolites are produced in genetically modified plants.

Analysis of the data by Testbiotech has revealed several major gaps in risk assessment as performed by European Food Safety Authority (EFSA):

(1) One crucial aspect in risk assessment is the dosage of the herbicides and the number of sprayings applied in the field trials. This aspect is relevant for the burden of residues found in the harvest, potential combinatorial impacts on health, as well as on overall plant composition.

The dosages applied by Bayer are much lower than those normally applied under practical conditions: In its field trials, Bayer only used about one kilo of glyphosate per hectare, or even less than that. In everyday agricultural practice, two, three or even eight kilograms per hectare are recommended. Moreover, the dosage of another herbicide that was sprayed i.e. glufosinate, was much lower than would be expected in farming practice.

Interestingly, Dow AgroSciences used much higher concentrations of the complementary herbicides in their field trials than Bayer. However, the genetically engineered soybeans used in their toxicological feeding trials appear to have been sprayed with the herbicides at much lower dosages. This observation raised concerns that the company was trying to hide relevant health risks arising from consumption of its soybean DAS-44406-6. Consequently, there is huge uncertainty regarding factual health risks from consumption of the soybeans. There is an ever bigger problem with Bayer: This company did not perform any toxicological feeding studies with the soybeans to investigate health risks.

(2) A further gap in risk assessment concerns the specific herbicides uses in the field trials. In this regard, the genetically engineered soybeans from Bayer and Dow were made resistant to more herbicide substances than tested in the field trials: The herbicides 2,4-D and isoxaflutole belong to larger groups of chemicals that encompasses many other herbicides that can also be sprayed onto the plants during cultivation. Any relevant data for the risk assessment of spraying crops with these other herbicides are completely missing.

(3) Further, there are some basic problems in the risk assessment of genetically engineered plants made resistant to herbicides: Such plants have been grown for many years in countries such as the USA, Brazil and Argentina. Over time, many of the weeds growing in these regions have adapted to herbicide use. This has in turn led to increasing amounts of herbicide being sprayed onto the crops and also an increase in the number of applications. However, as a report from EFSA shows, the available data on residues from spraying with glyphosate are generally insufficient to draw any conclusion on the safety of soybeans being imported into the EU. For example, in 2015, no samples of imported soybeans were analysed for residues from spraying with glyphosate.

According to the EU Commission, the health risks associated with genetically engineered soybeans can be assessed separately and independently of any herbicides they are resistant to. Testbiotech rejects this approach on the grounds that it is inadequate and misleading. In accordance with the guidelines for EU risk assessment, the plants have to be sprayed with the herbicides they are resistant to. But if the herbicides are not tested on the plants in realistic conditions, the risk assessment is flawed.

If the plants are sprayed with less herbicide in the field trials than would be usual in normal farming practice, this will not only influence the amount of herbicide residues in the plants from spraying. It can also influence changes in plant composition, which is dependent on the dosage of herbicides sprayed onto the plants. These changes can cause health risks by, for instance, increasing the effects of allergens or phytoestrogens. These risks were neither assessed under pesticide regulation, nor under GMO regulation.

Testbiotech is demanding that following investigations are performed before a decision is taken on risk assessment:

- Assessment of all residues of active substances taking various practical conditions into consideration (e.g. dosage and frequency of herbicide application);
- Assessment of all relevant active ingredients, additives and their residues;
- Investigation of combinatorial effects of the applied herbicides;
- Investigation of the changes in plant constituents taking into account various herbicide applications;
- Investigation of interactions between the herbicides and the plant constituents;
- Investigation of the long-term effects of consumption of the genetically engineered soybeans taking possible effects on endocrine systems, reproduction and intestinal microbiome into account.

Introduction

Bayer and Dow AgroSciences, similarly to Monsanto, produce genetically engineered herbicide-resistant plants. Their business model is simple: Selling patented seeds and herbicides in a double pack.

Specific herbicides (e.g. glyphosate) used in the cultivation of genetically engineered plants are known as complementary herbicides. Genetic engineering makes it possible for the plants to survive spraying with these specific herbicides. At the same time, newly emerging metabolic substances and herbicide residues in the crops mean new risks for consumers.

Genetically engineered plants are mainly grown in Argentina, Brazil and the USA. Soybeans that are genetically engineered to be resistant to glyphosate have been grown in these regions for over 20 years. In recent times, glyphosate has faced heavy criticism – and was classified as carcinogenic by the International Agency for Research on Cancer (IARC, 2015), which is part of the World Health Organisation (WHO). In addition, widespread use of glyphosate has been harmful to biodiversity (Pleasants & Oberhauser, 2012, Schütte et al., 2017).

At the same time, a number of weeds have adapted to the massive use of glyphosate and have become resistant.[1] These herbicide-resistant weeds are an increasing problem in the countries where the genetically engineered crops are grown. They have led to increasing amounts of herbicide being used on the crops, and to an “arms race” in genetic engineering technology. Essentially, genetic engineering technology is used to insert gene constructs into plants, such as soybean and maize, which will make the plants resistant to several herbicides.

New genetically engineered soybeans developed by Bayer and Dow

Bayer used genetic engineering technology to develop the FG72 soybean (Balance Bean). This new variety is not only resistant to applications of glyphosate – it is also resistant to herbicides, such as isoxaflutole, that cause the plants to “bleach” and die (so-called HPPD inhibitors). The genetically engineered FG72 soybean was allowed for import into the EU in 2016.

In an extreme extension of its business model, Bayer has now crossed this soybean with other genetically engineered varieties in order to make the plants additionally resistant to glufonsinate. This latter herbicide is known under brand names such as Liberty or Basta. The harvest of these soybeans (abbr. FG72 x A5547-127) is to be authorised for use in the food and feed industry and for import into the EU. It would be the very first time that approval is given to genetically engineered plants resistant to three different herbicides.

Table 1: Genetically engineered soybeans from Bayer that are resistant to three herbicides

Company	Genetically engineered soybean	Group of complementary herbicides	Complementary herbicide tested
Bayer	FG72 x A5547-127 trade name: 'Balance Bean'	glyphosate glufosinate HPPD-inhibitors	glyphosate glufosinate isoxaflutole

A similarly extreme approach is taken by Dow AgroSciences: They have also filed a market application for soybeans with a triple resistance to herbicides: The genetically engineered soybeans

1 www.weedscience.org/

are resistant to spraying with glyphosate, glufosinate and 2,4-D (this substance belongs to the group of phenoxy herbicides).

Table 2: Genetically engineered soybeans from Dow AgroSciences that are resistant to three herbicides

Company	Genetically engineered soybean	Group of complementary herbicides	Complementary herbicide tested in trials
Dow AgroSciences	DAS-44406-6 trade name:'Enlist™ traits'	glyphosate glufosinate phenoxy herbicides	glyphosate glufosinate 2,4-D

Analysis of the relevant data provided to EFSA by the companies has revealed three major gaps in EFSA risk assessment (EFSA 2017 a & b):

1. The Bayer soybeans were not assessed under realistic practical conditions

Testbiotech was able to partially access documents filed for the approval of soybeans FG72 and FG72 x A5547-127. The documents show that the risks associated with the genetically engineered soybeans were not assessed under realistic practical conditions. The way in which Bayer organised their investigations meant that many relevant data are completely missing..

The following specific conditions were chosen for the field trials:

- In field trials with FG72, the soybeans were sprayed with around 1 kg glyphosate/hectare.
- In field trials with FG72 x A5547-127, 863g of glyphosate/hectare was applied to the soybeans
- A maximum amount of 70 mg/hectare of isoxaflutole was applied to FG72 and FG72 x A5547-127.
- An additional 448g /hectare of glufosinate was applied to FG72 x A5547-127.
- The plants were only sprayed once at a relatively early stage of growth.

The amount of glyphosate used in the field trials was distinctly below that of the amounts used in agricultural practice:

- Commercially grown genetically engineered plants are mostly sprayed not just once, but several times.
- Only around 1 kg/hectare of glyphosate or even less (863g / hectare) was used in the field trials; Bayer, however, states that a minimum of 1,12 kg/ hectare should be used by farmers cultivating soybeans in the US and if glyphosate is applied to its soybeans without isoxaflutole.[2]
- Further, in the US, Monsanto officially recommends that dosages of around 2-3 kg / hectares are applied to the soybeans, with additional spraying before and after cultivation.[3]
- According to a patent application filed by Monsanto for different application combinations of glyphosate, the amount of glyphosate sprayed onto fields with genetically engineered soybeans can sum up 8 kg / hectare. Sprayings might be divided into several portions (WO 2008051633).
- Data on herbicide residues in soybeans grown in Argentina point to (Testbiotech 2013)

2 http://www.balancegtsoybeans.com/use-restriction-agreement/

3 http://www.rea-hybrids.com/Agronomy/Documents/Postemergence%20Herbicide%20Applications%20in%20Soybeans%20-%20RRPLUS%20-%20Spotlight.pdf.

rapidly increasing problems with herbicide resistant weeds[4]; and it can be expected that extremely high dosages will be applied in several regions of South America.

- From the group of HPPD inhibitors, only one additional active substance was tested in field trials – isoxaflutole. Other HPPD inhibitors that could be used in the cultivation of soybeans were ignored. According to available publications, at least one further active substance, mesotrione, could also be used in future (Schultz et al., 2015). In addition, over a dozen other HPPD inhibitors and their application on Bayer herbicide-resistant plants are claimed in patents held by the company.[5] Each one of these substances can leave specific residues in plants and/or lead to changes in the metabolism of the plants. Therefore, all relevant substances should be tested on the plants.
- For the use of glufosinate in the cultivation of soybeans, Monsanto (WO2008051633) recommends up to 905 g /hectares.

Table 3: Comparison of data on herbicide dosages (active ingredients, a.i.) applied in field trials for Bayer´s genetically engineered "Balance Beans" (FG27 and FG72 x A5547-127) with other sources in regard to herbicide resistant soybeans

	Field trial FG72	Field trial FG72 x A5547-127	Monsanto patent WO2008051633	recommended by Monsanto (2017)	recommended by Bayer (2017)
glyphosate	Ca 1 kg /hectare single spraying	0,863 kg /hectare single spraying	8 kg/hectare overall dosage before and during the cultivation of the soybeans three sprayings	2-3 kg /hectare as a maximum applied directly sprayed onto the soybeans during cultivation two sprayings	1,2 kg /hectare as a minimum if glyphosate is applied without isoxaflutoles one or two sprayings
glufosinate		448 g/hectare	863 g/hectare		
isoxaflutole	70 mg /hectares	70 mg /hectares			Not allowed in the US

Bayer did not perform any feeding studies with its soybeans to investigate potential health impacts at the stage of consumption.

2. Dow AgroSciences genetically engineered soybeans are engineered to be resistant to further herbicides not tested in field trials

According to the opinion of EFSA (EFSA 2017b), the Dow AgroSciences soybeans were made resistant to three classes of herbicides: glyphosate, glufosinate and the group of phenoxy-auxin herbicides of which 2,4-D is one specific substance.

But as the patent application WO2007053482 filed by Dow AgroSciences shows, genetically engineered plants such as DAS-44406-6 that inherit the enzyme AAD12 are also resistant to further herbicides named pyridyloxyacetate. Substances such as triclopyr, fluroxypyr and MCPA are members of this group. These herbicides were not tested in the trials for risk assessment and they are not even mentioned in the EFSA opinion.

Each one of these substances can leave specific residues in plants and/or lead to changes in the metabolism of the plants. Therefore, all relevant substances should be tested on the plants.

4 http://www.weedscience.org/
5 See patent application WO2017042259

Table 4: List of herbicides which, according to Dow AgroSciences, can be sprayed onto soybeans, such as DAS-44406-6[6]

Class of herbicides	Specific substances
Phenoxy herbicides	2,4 D 2,4,5-T 4-CPA 3,4-DA
Pyridyloxyacetate	MCPA Triclopyr Fluroxypyr

In regard to the dosages and number of times the herbicides were sprayed onto the crops, Dow did a much better job than Bayer, spraying several times and using higher dosages. Dow even performed a 90-day rat feeding study to investigate health risks. However, the soybeans used in the feeding study were sprayed with the herbicides at much lower dosages. Glufosinate was not sprayed at all. Further, the feeding study suffers from major deficiencies: For example, no dose-dependent effects were investigated. Instead only one low level dose of the soybeans was mixed into the diet. Thus, this feeding study is meant to create the impression that health risks at the stage of consumption were investigated, but in fact they were not. Nevertheless, the study was accepted by EFSA.

Table 5: Comparison of data on herbicide dosages (active ingredients, a.i or acid equivalents, a.e..) applied in field trials for Dow´s genetically engineered "Enlist" soybean (DAS-44406-6) used in the field trials and as applied on the soybeans used in the toxicological feeding study

	Field trial DAS-44406-6	Feeding study with DAS-44406-6
Glyphosate	Three sprayings, with 3780 g ae/ha in total	Two sprayings, with 1680 g ai/ha in total
2,4-D	Three sprayings, with 3360 g ae/ha in total	One spraying with around 1000 g ai / ha
Glufosinate	Two applications, with 800 g ai/ha in total	None

3. Missing data on residues in the harvest from spraying with herbicides

In general, it can be expected that the complementary herbicides will leave residues in the plants resp. the harvest. The kinds of residues and their degradation products is dependent on the plant species, the genetic constructs that were inserted, as well as the amount and frequency of herbicide application.

Glyphosate degradation in FG72: Data missing

Most research has been carried out on the residues of glyphosate. In particular, AMPA (aminomethylphosphonic acid) is one of the degradation products in this process. AMPA is thought to be just as toxic as glyphosate.

The amount of AMPA (and of other degradation products) that emerge in the plants can vary according to the constructs that were inserted. In addition, other degradation products can emerge. For the risk assessment of FG72, it would, therefore, be necessary to know just how high the concentrations of the respective glyphosate residues actually are for different applications (single or multiple applications, low or high dosage). However, relevant data was not submitted.

6 See patent application WO2007053482

HPPD inhibitors: Risks associated with degradation products are unknown
New degradation products will emerge with the application of isoxaflutole – which is classified as a "suspected human carcinogen". These metabolites have so far not been found in conventional soybeans, but are known to occur in the genetically engineered plants. The EFSA (EFSA, 2016) has asserted that they are unable to evaluate risks to health from these new substances due to a lack of necessary data. And therefore, the EU authority was not able to set maximum limits for the amounts of these new residues in the harvest even though this is a legal requirement (Regulation 396/2005).

Glufosinate: Data lacking on applications to soybeans
There is very little data available on which degradation products in which concentrations are to be expected from the application of glufosinate on herbicide-resistant soybeans. As far as Testbiotech knows, there are no publications or any official evaluations available on this issue. Glufosinate is classified as showing reproductive toxicity.[7]

Phenoxy herbicides and pyridyloxyacetates: Not tested
There were no field trials with substances such as triclopyr und fluroxypyr, and the only herbicide tested from the group of phenoxy herbiciden was 2,4-D. Metabolites stemming from 2,4 D such as 2,4-dichlorphenol are regarded as being more toxic than the herbicide itself (EFSA 2017d). Recent publications suggest that even carcinogenic metabolites are produced in genetically modified plants (Lurquin, 2016), but these were not assessed by EFSA.

Additives: Too many unknowns

Apart from the active ingredients, other additives and wetting agents are added to commercial herbicide mixtures, such as Roundup (glyphosate). The adjuvants can lead to the herbicide mixture being considerably more toxic than the single active substance. For this reason, the use of particularly problematic additives, such as tallowamine, is either restricted or prohibited in several EU countries.[8] However, the application of especially problematic additives, such as tallowamine, is not prohibited in countries where genetically engineered plants are grown.[9] Nonetheless, these substances are ignored in the approval process for genetically engineered plants for import. The EU Commission has even indirectly admitted that there are gaps in the approval process.[10]

The European Food Safety Authority also stated that further investigations were necessary, and that it is currently not possible to assess any harmful effects to health from herbicide residues (EFSA 2015a and 2015b). As current documents show – that should also be released by Monsanto in the USA – even the authorities there do not know in detail what is added to which herbicides resp. what residues can be expected to be found in the harvest.[11] From existing data, it has to be assumed that in commercial mixtures applied in the fields in Argentina, around 50 percent consists of glyphosate and about 15 percent are additives known as POEA tallowamine, which are much more toxic than glyphosate (Perez et a., 2011). The exact mixtures sprayed onto the plants are kept secret and treated as confidential business information.

It is of immense concern that EFSA in its 2015 European Union report on pesticide residues in food (EFSA 2017 c), showed that in the whole of the EU no samples at all were taken to investigate residues from spraying soybeans with glyphosate. As EFSA states:

„Since soybeans are an important globally traded commodity on which glyphosate is

7 http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=homepage&language=EN
8 https://ec.europa.eu/germany/news/glyphosat-eu-staaten-schr%C3%A4nken-beistoffe-und-nutzung-ein_de
9 http://dip21.bundestag.de/dip21/btd/18/073/1807373.pdf
10 www.testbiotech.org/node/1636
11 www.huffingtonpost.com/entry/5988dd73e4b030f0e267c6cd

frequently used, more detailed information on the occurrence of glyphosate residues would be desirable.“

The risks were not sufficiently investigated

Residues of the herbicides

The residues from active substances must be investigated according to pesticide regulation (regulation 396/2005), and respective maximum limits set for residues (MRL). In addition, the soybeans must be assessed according to EU regulation 1107/2009 for combinatorial risks of herbicide residues. Relevant methods for investigating biological substances and complex mixtures of substances are set out in the European Chemical Directive 1907/2006 (REACH).

The biology of the plants must also be included in risk assessment. This is the only way to determine which metabolic substances in which amounts actually emerge in the plants. In addition, investigations should include different dosages and combinations. Specific growing conditions and the genetic characteristics of the individual varieties should also be taken into account. As already mentioned above, such investigations are either completely or partially missing:

- Herbicide applications are not in line with farming practice.
- Feeding studies are missing or suffer from intentional and systemic flaws.
- For isoxflutole, the EFSA was unable to set maximum permitted residue levels (MRL) for the possibly very toxic residues (EFSA, 2016).
- As far as the application of glufosinate on herbicide-resistant soybeans is concerned, it appears that there are no specific investigations.
- On the question of which additives are mixed into the herbicides in the different countries where genetically engineered crops are grown, it appears that the European authorities do not have sufficient information (EFSA, 2015).
- In regard to imports, there is a major lack of data on residues from spraying with the complementary herbicides on soybeans.
- Finally, possible combinatorial effects need to be assessed. The combinatorial effects of residues can far exceed the toxicity of the single substances (Reuter, 2015). However, since a specific combination of complementary herbicides can be applied to the plants, it should be relatively easy to determine combinatorial effects. As yet, such investigations have not been carried out. The EU Commission has admitted that combinatorial effects should also be investigated.[12]

In the circumstances, it must be concluded that health risks due to residues left over from herbicides in soybean FG72 and FG72 x A5547-127 and DAS-44406-6 have not been sufficiently investigated.

Further risks to health

There are a number of further specific risks to health from the changed metabolism of the genetically engineered plants:

- The newly introduced metabolic pathways can cause unintended changes in the plant constituents. This is particularly relevant for soybeans since the beans contain a naturally high concentration of phytoestrogens and allergens – and these concentrations can increase. The respective changes can be dependent on which herbicide is used in which concentration. Zobiole et al (2012) and also Bøhn et al. (2014) found that application of the herbicide can cause significant changes in soybean plant constituents. Most relevant in this context is a

12 www.testbiotech.org/sites/default/files/11_letter_from%20Commission_August_2016.pdf

publication by Zobiole et al. (2012) on a study that used three different dosages of glyphosate applications (800 mg, 1200 mg and 2400 mg /hectare) which correlated to dose-dependent changes in the plant´s compositions. EFSA has so far ignored this issue.

- Furthermore, it has to be taken into account that there may be specific interactions between residues of herbicides and plant constituents. Natural allergens and phytoestrogens found in the plants are particularly relevant in this context - since their risks to health can be increased by interaction with diverse active substances, additives or degradation products of the herbicides. Studies have found disturbances in the endocrine system of young rats when fed with soy milk in combination with glyphosate (Nardi et al., 2016).

- It must be further taken into account that continuous exposure to these residues can have an effect on health in an indirect way. The residues can, for example, cause changes in the enteric flora of humans and animals, which might possibly promote diseases. It is known that the use of glyphosate can lead to changes in the composition of microbial soil flora (see, for example, EFSA, 2012). Additionally, glyphosate has an antibiotic effect on specific bacteria such as *E. coli* (Forlani et al., 1997; Carlisle & Trevors, 1988). Therefore, it seems obvious that permanent exposure to glyphosate can cause changes in the gut flora of humans.

These risks are as yet not taken into account in the EU approval process. One of the main reasons for these gaps in risk assessment is the EU Commission’s attempts to separate as far as it possibly can, the question of residues left over from the herbicides from the question of genetic technology approval. This is the approach followed by the EU Commission in, for example, the amendment of Annex 2001/18 of the EU Release Directive 2001/18. The EU Commission is prepared to defend this separation even in cases brought to the European court (C-82/17 P).

As this background shows, there are specific risks associated with the application of herbicides to genetically engineered plants that are neither covered by the approval processes for genetic technology, nor by pesticide regulation. These gaps in regulation are pertinent to the majority of the genetically engineered plants that have already been approved: Over 50 of the around 60 genetically engineered plants approved for import into the EU up until August 2017 have been engineered to be resistant to at least one herbicide.

Conclusions and Recommendations

Current practices in the assessment of herbicide-resistant genetically engineered plants mean that a great many of the actual risks are systematically excluded from risk assessment. Crucial data on changes in the plant constituents are missing, as are data on the herbicide residues. Additionally, central questions in risk assessment, such as possible interactions and combinatorial effects are completely ignored.

Soybean events engineered by Bayer and Dow AgroSciences cannot therefore be seen as safe. On the contrary, there is a high risk that consumption of these soybeans could have a harmful effect on health.

Current approval practice fundamentally contradicts EU laws on genetic engineering technology. Regulation 1829/2003 requires that genetically engineered plants can only be approved for import if they are deemed to be safe. If these plants contain a combination of residues that are possibly

damaging to health because the plants have been genetically engineered to be resistant to herbicides, then these must of course be investigated before approval is granted.

Against this background, no further genetically engineered plants that are engineered to be resistant to glyphosate or other herbicides should be approved for import until the health risks associated with the residues have been comprehensively investigated and the results are presented. At the same time, the approval process for genetic engineering technology should be linked to pesticide regulation. This is the only way to ensure that none of the risks are overlooked.
In particular, following requirements should be taken into account:

- Assessment of all residues of active substances taking various practical conditions into consideration (e.g. dosage and frequency of herbicide application);
- Assessment of all relevant active ingredients, additives and their residues;
- Investigation of combinatorial effects of the applied herbicides;
- Investigation of the changes in plant constituents taking into account various herbicide applications;
- Investigation of interactions between the herbicides and the plant constituents;
- Investigation of the long-term effects of consumption of the genetically engineered soybeans taking possible effects on endocrine systems, reproduction and intestinal microbiome into account.

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