Paper V: Review of published evidence

Title: Analysis of herbicide-residues is essentially missing in risk-assessment of herbicide-tolerant genetically modified cultivars.

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Analyses of herbicide-residues are still missing in risk-assessment of glyphosate-tolerant GMO-cultivars

Keywords: Glyphosate tolerant GMO, substantial equivalence, herbicide tolerance, Roundup-ready cultivars, herbicide residues, industrial agriculture chemistry

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Abstract

Background: Genetically modified glyphosate-tolerant cultivar varieties (GM-crops) have been a commercial success widely known as Roundup-ready plants. As new glyphosate-tolerant varieties are introduced to satisfy agriculture demand, it is relevant to review the scientific evidence that documents the quality and safety of such biotechnology. Assessment of genetically modified glyphosate-tolerant plants is partly based on reports from laboratory comparisons with non-modified plants (near isogenic relatives). Such comparative testing is typically performed as analysis of plant-material composition and in animal feeding studies. The material for testing is typically produced in test-fields set up as model-environments. Researchers employed by biotech industry companies plan, perform and report most of this research.

Perspective: The present paper aims to; i) review 15 reports on compositional analyses of glyphosate-tolerant cultivars and 15 reports from animal-feeding-studies, ii) discuss recent data indicating glyphosate residue in Roundup-ready soybean, iii) outline recent developments of cultivars with increased tolerance to glyphosate.

Findings: The reviewed industry studies show methodological flaws: Glyphosate-tolerant GM-crops are designed for use with glyphosate herbicide. However, glyphosate herbicides are often not applied in test-study cultivation. In the studies where glyphosate herbicides were applied to growing plants, the produced plant material was not analysed for glyphosate residues. This review has failed to identify industry studies that mention glyphosate residues in glyphosate-tolerant plants. This indicates that questions and evidence of importance for regulatory assessment have been systematically ignored. Independent research has investigated this issue and found that glyphosate-tolerant plants accumulate glyphosate residues at unexpected high levels. Glyphosate residues are found to have potential to affect plant material composition. Furthermore, these residues are passed on to consumers.

Conclusions: Industry studies are not sufficient for regulation. Despite decades of risk assessments and research in this field, specific unanswered questions relating to safety and quality aspects of food and feed from transgenic cultivars need to be addressed by regulators. Independent research gives important supplementary insight.

Introduction

Recent changes in the Europen Union (EU) legislative framework for assessments and approvals of genetically modified agriculture cultivars (GM-crops) have led to a delegation of responsibility to regulatory authorities in individual EU member states. The increased challenges of evaluating applications for import or cultivation of GM-crops accentuate the need for reliable and transparent evidence on GM-crop quality and safety issues.

In a 2013 review of two decades of research on possible unintended compositional changes in GM-crops, two senior scientists conclude that such GM-crops have been subjected to a large number of analytical studies which confirm compositional equivalence. They conclude that GM-crops are safe and rhetorically ask; "How much uncertainty remains after 20 years of research?" [1].

I see that the authors have concluded that compositional equivalence is sufficiently established and I hear their argument stating that further safety studies of GM-crops thus no longer are necessary. However, I still propose to answer the rhetorical question presented by these senior scientist authors, of whom one is representing a major industrial producer of GM-crops and the other is retired from the Food and Drug Administration of the United States.

Unresolved important uncertainties remain in relation to genetically modified crop quality and safety. One such specific issue will be reviewed here: the somewhat neglected fact that GM-cultivars designed and modified to be tolerant to herbicides such as glyphosate, will be subjected to application of such chemicals in the field and therefore must be expected to have biological interaction with these herbicidal sprays.

Background

Herbicides such as glyphosate disrupt plant metabolism by having chemical and physical qualities that facilitate penetration into the plant tissue and transportation within the plant, killing the recipient by systemic action [2]. Glyphosate is an important chemical; it is a best-selling herbicide with an annual application in the order of 0.6-1.2 million tonnes globally [3, 4]. Glyphosate is used in farming, parks, gardening, forestry and wetland management [5]. Glyphosate is widely used as a desiccant to induce ripening in semi mature crops [6] and it has been found to have antibiotic qualities [7]. In the context of this review it must be noted that the advent of glyphosate-tolerant crops has contributed to a sharp increase in global dispersal of this chemical [8].

Early findings justified that glyphosate has been widely recognized as having relatively low environmental impact [9], low toxicity for field workers handling the chemical, and low toxicity for consumers ingesting residues of it through food [10]. However, in recent years such established indications of safety have come under revision, as glyphosate is found to have more subtle and complex effects than what has previously been acknowledged [11, 86]. Furthermore, recent pesticide screenings of fruits, vegetables and other food in the EU have shown that a majority of the samples (97%) contain trace quantities of pesticide residues. Glyphosate stands out as the most common detected chemical in European food, present in approximately half of all samples [12]. However, the vast majority of samples show concentrations well below the existing acceptance levels. It must be noted that although acceptance levels of most pesticides are defined in ng/kg (ppt) or μg/kg (ppb) orders of magnitude, the acceptance levels for glyphosate in numerous foods and agriculture products are defined in mg/kg (ppm). Despite the detected wide-spread occurrence of glyphosate residues in food, animal feed, water [5], air [13], human blood [14], human milk [14] and human urine [14, 15], it is not within the mandate of this review to evaluate whether the relatively high acceptance levels for glyphosate residues in food and feed are scientifically justified, however relevant the question may seem.

Herbicide-tolerant cultivars dominate agriculture

It has been estimated that an overwhelming 81% majority of transgenic crops in cultivation, are herbicide-tolerant varieties [16]. The majority of those herbicide-tolerant crops are *Roundup-Ready* plant cultivars (RR-crops) genetically modified to tolerate glyphosate herbicides such as the commercial product Roundup. The first such varieties were introduced in 1996 and rapidly gained popularity amongst farmers. Herbicide-tolerance allows for post-emergence application and in principle eliminates the need for pre-plant tillage and manual weeding. This is an advantage which contributes to reduced soil erosion and reduced production expenses [16, 17, 18].

Despite challenges from increasing numbers of agriculture weeds that are resistant to glyphosate herbicide, glyphosate tolerant cultivars such as RR-soy, RR-corn, RR-canola and RR-cotton are still the most popular and widely grown genetically modified plant varieties [8]. Additional glyphosate-tolerant cultivars such as RR-sugar beet, RR-wheat and RR-alfalfa are introduced as promising and potentially important crops [4]. Glyphosate tolerant plants thus form a dominant and increasing proportion of the biomass produced globally from industrial agriculture. This biomass is used for farm-animal feed purposes and for important constituents in human food products.

Industry provides most data for risk-assessment of GM-crops

Regulatory assessments of applications for import and use of products from GM cultivars into the European Union/EEC area, and applications for open cultivation of such plants in Europe, have until recently been centrally processed by the European Food Safety Authority (EFSA) based on documentation submitted by applicants [19, 21, 22, 24]. Recent changes in regulation of GM-crops within the European Union delegate this responsibility, as individual member states now have the obligation to independently approve or reject specific applications on a national level.

In a standing controversy over GMO safety, the EU approval process as conducted by EFSA has been claimed to be unsupportive of independent research findings [19, 20, 87].

Typically industry applications for import and/or cultivation contain 3 main categories of information; 1) molecular information on the actual event including the structure and origin of transgenic construct, 2) information from compositional analysis where the transgenic cultivar in question is compared to near-isogenic mother-lines or other comparators representative of unmodified varieties grown under similar conditions, and 3) results from feeding studies in test-animals such as rodents or farm-animals such as pigs and poultry. Implicitly, the transgenic material in such tests should be representative of the actual material intended for consumption.

European regulation defines guidelines for animal feeding studies and compositional analysis to determine whether food and feed from transgenic cultivars reliably has qualitative equivalence to that of conventional non-modified cultivars [21, 22].

The concept of *substantial equivalence* [23] is used by regulators and industry scientists to validate transgenic crop quality. Comparative analysis of composition and comparative testing in animal feeding-trials are still the two fundamental methods in use for assessment of substantial equivalence of produce from herbicide-tolerant crops and other genetically modified biomass intended for consumption. Guidelines for such analysis and testing aim to ensure that the new varieties are as safe and nutritious as conventional plants. Therefore such testing includes risk-assessments which anticipate potentially adverse effects stemming from qualitative differences or undesirable constituents [23, 24]. The Food and Agriculture Organisation (FAO) and World Health Organisation (WHO) established the Codex Alimentarius commission in 1963 to develop harmonised international food standards, guidelines and codes of practice to protect the health of the consumers. The aim of the Codex regulation is to anticipate not only direct risk, but also *indirect/unaticipated risk* [25]. Thus it is interesting to note that the Codex Alimentarius commission in 1999-2001 had protracted evaluations on the possibility of establishing specific and unique standards for herbicide-residue-levels in herbicide-tolerant transgenic crops [26]. The reports of this regulatory process document that this question was seen relevant at that time. However, the result of this process was a decision not to establish separate residue limits for transgenic herbicide-tolerant cultivars.

Although generally recognized as safe by regulators in the United States Food and Drug Administration [27], safety assessment of produce from transgenic cultivars is a contested issue in Europe [19] and numerous other countries world-wide. Safety assessment is mostly based on testing performed by industry companies or by researchers working for such companies. Complex legal and commercial aspects of patented biotechnology products restrict independent researcher access to both such transgenic material (patented property of industry) and to data from development and testing, which is regarded as intellectual property and thus confidential [28, 29].

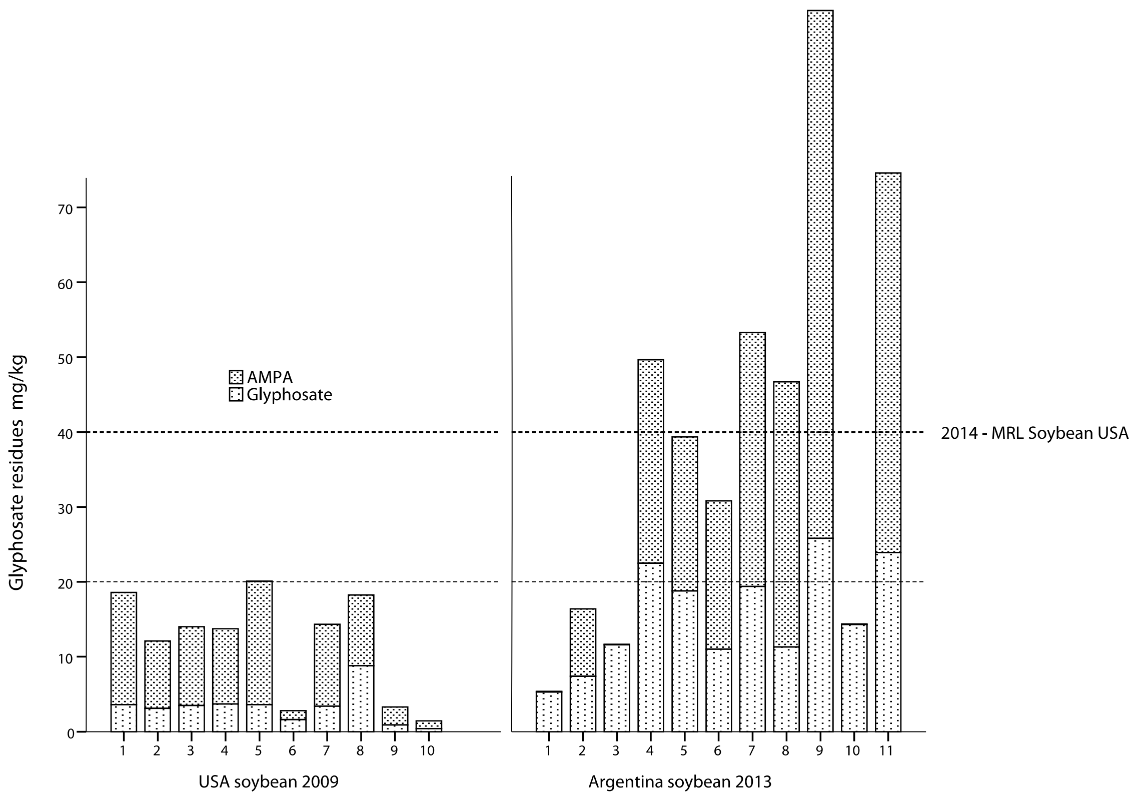

Figure 1. Recent data on glyphosate residues in glyphosate tolerant soybean. Data from analysis of samples from fields in Iowa, USA [30] and province of Salta, Argentina [90]. Residues are shown as detections of glyphosate and the primary metabolite, AMPA. Reference lines indicate maximum residue limit (MRL). Former European MRL of 0.1 mg/kg was raised 200-fold in 1999 to 20 mg/kg. US MRL at 20 mg/kg was raised to 40 mg/kg in 2014.

Review of published evidence

15 published reports from compositional analyses of plant material grown from glyphosate-tolerant cultivars and 15 published reports from tests of such material in animal-feeding-studies were extracted from peer-reviewed scientific journals (tables 1 & 2). The majority of these studies were designed and performed by researchers affiliated with biotech industry companies. These companies are also seen to have funded the research. Although the numbers are relatively low and not suited for statistical analysis, a graphic visualisation and percentual representation is appropriate.

Analyses of composition: Reviewing 15 publications on results from comparative analyses in which specific transgenic glyphosate-tolerant plant material was compared to near-isogenic unmodified material or other relevant conventional plant material, it was found that 14 of the 15 published analyses were industry studies (Table 1). Of these, only 7 (50%) reported to have applied glyphosate herbicide during cultivation. None of these 14 industry studies presented data from quantification of pesticide residues or gave indications that such analysis had been performed. Only the one independent study reported glyphosate residues [30] (Figure 1).

All 14 studies in which glyphosate had not been applied (the industry studies) found the various glyphosate-tolerant GM-crops (soybean, corn and canola) to be compositionally equivalent to non-modified comparators. The one study in which glyphosate had been applied found significant differences in composition of glyphosate-tolerant soybean compared to non-modified varieties of soybean [30](Table 1).

Animal feeding studies: Reviewing published reports from feeding-studies in which animals are fed feed from specific glyphosate-tolerant plant material and compared to animals fed near-isogenic unmodified material (or other relevant conventional produce), are also seen to lack information on herbicide-residues (Table 2). Through literature searches, 15 studies were identified. 6 of these studies were performed by researchers with industry affiliation. The remaining 9 studies were independent studies performed by researchers affiliated with government agencies, universities or other institutions recognized to be independent of the implicit financial issues associated with GM-crop commercialisation and production.

Of the 6 studies performed by industry, plant material for feed had been produced with application of glyphosate herbicide in 3 studies (50%). In the 9 independent studies, plant material for feed had been produced with application of glyphosate herbicide in 5 studies (56%).

3 of the 9 independent studies reported that pesticide analysis had been performed (33%). Of the 6 industry studies, only one (17%) reported that pesticide analysis had been performed [31](Table 2). However, although glyphosate herbicide was the only pesticide applied in the mentioned study, the subsequent analysis for pesticide residues included numerous chemical compounds known as active ingredients in various other commercial pesticide formulations. Paradoxically, the analysis did not include glyphosate or the main metabolite of this chemical. Due to those obvious shortcomings of the pesticide analysis in the mentioned study, it is concluded that none of the 6 industry studies include analyses for relevant pesticides (0%).

Based on data from test-animal performance and histology, 7 studies found that there were no significant effects from the GM-feed produced from glyphosate-tolerant plant material. These 7 studies consisted of one of the independent studies and all 6 industry studies. The remaining 8 independent studies found significant effects attributable to GM-feed produced from glyphosate-tolerant plant material (Table 2).

In the 8 studies reporting significant effects from GM-feed, 2 studies related these effects to residues of glyphosate. One of the studies found that test-animal fitness decreased in correlation with increasing levels of glyphosate residues [32].

Discussion

30 Published reports from studies of compostitional analysis glyphosate-tolerant GM-plant varieties and from feeding studies using glyphosate-tolerant GM-plant varieties have been reviewed. These studies were performed in the years 1996-2015. A simple synthesis of available information on study design, methods and results shows that:

- 14 of 15 studies on composition and 6 of 15 animal feeding studies were performed by biotech industry companies.
- 16 of 30 studies (53%), used material actually sprayed with glyphosate herbicide during cultivation.
- 4 of 30 studies (13%) address the issue of glyphosate residues. None of these 4 studies were funded by industry.

The findings of this review fundamentally challenge the basis for regulatory assumption of substantial equivalence between glyphosate-tolerant GM-varieties and unmodified comparators. The findings are a strong argument for mandatory inclusion of pesticide analysis data in regulatory assessment of GM-crop, notably in assessments of herbicide-tolerant crops. Two of the animal feeding studies performed by independent researchers [87, 88] used GM-crop material as well as unmodified comparators supplied by industry. No analysis was performed to control the compositional quality of this material.

The literature review indicates that there are relatively few studies available for regulatory evaluation of scientific evidence on herbicide-tolerant crop quality and safety. Furthermore, it is found that the majority of such studies are presented as reports from compositional analyses and animal feeding-studies, and predominantly performed either by biotech industry companies with potentially conflicting interests in research outcome or by subcontractors working for the biotech industry companies (Tables 1 & 2). Society should expect the biotech industry companies to continue to conduct such studies to peer-review standard and the industry should continue to bear associated costs. However, it is evident that appropriate revisions of standards are needed, and supplementary studies by independent researchers should be encouraged. Published evidence on safety testing presented by the industry has generally been recognized by EFSA as sufficient for regulatory purpose, despite the fact that several potentially conflicting issues have been continuously raised by independent researchers [19, 20, 28, 33, 34, 87]. Such critique has also questioned both the principle of delegated self-control and the validity of industry methods. Some of this critique has led to temporary adjustments of protocols and changes in methodology. A review by independent scientists in 1999 [33] examined results of three initial industry tests that were published in 1996. These first industry tests claimed substantial equivalence of transgenic glyphosate-tolerant GTS 40-3-2 soybean [34, 35] and seed from glyphosate-tolerant cotton [36]. However, the review noted that the industry reports were based on tests of glyphosate-tolerant material grown in artificial conditions without application of complimentary glyphosate herbicides. The GM-crop thus produced was claimed to be not representative of the crops actually produced in agriculture [33]. Several industry researchers immediately acknowledged the necessity to change these specific approaches and subsequent industry publications on quality of glyphosate-tolerant varieties of soy [37, 38, 39, 40], maize [41], alfalfa [42] and cotton [43] specified that normal cultivation practice had been used in production, including prescription rate application of glyphosate via commercial glyphosate herbicides such as Roundup. One paper published immediately following the 1999 criticism even specifies in its title that glyphosate herbicides have been applied [44]. Despite this change of practice and the acknowledged need for realistic field conditions to produce material for evaluation, numerous subsequent tests have been published where again produce of glyphosate-tolerant cultivars is used for comparison despite having been grown in artificial conditions without application of complimentary herbicides [34]. Recently10 studies presented by industry applicants as evidence for regulatory approval of glyphosate-tolerant cultivars were reviewed and the author concludes that lack of relevant herbicide application is still a discrediting flaw in such studies [34]. However, although this highlights one systematic flaw in studies currently accepted for regulatory purpose documentation, the role of herbicide-residues must be recognized as a subsequent and not least important aspect.

The relevance of testing for herbicide residues is highlighted by the findings of a recent study on the composition of plant-material [30] performed by independent researchers. The study reports high levels of glyphosate residues (Figure 1) in glyphosate-tolerant soybean (Roundup-ready soy GTS 40-3-2). The study also found that residues of glyphosate and the primary metabolite aminomethyphosphonic-acid (AMPA) are correlated to differences in crop composition. In 2003 and 2004 independent research demonstrated that residues of glyphosate herbicides will accumulate in glyphosate-tolerant plant material [45, 46] but showed lower quantities than the subsequent findings reported in 2014 [30]. Another recent report from tests performed in

Argentina by independent scientists working for the German NGO Test-Biotech have reported findings of even higher levels of glyphosate residues in harvests of glyphosate-tolerant soy, [65] (Figure 1). These results indicate very high glyphosate residue levels up to 100 mg/kg in soybean. The tests were performed at the University of Buenos Aires and although it is unclear whether this laboratory is formally accredited for the analytical methods used in quantification, the results stand as an important indication that justifies further sampling and analysis.

The results indicate a rise in glyphosate residue levels in recent decades. In 1999 a major producer of glyphosate and GM-crops declared that glyphosate residue levels of 5.6 mg/kg in glyphosate-tolerant soybean were considered to be extreme high values [30]. It seems apparent from figure 1 that such levels at present would be considered moderate or even low. To explain tendencies of rising residue levels it would be relevant to investigate actual application rates. Global production figures support the notion that very large quantities of glyphosate are being sold and dispersed.

It is interesting to note that several independent researchers have mentioned the specific question of glyphosate-residues in glyphosate-tolerant crops, demonstrating the need for more data to clarify this issue [45, 46, 61]. The question has also been addressed in a review of concepts and controversies in EFSA environmental risk assessment of GM-crops; it was found that also in the environmental context more data on glyphosate residues is needed, as post-harvest biomass is potentially affecting both soil and adjacent environments [19].

Studies of glyphosate-tolerant cultivar composition have identified differences in essential plant constituents, which have been attributed to *in-plantae* metabolic effects of glyphosate residues [47, 48, 49]. This research indicates, that glyphosate-residues have negative effects on composition. Contrary to this, a recent review by authors from the United States Department of Agriculture [50] conclude that there is not sufficient evidence for claiming that glyphosate in glyphosate-tolerant crops a) significantly affects mineral composition or b) changes rhizosphere microbial community or c) induces susceptibility to disease.

As a direct critique of the regulatory policies enforced of the European Food safety Authority EFSA, independent scientists have claimed that the present regime of industry self-control (autoregulation) is insufficient to provide necessary evidence and ensure the long-term interests of society. Industry studies therefore must be supplemented with additional, independent, research [19, 20]. This however is not a view shared by researchers representing interests of biotech companies, who often participate in systematic opposition to any results questioning industry-studies. It has been described as highly regrettable that independent scientific work is often attacked and discredited by concerted efforts of industry proponents and journal editors loyal to biotech sector interests [28]. A recent study [51] found clear evidence of double-standards in criteria for evaluation of safety-studies on GMO cultivars such as herbicide-resistant plants. The authors document that evidence confirming safety is not exposed to same the intensive scrutiny as evidence indicating possible harm. This is paradoxical, as it should be evident that faulty findings in the first of these categories has potential for inflicting negative effects on consumer health. Faulty findings in the second category will not have the same implications, but may lead to exaggerated precaution, which can be conflicting in relation to commercial interests.

Evidence has emerged during the compilation of this review, which to a certain degree confirms the claims of double-standards: One of the industry studies reviewed here serves as a noteworthy example of malpractice. The study [31] was published by journal Food and Chemical Toxicology. The scientists authoring the study were employees of commercial companies *Pioneer Hi-bred* and *DuPont*. They conducted a safety study on DP-356Ø43-5 glyphosate-tolerant soybean by testing cultivated material in a feeding-study using rats. According to the methods chapter of the study the tested DP-356Ø43-5 glyphosate-tolerant soybean was sprayed with glyphosate herbicide. Glyphosate herbicide was the only pesticide used in the strictly controlled production on parallel fields of; a) glyphosate-tolerant soy (sprayed) and b) unmodified soy (not sprayed). The irregular aspect relates to the fact that a wide array of subsequent tests for pesticides was performed on the produced soy materials, screening these for a variety of active ingredient chemicals. And, although glyphosate-herbicide was specified to be the only pesticide applied in the strictly controlled test-plot cultivation, an analysis for glyphosate residues was omitted. Instead the cultivated material was analysed for numerous herbicide ingredients that were fundamentally irrelevant. This published study should be seen as an example supporting the arguments demanding revision of the regulatory framework mandating self-control of biotech industry products. Furthermore, given the recent heightening of qualitative requirements for such studies, which in its utmost consequence is seen as retractions of publications, I nominate the mentioned study [31] as a prime candidate for editorial re-evaluation.

<u>Other reviews of published testing:</u>

Four recent reviews of produce from transgenic plants in agriculture [52, 53, 54, 55] present evidence confirming transgenic herbicide-tolerant cultivar equivalence, as compared to non-modified comparators. None of these reviews mention herbicide residues or their potentially conflicting nature in relation to concept of substantial equivalence. Contrary to this, three reviews by independent scientists approach the role of herbicide residues in transgenic cultivars or present indications of toxicity. In one of these [56] the authors review available safety assessment and speculate whether adverse effects reported in results of animal-testing published in 2002 [57], 2004 [58] and 2009 [59] could be attributable to pesticides contained in the tested transgenic material. Another recent review [60] concludes that parts of published evidence in assessments of health risks of GMO foods are indications of general toxicity.

The regulatory developments of standards for defining herbicide residues in herbicide resistant crops have been reviewed recently and important recommendations have been presented [61]. The recommendations include specific measures, such as the concept of *supervised field trials*, which is seen as important potential improvement of the current system of industry self-control and scientific autonomy.

<u>The future of herbicide-tolerant crops:</u>

Undoubtedly transgenic herbicide tolerant cultivars are popular amongst farmers in dominantly important agricultural sectors such as production of maize and soybean in countries of North- and South America. From a database listing transgenic crop varieties pending regulatory approval [62] it seems that a majority of these GM-crops are either herbicide tolerant varieties or varieties with stacked events which include herbicide tolerance.

Some new varieties have herbicide-tolerance traits which are selected from microorganisms systematically bred in environments with high glyphosate concentrations [63]. Traditional first-generation glyphosate-tolerant crops, such as the

GTS-40-3-2 soybean which still dominates global production, are only 45-50 times more tolerant than unmodified varieties (the glyphosate dose inducing LC_{50}-outcome in GTS-40-3-2 is about 50x that of unmodified soy).

By using new sources of transgenes and gene-stacks with combinations of several transgenes conveying multi-pathway tolerance to specific active ingredients, second-generation cultivars are seen as having significantly improved tolerance to specific herbicides or combinations of herbicides. This development should be seen primarily as a method allowing for increased herbicide application. It seems that in the on-going struggle to eradicate resistant weeds, the agriculture environments rely heavily on solutions offered by commercial producers of herbicides. A main strategy seems to be developments that allow for higher dosage of herbicides such as glyphosate.

It is recommended that such developments should be met by regulatory initiative to ensure necessary oversight of secondary consequences, such as compositional changes. These potential changes must be monitored in analysis of representative material, which can be taken as samples from the actual agro-ecological production systems.

The present maximal residue limits (MRLs) allow for relative high concentrations of herbicide residues. In Brazil in 2004 the MRL in soybean was increased from 0.2 mg/kg to 10 mg/kg: a 50-fold increase, but only for glyphosate tolerant soy [64]. In Europe, the MRL for glyphosate in soybean was raised by a factor 200 from 0.1 mg/kg to 20 mg/kg in 1999 [66] and the same MRL of 20 mg/kg was adopted by the US based on recommendations of the Codex Alimentarius Commission. In 2013 the MRL tolerance levels for glyphosate residues in US soybean were raised from 20 mg/kg to 40 mg/kg (Figure 1). The increases coincide with industry development of new transgenic varieties with stronger tolerance to glyphosate. In these cases the MRL values appear to have been adjusted in response to actual observed, or expected, increases in the content of residues in glyphosate-tolerant soybeans. In this context it would be appropriate to collect and review more of the existing data on glyphosate residues in glyphosate-tolerant crops. However relevant such a question may be, it cannot be satisfactorily answered here due to the fact that only sparse published information exists on this issue.

Despite the limited number of analyses for glyphosate residues in glyphosate tolerant crops, the few tests reported [30, 90] indicate surprisingly high levels of glyphosate residues. Such findings fundamentally challenge regulatory assumption of substantial equivalence between glyphosate-tolerant varieties and their unmodified comparators.

Substantial equivalence:

The principle of substantial equivalence is fundamental for assessment of genetically modified plants, so some explanation is justified here. Substantial equivalence is a concept developed by OECD in 1991-93 [23], establishing that a novel food, for example, one derived from genetic modification or engineering, should be considered the same as and as safe as a conventional food, if it demonstrates the same characteristics and composition as the conventional food [67]. In 1997, the European Commission regulated its policy on novel foods (from transgenic plants) stating that food and feed from such plants are expected not to "present a danger for the consumer", or "mislead the consumer", or "differ from foods or food ingredients which they are intended to replace to such an extent that their normal consumption would be nutritionally disadvantageous for the consumer" [68] The regulation goes on to state that "[this policy...] shall apply to foods or food ingredients [...] which, on the basis of the scientific evidence available [...] are substantially equivalent to existing foods or food ingredients as regards their composition, nutritional value, metabolism, intended use and the level of undesirable substances contained therein" [68]. This allows a discussion on the qualitative evaluation of substances which vary from benign to harmful. It seems evident that pesticide residues belong in the category "undesirable substances".

Post-market monitoring:

European Union legislation [69] specifies framework for post-market monitoring of transgenic produce, to ensure traceability of individual feed-lots entering the European common market. This is important, as only such traceability through proper labelling will ensure that possible adverse effects from specific harvests or specific batches of feed can be identified. At present the USA, which is the largest market for transgenic consumer products entering food for human consumption, has a lack of such traceability. In the USA, this situation has been established through commercial and political influence. Contrary to this, European legislation accommodates traceability of feed for industrial scale production of farmed animals. Such as pigs, poultry and cattle.

This traceability however, is not enforced at present. It has been claimed that such a deductive approach to material quality would be unfeasible [22]. Contrary to this it can be argued, that labelling and traceability should be used systematically in enforced post-market monitoring. Especially as this systematic approach allows for efficient identification of possible adverse effects from novel feed ingredients following large-scale introduction. In guidance documents for risk-assessment of food and feed from transgenic plants, EFSA has specifically stated the need for post market monitoring of "undesirable substances" [70]. This is a clearly defined regulatory intension. Based on the findings on potentially high residue levels reported here, it is recommended that EFSA gives priority to implementation of the existing regulation.

Conclusion

Of 30 reviewed studies on composition and feed-quality of glyphosate-tolerant GM-crop material, only half of the studies use material produced with application of glyphosate herbicide. Only one of the 30 studies has analysed the material for glyphosate residues.

Application of representative dosage of herbicides as well as subsequent analysis of herbicide residues is missing in industry testing of glyphosate-tolerant GM-crops. This implies that central data from compositional analysis, animal feeding studies and overall risk-assessment performed by industry and submitted to national and international regulatory bodies as evidence as safety, is not representative of the materials actually delivered onto the commercial market. In part the scientific evidence produced by industry is found to have unacceptable standard for regulatory purpose. Such evidence should be disregarded and demands for new evidence should be brought forward.

Published data on glyphosate residues in glyphosate-tolerant crops are sparse. The findings presented here suggest that this could be an issue with important implications.

Scientific evidence produced by biotech-industry companies should be supplemented with data from independent research. Alternatively, the risk-assessments and analyses performed by industry should be competently supervised to ensure transparency and an overall satisfactory standard of testing.

This leads to a recommendation to regulatory authorities such as the European Food Safety Authority (EFSA) and the Organisation for Economic Cooperation and Development (OECD) to apply necessary measures and enforce routines.

Regular revision of regulatory framework, routines and operating procedures is needed to secure future quality of important food and feed material. Such action is fundamental for safeguarding coherence, relevance and public trust.

Competing interest: The author declares that he has no competing interests.

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Reference	Year published	Author	Author affiliation	Crop studied	Subject	Main finding	Relevant co-technology	Relevant analysis for herbicide residues
[35]	1996	Padgette *et al*.	Industry	GTS 40-3-2 soybean	Compositional analysis	Substantial equivalence assumed	Glyphosate herbicide not applied	Not relevant
[36]	1996	Nida et al.	Industry	GT-cotton	Compositional analysis	Substantial equivalence assumed	Glyphosate herbicide not applied	Not relevant
[44]	1999	Taylor *et al*.	Industry	GTS 40-3-2 soybean	Compositional analysis	Substantial equivalence assumed	Glyphosate herbicide applied at prescribed rate	No analysis
[71]	2000	Sidhu *et al*.	Industry	GT-corn	Compositional analysis	Substantial equivalence assumed	Unclear	No analysis
[43]	2002	Ridley *et al*.	Industry	GT-maize NK603	Compositional analysis	Substantial equivalence assumed	Glyphosate herbicide applied at prescribed rate	No analysis
[72]	2004	Sidhu *et al*.	Industry	GT-corn	Compositional analysis	Substantial equivalence assumed	Unclear	No analysis
[73]	2004	Obert *et al*.	Industry	GT-wheat MON71800	Compositional analysis	Substantial equivalence assumed	Glyphosate herbicide not applied	Not relevant
[40]	2005	McCann *et al*.	Industry	GTS 40-3-2 soybean	Compositional analysis	Substantial equivalence assumed	Glyphosate herbicide applied at prescribed rate	No analysis
[42]	2006	McCann *et al*.	Industry	GT-alfalfa	Compositional analysis	Substantial equivalence assumed	Glyphosate herbicide applied at prescribed rate	No analysis
[38]	2007	Harrigan et al	Industry	GTS 40-3-2 soybean	Compositional analysis	Substantial equivalence assumed	Glyphosate herbicide applied at prescribed rate	No analysis
[41]	2007	McCann *et al*.	Industry	GT-corn MON88017	Compositional analysis	Substantial equivalence assumed	Unclear	No analysis
[39]	2008	Lundry *et al*.	Industry	GT-soybean MON89788	Compositional analysis	Substantial equivalence assumed	Glyphosate herbicide applied at prescribed rate	No analysis
[74]	2010	Berman *et al*.	Industry	GT-soybean MON89788	Compositional analysis	Substantial equivalence assumed	Glyphosate herbicide not applied	No analysis
[30]	2014	Bøhn et al.	Public (university)	GTS 40-3-2 soybean	Compositional analysis	Significant differences found	Material from farm-fields: Glyphosate herbicides applied at realistic representative rate	Pesticiode analysis performed and reported
[75]	2014	Delaney *et al*.	Industry	GT-canola DP-Ø73496-4	Compositional analysis	Substantial equivalence assumed	Glyphosate herbicide applied at prescribed rate	No analysis

Table 1. **Compositional analysis.** 15 Published studies comparing compositional quality of transgenic glyphosate-tolerant crop varieties with unmodified conventional comparators.

Reference	Year published	Author	Author affiliation	Crop studied	Subject	Main finding	Relevant co-technology	Relevant analysis for herbicide residues
[34]	1996	Hammond *et al.*	Industry	GTS 40-3-2 soybean	Feeding study in rat, chicken, catfish and cattle	No significant effects found. Equivalence assumed	Glyphosate herbicide not applied	Not relevant
[37]	2002	Cromwell *et al.*	Industry	GTS 40-3-2 soybean	Feeding study in swine	No significant effects found. Equivalence assumed	Glyphosate herbicide applied at prescribed rate	No analysis
[76]	2004	Brake *et al.*	Public (university)	GTS 40-3-2 soybean	Feeding study in mouse	No significant effects found. Equivalence assumed	Glyphosate herbicide applied at prescribed rate	No analysis
[77]	2004	Zhu et al.	Public (university)	GTS 40-3-2 soybean	Feeding study in rat	Reduced feeding and weight gain significant in young rat treatment group. Not significant in adult rat	Unclear	No analysis
[84]	2007	Taylor *et al.*	Industry	GT-soy MON 89788	Feeding study in broiler	No significant effects found. Equivalence assumed	Unclear	No analysis
[88]	2007	Bakke-McKellet *et al.*	Public (university)	GTS 40-3-2 soybean	Feeding study in salmon	Significant effects found	Unclear	No analysis
[31]	2008	Appenzeller *et al.*	Industry	GT-soy DP-356Ø43-5	Feeding study in rat	No significant effects found. Equivalence assumed	Glyphosate herbicide applied at prescribed rate	Irrelevant analysis presented
[78]	2008	Healy *et al.*	Industry	GT-maize MON88017	Feeding study in rat	No significant effects found. Equivalence assumed	Glyphosate herbicide applied at prescribed rate	Pesticiode analysis performed and reported
[79, 80]	2008	Malatesta *et al.*	University	GTS 40-3-2 soybean	Feeding study in mouse	Significant effects found	Unclear	No analysis
[89]	2009	Sissener *et al.*	Public (university)	GTS 40-3-2 soybean	Life-long feeding in salmon	Significant effects found	Unclear	No analysis
[81]	2012	Seralini *et al.*	Public (university)	GT-maize NK603	Life-long feeding study in rat	Significant effects found	Glyphosate herbicide applied at prescribed rate	No analysis
[82]	2013	Carman *et al.*	Public	Mixed diets with NK603 GT-maize	Long-term study in pig	Significant effects found	Material from farm-fields: Glyphosate herbicides applied at realistic representative rate	No analysis
[83]	2014	Cuhra *et al.*	Public (university)	GTS 40-3-2 soybean	Life-long feeding study in crustacean *D. magna*	Significant effects found	Material from farm-fields: Glyphosate herbicides applied at realistic representative rate	Pesticiode analysis performed and reported
[75]	2014	Delaney *et al.*	Industry	HT-canola DP-Ø73496-4	Rodent	No significant effects found. Equivalence assumed	Unclear	No analysis
[32]	2015	Cuhra *et al.*	Public (university)	GTS 40-3-2 soybean	Life-long feeding study in crustacean *D. magna*	Significant effects found	Material from farm-fields: Glyphosate herbicides applied at realistic representative rate	Pesticiode analysis performed and reported

Table 2. **Animal feeding studies.** 15 Published studies comparing transgenic glyphosate-tolerant crop varieties with unmodified conventional comparators as feed in animal feeding studies.

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