GlobalResearch
Center for Research on Globalization

The Toxicity of Monsanto's Glyphosate Roundup Herbicide

By Corporate Europe Observatory
Global Research, December 06, 2015
Corporate Europe Observatory 25 November 2015

Region: Europe
Theme: Biotechnology and GMO, Science and Medicine

Monsanto and the pesticide industry breathed a collective sigh of relief on 12 November 2015. The findings of an investigation into the toxicity of glyphosate by the European Food Safety Authority (EFSA) and EU Member States were in stark contradiction to the March 2015 conclusion by the International Agency for Research against Cancer (IARC), a body of the World Health Organization (WHO), that this agricultural herbicide was probably causing cancer to humans. If validated, this conclusion could cause a partial ban of glyphosate in the EU. [UPDATED on 30 11 2015 16.30 CET]

This article takes a closer look at the arguments from both parties, and reveals two strikingly different processes that led to these conflicting assessments. In short, the WHO process was transparent, stuck to conventional scientific methodology and looked at glyphosate-containing herbicides (as glyphosate is never used alone in the real world), whereas EFSA's route was based on a 'peer review' by anonymous EFSA and national public officials relying on undisclosed industry-sponsored studies that looked at glyphosate alone. The European Commission, which will have the last say on whether or not glyphosate will be re-authorized in the EU, and under which conditions, must now decide what to make of this interesting piece of 'science'.

On 12 November 2015, following a long saga (see our previous article), unnamed officials from EFSA and experts from EU Member States published the outcome of their joint re-assessment of the toxicity of glyphosate, the most widely used herbicide in the world. More commonly known as 'Roundup', which is the original Monsanto trade name, it is applied to more than 150 food and non-food crops 1 and is used by millions of home-owners, businesses and public authorities to keep lawns, gardens, buildings and other land free of weeds. Glyphosate is also a cornerstone of GM crop cultivation. According to GMproponents, 57 per cent of all genetically modified crops grown commercially around the world in 2013 were herbicide tolerant, and the vast majority of these were engineered to tolerate glyphosate-based herbicides. This simplifies their cultivation in large-scale, socially and environmentally harmful monocultureplantations, also known as 'green deserts'.2

Following a peer review of available data, these anonymous officials issued several conclusions about the toxicity of glyphosate. Two of the most important outcomes were:

– Glyphosate was deemed "unlikely" to cause cancer in humans;

– It was suggested that the legally permissible exposure levels of EU consumers to glyphosate be increased by 66 per cent.[3] [4]

The first conclusion was anxiously anticipated in the pesticides world, and was met with relief by industry. “Science wins!!” exulted Monsanto’s Chief Technology Officer Robb Fraley. With this assessment, EFSA had reached a verdict opposite to that of the panel of scientists convened by the WHO’s International Agency for Research against Cancer (IARC). These expertsdetermined in March 2015 that glyphosate was “probably carcinogenic to humans”[5] after having found “limited evidence” of cancer in people and “sufficient evidence” in experimental animals. The complete Monograph waspublished by the IARC in July 2015.

This conclusion was not in itself a death sentence for glyphosate: the IARC’s conclusion is a hazard characterisation, most studies documenting harm were based on high doses and in the EU it is up to the European Commission to regulate glyphosate[6]. However, the EU pesticides legislation foresees that pesticides that are linked to “presumed human carcinogenicity” based on “sufficient evidence” in animals must be banned[7]. Since what the IARC found was precisely such sufficient evidence, industry reacted with fury to the threat. The business model of Monsanto, in particular, is still heavily dependent on sales of glyphosate-based Roundup and crops genetically engineered to resist this weed killer. The company publicly demanded the retraction of what they termed “junk science” and lobbied WHO director Margaret Chan to “rectify” the conclusions of the report.

Interpretations

The WHO organized a task force over the summer of 2015 to compare IARC’sfindings with those of another WHO body that had come to opposite conclusions in 2004 and 2011. This body, the Joint FAO/WHO Meetings on Pesticide Residues, was asked by the task force to perform a “full re-evaluation of glyphosate” and to review its “internal guidelines to consolidate the criteria for data inclusion/exclusion with respect to published and/or proprietary data sources”. IARC conclusions were left untouched.

Subsequently, Germany’s national risk assessment agency (BfR), the lead agency in the EU assessment process, scrutinized[8] the published IARC Monograph in considerable detail and agreed[9] that the IARC classification of the available data as “limited evidence in humans for the carcinogenicity of glyphosate” was adequate.

But BfR adopted a “more cautious view” than IARC in the interpretation of the human evidence, arguing that the IARC review had found “no consistent positive association” documenting human exposure to glyphosate, and that it was not possible to “differentiate between the effects of glyphosate and the co-formulants” in most of the studies at stake.

When it came to the animal evidence, BfR squarely dismissed IARC’s interpretation: “The weight of evidence suggests that there is no carcinogenic risk related to the intended herbicidal uses and, in addition no hazard classification for carcinogenicity is warranted for glyphosate according to the CLP [EU] criteria.”

Differences in interpretation are the daily bread of scientists, but one Member State in particular was caught off guard by BfR’s agreeing with IARC’s classification but coming to such a different overall conclusion. An anonymous Swedish official noted in his country’s official comments[10] that “the IARC conclusion is admittedly precautionary but still feasible”

as far as evidence in humans was concerned. He also defended the IARC's choice of statistical tests for measuring the evidence in animals as "more sensitive", and criticized the use of historical data to balance the control groups in the experiments: "We don't believe that reference to historical control data can abrogate the positive results from the trend tests."

But within the EU, Sweden was more or less alone on this one. Although Norway also voiced strong criticism of BfR's statistical treatment of animal evidence, it is not an EU country. All other Member States followed the BfR judgment, with Belgium agreeing[11] with Germany's (reported) description of the IARC classification choices as "merely driven by the precautionary principle". France was also in complete agreement with BfR, and surprisingly concise in its reaction[12], praising the "huge work provided by Germany on the IARC conclusions". Denmark, the UK and Spain were also unified in their acquiescence. Ireland asked why the two statistical approaches yielded such different results but did not oppose BfR's.

EFSA took note of the quasi-unanimity around Germany and, while acknowledging the consensus on the appropriateness of the IARC classification, embraced the general opinion on the statistical flaws in IARC's data on animal carcinogenicity. IARC's conclusion that glyphosate "probably" caused cancer in humans thus became an "unlikely" in the EU review's final conclusions (although Sweden and Norway insisted on their dissenting minority opinion). Both terms refer to a probability, but from an opposite viewpoint. How could the perspectives of IARC scientists and EFSA and EU Member States officials have come to differ so widely?

As EFSA was requested by the European Commission to include the IARC findings in its review, the EFSA officials who published the peer review provided some explanation.

'Pure' glyphosate vs. real-world formulations

First of all, EFSA officials explained that the two reviews used different sets of data. As glyphosate is almost never used alone in the real world but in hundreds of different combinations, IARC scientists had reviewed several studies assessing glyphosate formulations.[13] These studies of real-world exposures – to agricultural and forestry workers, and to community residents – were obviously essential in their assessment although IARC also reached its conclusions based on laboratory studies of pure glyphosate alone, concluding "sufficient" evidence of cancer in animals and "strong" evidence of genotoxicity.

EFSA and national officials, on the other hand, had a narrower mandate. They were confined to EU pesticide legislation, in which only the declared "active substance" of the pesticide is considered, whereas the assessment of the toxicity of formulations is left to Member States. So EFSA and Member States barely acknowledged IARC's real-world exposure studies as the products at stake were not pure glyphosate.

This separate assessment in the EU regulation of the different compounds in pesticides is reductionist, and is a fundamental problem. In fact, the final product combines these different compounds to obtain a synergistic effect (greater than the sum of its parts), and as a consequence the health impact of commercial formulations escape assessment at the EU level. For example, Germany had earlier banned a common Roundup adjuvant known as POEA,explaining: "There is convincing evidence that the measured toxicity of some glyphosate containing herbicides is the result of the co-formulants in the plant protection

products (e.g., tallowamines used as surfactants)" and concluding[14]that "Member States are encouraged to consider the substitution of alkylamine ethoxylates (POEA) in plant protection products with less toxic surfactants." However, no other Member State has yet followed suit: EFSA was mandated by the Commission to look at POEA, but called for more research to be done before it could issue any recommendation.

To their credit, our anonymous experts "recognized that the issue of toxicity of the formulations should be considered further as some published genotoxicity studies[15] … on formulations presented positive results in vitro and in vivo." In particular, they noted[16] that "other endpoints should be clarified, such as long-term toxicity and carcinogenicity, reproductive/developmental toxicity and endocrine disrupting potential of formulations."

Acknowledging such an enormous data gap means that the safety of existing glyphosate formulations used in Europe is in doubt. Indirectly, it is also a damning indication that existing EU regulations are not fit for purpose, and that Member States are not doing their jobs.

Secret data

The second reason provided by the public officials to defend the superiority of their conclusion over that of IARC's scientists was that their assessment included more data. Indeed, IARC had no access to confidential industry studies, but rather only to summaries that were missing important information. And in particular, they were not privy to five mouse studies carried out by industry.[17]

This is very unfortunate, because José Tarazona, head of EFSA's Pesticides Unit, called these studies "key" and "pivotal" during the agency's press briefing on the matter. Kathryn Guyton, the Senior Toxicologist at the IARC Monographs Programme who followed the file at IARC, said that what was particularly interesting about the two mouse studies IARC looked at was that they showed a statistically significant correlation between exposure to glyphosate and the occurrence of a very rare type of tumour.[18] Apparently, a correlation with rare tumours also appeared in the three studies that only EFSA had been able to review in detail. As these studies were not however available for independent scientific review, Guyton could not explain how EFSA had reached a conclusion so divergent from that of IARC after having looked at them. In its comments, Belgium insisted[19] that "it was unfortunate that IARC did not take into account 3 guideline studies in both mice and rats, since this could have put the overall conclusions in another perspective". This sentiment was echoed by Ireland: "IARC's failure [sic] to evaluate the 3 other studies is not helpful."

This is in fact a second, fundamental problem with the EU's pesticides regulation (and practically all regulated economic sectors in the EU): the studies used by EFSA and Member States to assess the risk of regulated products such as pesticides' active substances are paid for and provided by their producers. But most are only accessible to regulators, and not to the scientific community or the public, because according to industry they contain trade secrets and could be used by competitors to obtain market authorization elsewhere.[20]

There are some non-industry-sponsored studies on common active substances such as glyphosate that allow EU and national regulators to double-check the information (or absence thereof) submitted by producers.[21] However, there are very few independent studies on existing formulations, such as those used by IARC, in the public scientific literature. The ability of Member States to systematically assess the formulations used in the

EU is therefore limited, as they would need to finance studies assessing each commercial formulation independently of its producers. This simply does not happen.

As a result, information about the toxicity of glyphosate formulations used in the real world is not available to the public. Industry probably knows more than anyone else, but rarely publishes detrimental findings.

Anonymous authors vs. reproducible process

Other factors, in this case unreported by EFSA, might also have played a role. Throughout the process, whether at BfR or EFSA, the risk assessment process has been anonymous. Bfr did not disclose the authors of its original report, although there are pesticide (including glyphosate) producers on its panel. Furthermore, the agency revealed that the number of studies sent to them by glyphosate producers was so huge that they simply used summaries provided by the producers, adding comments where appropriate.

Similarly, EFSA did not give the work to its pesticides scientific panel, which consists of external scientists who contribute to the agency's work, but to officials in its Pesticides Unit. The same anonymizing treatment was applied to all officials representing EU Member States who participated in the peer review. This was justified as follows22: "As an EU organization, EFSA has an obligation to protect the personal data of its employees, [and] also to avoid undue influence". This secrecy is understandable during the process, but less so once the study has been published – many comparable regulatory agencies such as the Environmental Protection Agency, in charge of pesticides evaluation in the USA, do publish such names. Nonetheless, EFSA refused to disclose the names of its officials and those from the Member States (the name of one national expert appears by mistake in the document).

In contrast with EFSA's 'peer review' process of relying on anonymous officials based on undisclosed studies for key decisions, IARC's process is completely transparent and reproducible. "We only use publicly available data," explained Guyton. "This is the cornerstone of the Monographs scientific procedures." This open process makes it possible to access and review all of the original scientific studies, thus ensuring post-publication review that the evidence and conclusions are scientifically valid. In addition, IARC's panel was composed of "world leading experts" according to Guyton, carefully screened for possible conflicts of interest by IARC staff, with declarations of interest disclosed two months ahead of the meetings for public scrutiny.

"We take our independence very seriously," said Guyton. "Everybody can know who was in the room all along the process. Under no circumstances could scientists with any perceived conflicts of interest draft Monograph text." For example, one scientist attending the group's meetings, C. Portier, could not be appointed on the panel due to his part-time employment by the US NGO Environmental Defense Fund. Nonetheless, as his expertise was deemed important to the assessment, he attended as an 'Invited Specialist'. This is a category created by IARC to enable scientists with interests conflicting with those of the agency to participate in meetings but not to write monographs or contribute to evaluation decisions.23

"What we did was very rigorous," Guyton continued, adding that this strict independence policy combined with the use of solely publicly available evidence guaranteed the agency's reputation. "All scientists can replicate our results." Questioned about the lobbying they had to face from industry, Guyton said: "The pesticides industry is very concentrated, and on this file we were dealing with one manufacturer in particular that has an history of getting

involved in scientific processes. However, they could follow the entire process as observers so they always knew what was happening."[24]

And now?

What can we make of these two divergent processes? Which body's assessment of the safety of glyphosate is correct? One obvious way to progress would be to publish the three famous confidential studies and agree on their statistical treatment, but this looks far from straightforward.

EFSA confirmed that they would not publish the raw data of these studies, asserting that what they have already published is comparable to the "amount of information contained within articles published in the open scientific literature". However, accessing the raw data would be the only way to double-check how these studies' findings were obtained; the expert NGO Pesticides Action Network Europe has been fighting in courts for years trying to obtain this very data on glyphosate and so far companies have always refused to disclose it and let independent scrutiny on their data take place.

Regarding the statistical methodology, IARC scientists have strongly critiqued the peer review carried out by EFSA and Member States, saying[25] they are "astonished" by BfR's treatment of IARC's statistical interpretation of animal data. Greenpeace Europe and PAN Europe accused the EU and national public officials of using flawed historical control data to dismiss the significant evidence observed by IARC (and later by BfR itself). EFSA has defended its use of historical control data, asserting that it was selected according to valid guidelines. Which, in turn, is strongly contested by IARC scientists.

[30 NOVEMBER UPDATE] An open letter signed by 96 scientists including nine of the IARC authors, all specialised in relevant disciplines (cancer research, epidemiology, toxicology, occupational health…) was sent on November 30 2015 to the European Commission and EFSA urging them to consider the differences in IARC and BfR conclusions. The scientists, presenting themselves as having "dedicated [their] professional lives to understanding the role of environmental hazards on cancer risks and human health", argue that "the BfR decision is not credible because it is not supported by the evidence and it was not reached in an open and transparent manner" and call the European Commission to "disregard the flawed EFSA finding on glyphosate in your formulation of glyphosate health and environmental policy for Europe and to call for a transparent, open and credible review of the scientific literature." The tone of the letter is very angry and they list several reasons to complain about the EFSA/BfR process:

– "the arguments promoted by the BfR to negate the human, animal
and mechanistic evidence are fundamentally and scientifically flawed and should be rejected."

– "We strongly object to the almost non-existent weight given to studies from the literature by the BfR and the strong reliance on non-publicly available data in a limited set of assays that define the minimum data necessary for the approval of a pesticide." [/30 NOVEMBER UPDATE]

A story of two processes

A hopefully swift resolution of this dispute is pending, but is it really about science in the

end? It is striking that the argument revolves so much around the interpretation of legal texts (OECD guidelines etc) for the inclusion/exclusion of data and so little about the real-world dimension of the problem and the actual experiments. In any case, comparing the integrity of the two processes is sobering. IARC strictly adhered to conventional scientific methodology (with reproducible results), while our European anonymous public officials did not. From that perspective, the Monsanto's Chief Technology Officer's exclamation that "science wins" means that the company's position did indeed prevail in this battle, but it really does not say much about the quality of the science at stake.

The obvious conclusion is that the EU's pesticides risk assessment system sorely needs reform. While glyphosate is the most frequently used herbicide in Europe, "there is little information available on occupational or community exposure to glyphosate," according to IARC. Asked whether IARC had taken into account a small study commissioned by the NGO Friends of the Earth Europe on the presence of glyphosate in people's urine across Europe, Guyton commented: "that study was half the data we had! We don't know the levels, we don't know the frequency. … Basically, we don't have any information." Ultimately, this means that the largest economic entity on the planet, the European Union, does not monitor its own population's exposure to the top herbicide used in its territory.

Glyphosate has been a commercial blockbuster since its entry on the market. This is because it combines formidable efficacy with toxicity levels that are, as far as known, comparatively lower than those of other broad spectrum herbicides. However, the monoculture agronomic model facilitated by glyphosate is disastrous for the preservation of biodiversity and soils. Also entrenched in this industrialized, large-scale model is the destruction of rural communities.[26]

In conclusion, we offer one remark and two questions. Germany's recommendation to increase EU consumers' legal exposure levels by 66 per cent – supported by EFSA – has hardly been discussed (not just in this article, but anywhere). This is surprising, and EFSA has already announced that it is going to revise approved residue levels in 2016. Secondly, the never-asked question that lurks in the shadows of this process: can the EU really execute its own pesticide policy and ban glyphosate if the law demands so; or is TTIP throwing a spanner in the works again, since glyphosate is of too great strategic importance to US interests (ie GM crop exports)? Finally, if the EU doesn't want to implement a ban, can it afford to acknowledge that IARC might be right?

At any rate, having independent scientists whose work and background can be checked rather than anonymous officials and confidential references in charge of this evaluation would have increased trust in the outcome of the entire exercise.

Picture: "Herbicide Path", by Angus Wilson (Creative Commons – CC BY-NC-ND 2.0)

Notes

1. The producers asked for the following uses: "herbicide on emerged annual, perennial and biennial weeds in all crops [crops including but not restricted to root and tuber vegetables, bulb vegetables, stem vegetables, field vegetables (fruiting vegetables, brassica vegetables, leaf vegetables and fresh herbs, legume vegetables), pulses, oil seeds, potatoes, cereals, and sugar- and fodder beet; orchard crops and vine, before planting fruit crops, ornamentals, trees, nursery plants etc.] and foliar spraying for desiccation in cereals and oilseeds (pre-harvest)."
2. The glyphosate tolerance genes inserted in these plants have now spread to a large number of

weeds, making the use of glyphosate less and sometimes not at all effective. To fight this, the biotech industry is now selling (or planning to sell) GM crops tolerating several herbicides at the same time. However, these herbicides, which include glufosinate, 2,4 D, and dicamba, are more toxic to humans than glyphosate.

3. The Acceptable Daily Intake (ADI) was increased from 0.3 to 0.5mg/kg of body weight.

4. This has been proposed by Germany's national agency BfR. (The EU's Pesticides Regulation foresees that Member State do the first examination of a pesticide and that EFSA then does a peer review of this opinion together with all other Member States).

5. The second category (2A) in IARC classification, seehttp://monographs.iarc.fr/ENG/Classification/

6. CEO is currently supporting an EU-wide petition to the European Commission demanding that glyphosate is banned, seehttps://act.wemove.eu/campaigns/stop-glyphosate

7. Specifically, the regulation says: "classification in Category 1A and 1B is based on strength of evidence […] [which] may be derived from human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen); or animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity (presumed human carcinogen). In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals." Regulations (EC) No 1107/2009 on Pesticides and (EC) No 1272/2008 on Classification, Labelling and Packaging (CLP), p. 104.

8. Addendum 1 to the RAR Assessment of IARC Monographs, Final addendum to the Renewal Assessment Report (public version), Risk assessment provided by the rapporteur Member State Germany and co-rapporteur Member State Slovakia for the active substance GLYPHOSATE according to the procedure for the renewal of the inclusion of a second group of active substances in Annex I to Council Directive 91/414/EEC laid down in Commission Regulation (EU) No. 1141/2010, October 2015, p. 4156.

9. Ibid, p. 4244

10. Comments of Sweden on the addendum of September 2015 for glyphosate, European Food Safety Authority, Peer Review Report on Glyphosate, October 2015, p.887

11. Peer review report, p.870

12. The country banned glyphosate from garden centers and could have been expected to defend interpretations supporting this decision

13. With adjuvants (substances that change/increase the effect of glyphosate).

14. Glyphosate Addendum 1 to RAR Part Ecotoxicology, Final addendum to the Renewal Assessment Report (public version), Risk assessment provided by the rapporteur Member State Germany and co-rapporteur Member State Slovakia for the active substance GLYPHOSATE according to the procedure for the renewal of the inclusion of a second group of active substances in Annex I to Council Directive 91/414/EEC laid down in Commission Regulation (EU) No. 1141/2010, October 2015, p. 4316.

15. "(Not according to GLP or to OECD guidelines)"

16. EFSA, 2015. Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate. EFSA Journal 2015;13(11):4302, 107 pp. doi:10.2903/j.efsa.2015.4302, p. 11.

17. Two were however included in their evaluation because public, final peer reviews of the data by the US government and the World Health Organization was available.

18. Phone interview with CEO, 19 November 2015.

19. Peer review report, p. 870

20. This problem exists in all regions of the world, and the very high entry cost on the market created by this situation protects large companies against competition: the market is concentrating rapidly, with the 10 largest pesticide producers controlling 94.5 per cent of the global market.

21. Provided of course they actually try to find it: EFSA has to include all available independent information in its work but often fails to do so.
22. Email correspondence with CEO, 17 November 2015
23. In our 2013 “Unhappy Meal” report documenting large numbers of conflicts of interests among EFSA experts, CEO actually recommended that EFSA adopt this approach in order to improve the agency’s independence without cutting it off from the expertise it needs. For more details on IARC’s “Invited Specialist” status, seehttp://monographs.iarc.fr/ENG/Preamble/currenta5participants0706.php
24. Among the observers to IARC meetings were T. Sorahan, a Monsanto employee, and C. Strupp, an employee of the pesticides manufacturer Adama representing the EU pesticides lobby ECPA, seehttp://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045(15)70134-8.pdf
25. Correspondence between CEO and C. Portier, 24 November 2015
26. This is starting to be acknowledged: in the Ecotoxicology section of its review of the IARC findings, BfR re-stated that such broad-spectrum herbicides cause considerable disruption in entire ecosystems: “In addition to the evaluation of the information from the IARC monograph, [Germany] reiterates in this addendum the knowledge regarding the effects of glyphosate and other broad spectrum herbicides on the populations of non-target species (especially insects and farmland birds), caused by an alteration of the food web.”

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