Editorial

Conflicting views on the potential carcinogenicity of glyphosate: how did we get here and what should we do?

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The advent of the internet and the information age has allowed the public to become keenly aware of the perceived dangers to health from polluted air and water, pesticide residues in foods, and global warming. Much of the available information on the worldwide web is not vetted, resulting in opinions that are based on anecdotal, emotional and alarming misinformation that runs counter to well-established, science-based medical knowledge. If the ensuing sense of trepidation in the public goes unchecked in social media, it provides the impetus for misguided social activism such as the anti-vaccine movement (due to fears of autism) or the notion that wearing a brassiere or using an underarm antiperspirant contributes to a woman's risk of breast cancer. It is incumbent on the scientific community to debunk the myths and untruths that surround many of the false health claims that have seduced segments of the public. Accomplishing this effectively is a daunting task that begins through interactions with the public and the clear communication of health risk information based on the totality of relevant, credible data.

Communication difficulties arise when recognized scientific expert organizations assess the potential health effects of a substance that is of particular interest to the public and announce completely different conclusions. This occurred recently with glyphosate, the most widely used herbicide in the world. The International Agency for Research on Cancer (IARC), an arm of the World Health Organization, prepared a monograph on glyphosate and glyphosate-based formulations, which concluded that glyphosate was a Group 2A substance, and thus, is probably carcinogenic to humans (1). The IARC assessment (announced in 2015) triggered a thorough re-evaluation of glyphosate by the European Union's European Food Safety Authority (2,3), which in contrast, concluded that glyphosate is unlikely to be carcinogenic in humans and, thus, did not require a cancer classification. This controversy has spilled over into the regulatory and scientific literature (4-8) and has resulted in several communications between representatives supporting IARC [e.g., (9,10)] and EFSA (11,12) defending their respective conclusions.

Due to the stark contrast in the conclusions of IARC and EFSA regarding the carcinogenic potential of glyphosate, we explored the differences in the basis for each organization's conclusion. This analysis showed that the first major difference between the assessments performed by IARC and EFSA pertains to the body of data evaluated by each of the two groups. For the purpose of transparency, IARC restricts its evaluations to data that have been published (or are accepted for publication) in the open scientific literature. If government agencies have published data in reports that are accessible to the public, they may also be considered. But not all the best data are necessarily reported in the peer-reviewed literature. Epidemiological (human) studies—typically, case-control or cohort studies—are often published and thus, readily available to the public in the peer-reviewed literature. However, some chemical manufacturers may have conducted these

types of studies and submitted to regulatory agencies as proprietary reports, which often are not readily available to the public. Nonclinical (animal) toxicology and safety data can also be made available to the scientific public through the publication of results in the open scientific literature. Nevertheless, a much larger proportion of the nonclinical toxicology and safety data for a chemical is generated in contract research organizations (CROs), which are considered proprietary information, and while submitted to regulatory bodies to meet testing requirement, often not available to the public. While these types of studies are typically not published, they are performed under a set of standards called Good Laboratory Practices (GLPs) to meet guidelines for design and quality that have been set by various international regulatory agencies. Additionally, the amount of data collected in guideline studies is often far greater than that provided in published studies and is typically of higher quality with regard to experimental group sizes and the breadth of investigation (e.g., requirement for a dose-response design; histopathology of 35+ tissues from all animals in high dose and control groups; toxicokinetic data for subchronic and chronic/carcinogenicity studies). In contrast to IARC, EFSA considers the entire corpus of credible and relevant scientific data, regardless of the publication status, provided that they meet the criteria for scientific quality, such as those outlined by GLPs.

It is our opinion that this approach, of considering the entire body of data although it may not all be publicly available in the peer-reviewed literature, is more robust—particularly when much of the highest quality data are generated by GLP, but unpublished. It is important to note that published research often emanates from academic laboratories and is typically of very high quality with regard to insightful, cutting-edge mechanistic experiments. Unfortunately, the results of these experiments are often of limited use for safety evaluations. In contrast, the results of experiments performed according to guidelines that have been promulgated by regulatory agencies for safety evaluations are typically not of interest to the general scientific community (especially when the results are negative) and usually are not published in the open literature. These latter studies are often the source of dose-response data as well as being the studies upon which effect levels are defined. Thus, IARC's process of using only publicly available studies, while transparent, provides an incomplete body of data for evaluation.

The second major difference between the assessments of these two organizations relates to their work products. IARC clearly states in its Preamble that: "*The (IARC) Monographs are an exercise in evaluating cancer hazards, despite the historical presence of the word 'risks' in the title. The distinction between hazard and risk is important, and the Monographs identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher.*" (13).

Thus, IARC performs a hazard assessment only. Hazard assessment is the first step in the process of assessing actual risks. In addition, IARC seems to rely mainly upon statistical analyses to form its opinions with rather limited interpretations of biological plausibility [see discussion in (10)]. EFSA (and other regulatory bodies), in contrast, generates risk assessments (i.e., an estimate of the likelihood of developing cancer after being exposed). This is a key distinction. Thus, EFSA examines additional and more complete toxicological data by gathering numerous additional studies that have been performed according to regulatory guidelines for the purposes of determining both dose-response relationships and internal exposures achieved by various routes of administration over various durations. They also consider mechanism of action studies. In addition, EFSA carefully evaluates environmental data that measured actual exposures to humans under various scenarios.

Thus, in EFSA's evaluation, the information available from all of the toxicology studies was assembled and considered with the exposure data in their final determination of potential carcinogenic risks to people under a variety of scenarios. The results of this assessment found no basis for classifying glyphosate as a carcinogenic risk to humans (3). Importantly, other regulatory bodies have also re-evaluated glyphosate and have come to the same conclusion that it is not a carcinogenic risk to humans [e.g., (7,14,15)]. We believe that this approach—of considering not only hazard, but also the potential for sufficient exposures to result in actual risks—is the more informative one.

Third, as noted previously, the EFSA assessment was restricted to the evaluation of glyphosate only, whereas the IARC review included consideration of not only glyphosate, the active ingredient, but also of glyphosate-based formulations. This latter category comprises mixtures of glyphosate with various surfactants and excipients. Although some of the additional ingredients, especially the surfactants, have toxicologic properties of their own [e.g., (16,17)], the IARC assessment made no attempt to parse out the effects of other substances present in these mixtures. The rationale for IARC's consideration of glyphosate-based formulations is that people are typically exposed to the

formulated products and not the active ingredient alone. The shortcoming to this approach is that carcinogenic risk can be falsely applied to the active ingredient in a formulation instead of to the actual causative chemical that may be present in the mixture.

Taken together, the preceding assessment shows that the inputs to and written products of IARC and EFSA are actually quite different. Nevertheless, the vocabulary used by both organizations is strikingly similar. Both speak of the carcinogenicity of substances and use the term "carcinogen", although their criteria and meanings differ. Because both EFSA and IARC are held in high regard by the public, both organizations need to be transparent in communicating their assessment approaches and what their conclusions mean in terms of actual risks to the public. In particular, when IARC classifies a substance as "probably carcinogenic to humans (Group 2A)" the public hears that "it causes cancer" and is a reason to worry. Without further clarifying or revamping their assessment process or more clearly communicating to the public what their determinations mean for the average person, IARC may erode its credibility within the scientific community. This, in turn will ultimately result in the Agency's becoming a less reliable source of information to the public.

In closing the IARC reassessment of glyphosate served as a stimulus for multiple regulatory agencies to carefully re-evaluate all of the data available to them in separate risk assessments (3,7,14,15,18). The results of these new risk assessments unanimously concluded that glyphosate does not pose a carcinogenic risk to humans and that there was no cause for classification. We concur with those risk assessments and urge the scientific community to communicate these conclusions regarding glyphosate to the public.

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Footnote

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References

1. International Agency for Research on Cancer. Some organophosphate insecticides and herbicides: tetrachlorvinphos, parathion, malathion, diazinon and glyphosate. Lyon: IARC Monogr Eval Carcinog Risk Chem Hum, 2017;112:321-412.
2. European Food Safety Authority. Peer review report to the conclusion regarding the peer review of the pesticide risk assessment of the active substance glyphosate.2015a. Available online: http://registerofquestions.efsa.europa.eu/roqFrontend/outputLoader?output=ON-4302
3. European Food Safety Authority. Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate. EFSA J 2015;13:4302.
4. Cressey D. Widely used herbicide linked to cancer. Nature [Internet]. 24 Mar 2015. Available online: https://www.nature.com/news/widely-used-herbicide-linked-to-cancer-1.17181
5. Williams GM, Aardema M, Acquavella J, et al. A review of the carcinogenic potential of glyphosate by four independent expert panels and comparison to the IARC assessment. Crit Rev Toxicol 2016;46:3-20.
6. EU chemicals agency sweeps glyphosate cancer evidence under the carpet. Available online: http://www.greenpeace.org/eu-unit/en/News/2017/EU-chemicals-agency-sweeps-glyphosate-cancer-evidence-under-the-carpet/
7. Glyphosate issue paper: evaluation of carcinogenic potential. Washington DC: EPA's Office of Pesticide Programs. Available online: https://www.epa.gov/sites/production/files/2016-09/documents/glyphosate_issue_paper_evaluation_of_carcincogenic_potential.pdf
8. Does Monsanto's Roundup Herbicide Cause Cancer or Not? The Controversy, Explained. Available online: https://www.wired.com/2016/05/monsantos-roundup-herbicide-cause-cancer-not-controversy-explained/
9. Portier CJ, Armstrong BK, Baguley BC, et al. Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA). J Epidemiol Community Health 2016;70:741-5.
10. Portier CJ, Clausing P. Re: Tarazona et al. (2017): Glyphosate toxicity and carcinogenicity: a review of the scientific basis of the European Union assessment and its differences with IARC. doi: 10.1007/s00204-017-1962-5. Arch Toxicol 2017. [Epub ahead of print].
11. Tarazona JV, Court-Marques D, Tiramani M, et al. Glyphosate toxicity and carcinogenicity: a review of the scientific basis of the European Union assessment and its differences with IARC. Arch Toxicol 2017;91:2723-2743.
12. Tarazona JV, Court-Marques D, Tiramani M, et al.

Response to the reply by C. J. Portier and P. Clausing, concerning our review "Glyphosate toxicity and carcinogenicity: a review of the scientific basis of the European Union assessment and its differences with IARC". Arch Toxicol 2017. [Epub ahead of print].
13. International Agency for Research on Cancer. Some organophosphate insecticides and herbicides: tetrachlorvinphos, parathion, malathion, diazinon and glyphosate. IARC Working Group. Lyon: IARC Monogr Eval Carcinog Risk Chem Hum, 2017;112:9-31.
14. BfR-contribution to the EU-approval process of glyphosate is finalised. Available online: http://www.bfr.bund.de/cm/349/bfr-contribution-to-the-eu-approval-process-of-glyphosate-is-finalised.pdf
15. Re-evaluation Decision RVD2017-01, Glyphosate. Available online: https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/pesticides-pest-management/decisions-updates/registration-decision/2017/glyphosate-rvd-2017-01.html
16. Mesnage R, Bernay B, Séralini GE. Ethoxylated adjuvants of glyphosate-based herbicides are active principles of human cell toxicity. Toxicology 2013;313:122-8.
17. Seok SJ, Park JS, Hong JR, et al. Surfactant volume is an essential element in human toxicity in acute glyphosate herbicide intoxication. Clin Toxicol (Phila) 2011;49:892-9.
18. Opinions of the Committee for Risk Assessment on proposals for harmonised classification and labelling. Available online: https://echa.europa.eu/opinions-of-the-committee-for-risk-assessment-on-proposals-for-harmonised-classification-and-labelling/-/substance-rev/16901/term

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