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Invited Perspective: The Continuing Debate—Is Glyphosate a Problem, and Can an Organic Diet Protect Us from Exposures?

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The safety of glyphosate-based pesticide products has been questioned for decades particularly as they are extensively used worldwide and there is a lack of consensus on their potential adverse health effects for humans. The debate on glyphosate's carcinogenicity continues across stakeholders, including two international beacons of science, the U.S. Environmental Protection Agency (EPA) and the International Agency for Research on Cancer (IARC), who have come to diametrically opposing conclusions.[1] Concerns over glyphosate's potential carcinogenicity tend to dominate the debates, but studies on other adverse effects also require attention (e.g., the association of adverse effects with prenatal glyphosate exposures).

Undoubtedly, glyphosate has been a commercial success, with the active ingredient used in >750 products, including the most highly used herbicides worldwide, the Roundup products.[2,3] Glyphosate is highly versatile and used in agriculture, horticulture, and personal gardening for a multitude of uses, from a preharvest desiccant to eliminating invasive plant species. A major boost to its use was the development of genetically modified glyphosate-resistant (i.e., Roundup Ready) crops; it is now ubiquitous in the environment.[2]

For a chemical that has been used for so long and in such high quantities worldwide, one would expect an abundance of data on human exposure, human toxicokinetics, and health and risk assessments based on human data. This is contrary to the case; consequently, glyphosate has been recently been selected as a priority substance in numerous large-scale human biomonitoring initiatives and is currently being investigated in various national monitoring programs—the European Human Biomonitoring Initiative (HBM4EU),[4] the U.S. National Health and Nutrition Examination Survey (NHANES),[5] the Canadian Health Measures Survey,[6] the German Environmental Specimen Bank (ESB),[7] and the German Environmental Survey (GerES).[8]

Glyphosate exposure is assumed to occur from numerous sources, including occupational uses with a wide variety of applicators,[9] residential exposures from living near farmland,[10] take-home exposures from living with an occupational user,[10,11] dietary ingestion of residues in and on foodstuffs, ingestion of contaminated water,[12] and secondary exposures from walking through recently sprayed areas. This adds another level of difficulty for assessing risk and exposure, and for controlling or reducing these exposure types.

In a human biomonitoring study published in this issue of *Environmental Health Perspectives*, Hyland et al.[13] investigated the effect of eating a conventional vs. organic diet on glyphosate exposure among pregnant women (a population deemed among the most susceptible to the potential effects of glyphosate). This 2-wk nested randomized cross-over trial took place during the spraying season; half the pregnant women lived near farmland (<500 m; "near-field") and the other half far from farmland (>500 m; "far-field").

Hyland et al. detected glyphosate in 68.4%–78.9% of the urine samples, with geometric mean concentrations from 0.14 to 0.21 μg/L, depending on the subgroups, confirming widespread glyphosate exposure in this population. Although exposure trends certainly followed expectations, with the lowest geometric mean concentrations in the far-field organic diet group and highest in the near-field conventional diet group, differences were statistically nonsignificant. After the investigators excluded individuals with four or more missing samples or food logs, changes in urinary glyphosate levels in far-field participants were found to be 43% lower during the organic diet intervention than during the conventional diet, a change that reached statistical significance. However, the source of the remaining exposure is unexplained, suggesting that it could be from a lack of compliance by some of the participants, traces of glyphosate that may also be components of an organic diet, or the presence of glyphosate exposure sources outside of the diet. This also suggests that avoiding exposure is challenging, even under the most ideal settings (e.g., eating an organic diet and living away from farms).

How meaningful are these findings? A particular strength of the Hyland et al. study is that the analytical method has been certified by successful participation in international external quality assessment programs, making the data comparable to similarly measured data in other cohorts, such as from HBM4EU, GerES, or NHANES. Unfortunately, much of the previously published glyphosate data were measured with analytical methods without external quality assurance, or with analytical approaches, such as enzyme-linked immunosorbent assay (ELISA), that are known to be less specific[14] than the mass spectrometric method used by Hyland et al. In addition, Hyland et al. present a stringent protocol for collecting contextual information, enabling detailed investigation of the data. Even if the participant number is only 34–39 (depending on the exclusion criteria), the analyses are based on 531 first-morning urine voids, a sample size achieved in only a few previous studies.[15,16] Although there was an intervention effect, it was detected only among far-field participants, implying the consumption of an organic diet is easily overshadowed by other exposure routes, such as living near agricultural land where pesticides are sprayed. Studies of farm families have also seen family members' urinary glyphosate concentrations correlate with pesticide users within the household.[10,17]

Naturally, there is always scope for advancement in research. Hyland et al. did not measure the main environmental breakdown product of glyphosate, aminomethylphosphonic acid (AMPA). The authors make a reasonable argument that AMPA measured in urine does not directly reflect glyphosate exposure, given that the AMPA measured in urine is not metabolized AMPA from glyphosate exposures (i.e., only very minute amounts of glyphosate are metabolized to AMPA in humans).[18,19] We would argue for the inclusion of AMPA to evaluate the simultaneous exposure to this

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metabolite from the environmental breakdown of glyphosate via microbial degradation. Different glyphosate-to-AMPA ratios in participants may indicate different sources of exposure[20] (e.g., more agricultural land use around the residence is associated with an increase in the levels of urinary AMPA[21]). Furthermore, AMPA is assumed to have a toxicological profile similar to glyphosate.[22] Thus, toxicological testing of AMPA alone is not enough; an evaluation of AMPA's co-exposure with glyphosate is needed to elucidate the reasons for differences in internal concentrations potentially caused by different exposure sources and pathways for AMPA.[4,7]

Of note, human toxicokinetic data for both glyphosate and AMPA are still very limited. However, the newest human data strongly contradict earlier animal data in regard to urinary excretion characteristics.[18,23] Changes found in the toxicokinetic data should be assessed regularly and embedded in future health-based reference values for glyphosate and AMPA, as well as in cumulative exposure reference values (e.g., for glyphosate plus AMPA).[14] Furthermore, human biomonitoring guidance values should be derived[24,25] that directly refer to urinary biomarker concentrations at which there is no appreciable health risk to allow direct exposure and risk assessment without the need for complicated extrapolations.

Future research should also consider the effect of products containing glyphosate in combination with other ingredients, a point that is highlighted by Hyland et al. Regulatory assessments focus on active ingredients alone, although products on the market include adjuvants and inert ingredients, each of which has its own toxicological profile. With hundreds of glyphosate-based products on the international market, all with varying ingredients, the need for further investigation is clear.

Although debates on the use of glyphosate have varying concerns, there is one dominant consensus among the majority of the scientific community, which is the requirement for more quality-assured data to evaluate glyphosate exposures and their potential adverse health effects in both occupationally and environmentally exposed populations. Currently, the European Commission and the U.S. EPA are reviewing this chemical, which has received unprecedented interest from stakeholders and the general public.[26,27] Given this interest, it is more crucial than ever to have high-quality, comparable data and full transparency in the evaluation of this chemical substance. The study by Hyland et al. is the first step to generating more of the necessary, insightful, and reliable data on glyphosate exposure in susceptible populations, but this is only a first step. It illustrates that sources and pathways of human glyphosate exposure are strikingly complex, even without adding AMPA to the equation.

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