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JNCI J Natl Cancer Inst (2019) 111(2): djy200

doi: 10.1093/jnci/djy200
First published online December 28, 2018
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CORRESPONDENCE

Re: Glyphosate Use and Cancer Incidence in the Agricultural Health Study

Lianne Sheppard, Rachel M. Shaffer

See the Notes section for the full list of authors' affiliations.
Correspondence to: Lianne Sheppard, PhD, Department of Biostatistics, University of Washington, Box 357232, Seattle, WA 98195-7232 (e-mail: sheppard@uw.edu).

Exposure to glyphosate, a broad-spectrum herbicide, and its consequent health impacts are critically important to understand. Its use and potential to enter the food supply have increased dramatically worldwide over recent decades (1). The Agricultural Health Study (AHS) is a crucial piece of evidence because there are no other large cohort studies of the potential carcinogenic effects of glyphosate. Thus, the recent AHS results (2), adding 11 years of follow-up to the previously reported AHS results (3), have huge potential to improve our understanding of glyphosate toxicity—which in turn informs national and international evaluations that influence policy. We wish to describe a feature of the study analyses that most likely attenuated the effect estimates towards the null. The exposure modeling introduced noise into the exposure estimates because it used a multiple imputation procedure that did not consider the study outcomes (4).

Exposure assessment in the AHS was complete at baseline. The investigators faced a huge challenge because 20 968 individuals, 37% of AHS participants, failed to complete the follow-up questionnaire. The authors used a well-respected approach to fill in missing data with multiple draws of the distribution of the missing exposures conditional on information available from baseline, including demographics, farm characteristics, pesticide use history, and existing medical conditions (4). They called their procedure multiple imputation, because it has the appearance of the multiple imputation approach described by Rubin (5). However, the AHS multiple imputation did not consider any of the health outcomes analyzed by Andreotti et al. (2), including non-Hodgkin lymphoma and multiple myeloma. As was elegantly stated in his review, "Regression with missing X's," Little noted that when realizations of the distribution of missing exposures (X_1 in his notation) given other covariate data (X2, …, X_p) are used to estimate regression coefficients, failure to condition on the health outcome (Y) leads to bias. The direction of the bias is attenuation towards no increased risk. Little explained that for an exposure X_1, "… then the regression coefficient of X_1 is attenuated, because the noise added to the conditional means doesn't account for the partial correlation of X_1 and Y given X_2, …, X_p." (p. 1235) (6). Gryparis et al. (7) name this misguided approach to multiple imputation "exposure simulation."

We do not know the size of the exposure model residual in the AHS or the magnitude of the resulting bias. However, because the phase II nonrespondent group was large (37%) and the phase II respondent group reported a high prevalence of glyphosate use (52%), there is reason to suspect that the consequence of using this imputation procedure is to meaningfully attenuate the cancer risk estimates. Unfortunately, it is unlikely that the conclusion of Heltshe et al. (4)—"This multiple imputation will allow for bias reduction and improved efficiency in future analyses of the AHS"—is correct. We encourage the AHS investigators to refine their approach and improve our ability to understand the true impacts of pesticide exposures, which—particularly for glyphosate—could have tangible consequences for public health policy.

Funding

RMS is supported by NIEHS T32ES015459.

Notes

Affiliations of authors: Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA (LS, RMS); Department of Biostatistics, University of Washington, Seattle, WA (LS).

Dr Sheppard was an ad hoc member of the EPA Federal Insecticide, Rodenticide, and Fungicide Act Scientific Advisory Panel for Evaluation of the Carcinogenic Potential of Glyphosate in 2016–2017.

Received: August 28, 2018; **Revised:** October 17, 2018; **Accepted:** October 17, 2018

The funder had no role in the writing of this correspondence or decision to submit it for publication.

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