OXFORD

JNCI J Natl Cancer Inst (2019) 111(2): djy201

doi: 10.1093/jnci/djy201
First published online December 28, 2018
Response

Response to Sheppard and Shaffer

Gabriella Andreotti, Jay H. Lubin, Stella Koutros, Jonathan N. Hofmann, Dale P. Sandler, Catherine C. Lerro, Christine G. Parks, Debra T. Silverman, Laura E. Beane Freeman

See the Notes section for the full list of authors' affiliations.

We thank Dr Sheppard and Ms Shaffer for their interest in our report of glyphosate and cancer risk in the Agricultural Health Study (AHS) (1) and the opportunity to discuss the potential impact of our method of assigning glyphosate exposure for participants who did not complete the follow-up questionnaire. As they correctly state, we did not account for health outcome when imputing exposure. Although we agree that this method could theoretically bias risk estimates towards the null, based on sensitivity analyses that we conducted and reported in the manuscript and describe more fully below, we demonstrate that our imputation likely did not materially impact risk estimates. For example, when analyses are restricted to exposure reported at enrollment, the rate ratios are similar to the estimates for the total data set including the imputed exposure data (Table 1). Also, the patterns of risk are similar for those who completed the follow-up questionnaire (ie, self-reported use, yes/no) and those who did not (ie, imputed use, yes/no), with no statistically significant interaction between glyphosate use and completion of the follow-up questionnaire. In addition, the median lifetime days of glyphosate use was nearly the same for those who completed the follow-up questionnaire (38.8, interquartile range 15–108.5) and those who did not (38.0, interquartile range 11.8–108.5).

To determine the number of participants whose classification of glyphosate use would potentially be affected by including the outcome in the imputation, we compared the predicted probability of exposure from the binary logistic regression used in our imputation model with the predicted probability of exposure based on outcome-augmented models from the complete-data subjects, that is, adding an indicator variable for each of the following: all cancers, non-Hodgkin lymphoma, multiple myeloma, and acute myeloid leukemia. As an example, for total cancer, the addition of the outcome to the imputation model would have affected the exposure status of five or fewer cases among those who did not complete the follow-up questionnaire (Table 1). This estimate is based on the mean absolute difference (SD) of 0.0021 (0.0005) in the predicted probabilities of glyphosate exposure from the logistic regression models with and without total cancer outcome (Supplementary Table 1). The predicted probabilities, mean absolute differences, and estimated number of subjects affected by the alternative imputation method by outcome (total cancer, non-Hodgkin lymphoma, multiple myeloma, or acute myeloid leukemia) for subjects who did not complete the follow-up questionnaire are shown in Supplementary Table 1.

The AHS evaluates multiple health outcomes and pesticide exposures. In the 2018 article focused on glyphosate, for example, we evaluated 23 different cancer sites. Rather than carry out 23 separate imputations, we chose to develop one imputation model based on data available from enrollment, irrespective of outcome information (2). Because we continually update outcome information, our approach also facilitates updated analyses and standardizes exposure estimates across analyses.

Overall, we believe that these data demonstrate that not including outcome information in our imputation of glyphosate exposure did not introduce meaningful bias in our cancer risk estimates associated with this pesticide.

Funding

This work was supported by the Intramural Research Program of the National Institutes of Health, NCI, Division of Cancer Epidemiology and Genetics (Z01CP010119), and National Institute of Environmental Health Science (Z01ES0490300).

Notes

Affiliations of authors: Occupational and Environmental Epidemiology Branch (GA, SK, JNF, CCL, DTS, LEBF) and Biostatsitics Branch (JHL), Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD; Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC (DPS, CGP).

Received: October 9, 2018; **Accepted:** October 17, 2018

Table 1. Evaluation of the imputation method used in the glyphosate and cancer analysis in the Agricultural Health Study: cancer incidence by completion of the follow-up questionnaire, and the estimated number of cases affected by alternative imputation method

	Exposure reported at enrollment and at follow-up (all subjects, using completed and imputed data)			Exposure reported at enrollment only (all subjects)			Exposure reported at enrollment and at follow-up (only subjects with completed follow-up questionnaire)			Exposure reported at enrollment and imputed at follow-up (only subjects without follow-up questionnaire)			
Glyphosate use*	No. of cases	RR (95%CI)†	P_{trend}†	No. of cases	RR (95%CI)†	P_{trend}†	No. of cases	RR (95%CI)†	P_{trend}†	No. of cases	RR (95%CI)†	P_{trend}†	$P_{interaction}$†
All cancer													
None	1511	1.00		1954	1.00		918	1.00		593	1.00		
Q1	1445	0.99 (0.91 to 1.07)		1338	0.99 (0.92 to 1.06)		897	0.98 (0.89 to 1.09)		548	1.01 (0.88 to 1.15)		
Q2	1443	0.99 (0.91 to 1.07)		1339	0.99 (0.92 to 1.07)		999	1.03 (0.93 to 1.13)		444	0.93 (0.81 to 1.07)		
Q3	1440	1.04 (0.96 to 1.13)		1328	1.03 (0.95 to 1.11)		950	1.01 (0.91 to 1.12)		490	1.14 (0.99 to 1.31)		
Q4	1451	0.99 (0.91 to 1.08)	.91	1325	0.97 (0.90 to 1.05)	.74	1012	1.01 (0.91 to 1.12)	.66	439	0.97 (0.84 to 1.12)	.70	.73
Affected cases‡	—	—	—	—	—	—	—	—	—	5	—	—	—
Non-Hodgkin lymphoma													
None	135	1.00		159	1.00		81	1.00		54	1.00		
Q1	113	0.83 (0.59 to 1.18)		116	0.98 (0.76 to 1.25)		67	0.75 (0.52 to 1.07)		46	0.86 (0.55 to 1.36)		
Q2	104	0.83 (0.61 to 1.12)		91	0.75 (0.57 to 0.98)		74	0.83 (0.59 to 1.18)		30	0.67 (0.41 to 1.10)		
Q3	112	0.88 (0.65 to 1.19)		108	0.98 (0.75 to 1.28)		79	0.88 (0.62 to 1.25)		33	0.89 (0.54 to 1.44)		
Q4	111	0.87 (0.64 to 1.20)	.95	98	0.82 (0.62 to 1.80)	.82	86	0.90 (0.63 to 1.27)	.54	25	0.59 (0.34 to 1.03)	.10	.58
Affected cases‡	—	—	—	—	—	—	—	—	—	3	—	—	—
Multiple myeloma													
None	30	1.00		32	1.00		19	1.00		11	1.00		
Q1	19	0.70 (0.36 to 1.36)		19	0.85 (0.47 to 1.53)		11	0.57 (0.26 to 1.27)		8	1.02 (0.33 to 3.12)		
Q2	26	0.94 (0.50 to 1.76)		20	0.87 (0.49 to 1.57)		18	0.89 (0.44 to 1.81)		8	1.24 (0.41 to 3.74)		
Q3	19	0.78 (0.39 to 1.56)		26	1.23 (0.70 to 2.16)		15	0.80 (0.38 to 1.68)		4	0.79 (0.22 to 2.92)		
Q4	24	0.87 (0.45 to 1.69)	.84	18	0.73 (0.39 to 1.38)	.76	20	1.00 (0.49 to 2.05)	.66	4	0.54 (0.13 to 2.32)	.42	.65
Affected cases‡	—	—	—	—	—	—	—	—	—	1	—	—	—
Acute myeloid leukemia													
None	9	1.00		10	1.00		3	1.00		6	1.00		
Q1	13	1.62 (0.60 to 4.38)		14	2.25 (0.96 to 5.27)		8	2.65 (0.69 to 10.18)		5	1.01 (0.30 to 3.41)		
Q2	14	1.70 (0.61 to 4.73)		10	1.64 (0.65 to 4.13)		8	2.24 (0.56 to 8.95)		6	1.29 (0.40 to 4.18)		
Q3	12	1.46 (0.49 to 4.37)		15	2.70 (1.14 to 6.43)		7	2.01 (0.48 to 8.41)		5	0.98 (0.26 to 3.72)		
Q4	18	2.44 (0.94 to 6.32)	.11	17	2.62 (1.14 to 6.07)	.03	12	3.87 (1.02 to 14.75)	.09	6	1.54 (0.44 to 5.32)	.55	.79
Affected cases‡	—	—	—	—	—	—	—	—	—	1	—	—	—

*Quartiles of intensity weighted days of glyphosate use: Q1 = 1–598.9, Q2 = 599–1649.9, Q3 = 1650–4339.9, Q4 = ≥4340.0.

†Poisson regression was used to model rate ratios (RR) and 95% confidence intervals (CI). P_{trend} was calculated using a two-sided Wald test. $P_{interaction}$ was calculated using the log-likelihood ratio test for the interaction between completion of the follow-up questionnaire and glyphosate use. All models adjusted for age, state of recruitment, education, cigarette smoking status, alcohol per month, family history of cancer, atrazine, alachlor, metolachlor, trifluralin, 2, 4-D.

‡Estimated number of cases that would change exposure status from never to ever or vice versa among participants who did not complete the follow-up questionnaire. Affected cases are based on the mean absolute difference in the predicted probabilities from the logistic regression models with and without the designated cancer outcome (see Supplementary Table 1).

There are no financial disclosures from any of the authors. The study sponsor had no role in the design of the study, the data collection, and the analysis or interpretation of the data, the writing of the article, or the decision to submit for publication. All analyses were conducted with AHS data release P1REL201701 and P2REL201701.

References

1. Andreotti G, Koutros S, Hofmann JN, et al. Glyphosate use and cancer incidence in the Agricultural Health Study. *J Natl Cancer Inst*. 2018;110(5):509–516.
2. Heltshe SL, Lubin JH, Koutros S, et al. Using multiple imputation to assign pesticide use for non-responders in the follow-up questionnaire in the Agricultural Health Study. *J Expo Sci Environ Epidemiol*. 2012;22(4):409–416.