Comments from Consumers Union to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)
Scientific Advisory Panel (SAP) on the Carcinogenic Potential of Glyphosate
Docket ID EPA-HQ-OPP-2016-0385

By
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Thank you for the opportunity to address the Scientific Advisory Panel (SAP) on the topic of the carcinogenic potential of glyphosate. My name is Michael Hansen and I am a senior scientist at Consumers Union[1] (CU), the policy and advocacy arm of *Consumer Reports*. This assessment of the carcinogenicity of glyphosate is needed given that total use of glyphosate in the US is estimated at 280 -290 million pounds in 2014, a 250-fold increase in usage compared to 1974 when it was first introduced and a 10-fold increase since 1993[2], when it was last reviewed by US Environmental Protection Agency (EPA). We urge the SAP to tell EPA that their present assessment of the carcinogenic potential of glyphosate is inadequate and needs to be redone. We feel that if this reassessment is done properly, the EPA would make a conclusion similar to that made by the World Health Organization's International Agency for the Research on Cancer (IARC), e.g., that glyphosate is a probable human carcinogen.

Charge Question 1: Systematic review of additional relevant studies that may inform the human carcinogenic potential of glyphosate

We agree with EPA's call for more data on formulated products containing glyphosate, particularly given the evidence that surfactants such as POE-tallowamine may make the formulated product much more toxic, as noted by a study submitted to USDA in 1997[3] and by the conclusion of a 2015 European Food Safety Authority (EFSA) report that noted that "Compared to glyphosate, a higher toxicity of the POE-tallowamine was observed on all endpoints investigated,"[4] and noted that "genotoxicity, long-term toxicity and carcinogenicity, reproductive/developmental toxicity and endocrine disrupting potential of POE-tallowamine

[1] Consumers Union is the public policy and advocacy arm of Consumer Reports. Consumers Union is an expert, independent, nonprofit organization whose mission is to work for a fair, just, and safe marketplace for all consumers and to empower consumers to protect themselves. It conducts this work in the areas of food and product safety, telecommunications reform, health reform, financial reform, and other areas. Consumer Reportsis the world's largest independent product-testing organization. Using more than 50 labs, auto test center, and survey research center, the nonprofit organization rates thousands of products and services annually. Founded in 1936, Consumer Reports has over 7 million subscribers to its magazine, website, and other publications.

[2] Benbrook, C. 2016. Trends in glyphosate herbicide in the United States and globally. *Environmental Sciences Europe*, **28**:3. At: https://enveurope.springeropen.com/articles/10.1186/s12302-016-0070-0

[3] Diamond GL and PR Durkin. 1997. Effects of Surfactants on the Toxicity of Glyphosate, with Specific Reference to RODEO. Report submitted to Leslie Rubin, COTR, Animal Plant Health Inspection Service, United States Department of Agriculture. At: http://www.fs.fed.us/foresthealth/pesticide/pdfs/Surfactants.pdf

[4] Pg. 9. EFSA. 2015. Request for evaluation of the toxicological assessment of the co-formulant POE-tallowamine. *EFSA Journal*. At: http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2015.4303/epdf

should be further clarified."[5] This information led the European Union member states, in July 2016, to ban POE-tallowamine from glyphosate-based products.[6] In contrast, POE-tallowamine is still allowed for food and nonfood uses in the US, and its use could be putting people at risk. We urge the SAP to explicitly support the call for more data on formulated glyphosate products and to incorporate these data into the carcinogenicity risk assessment.

Charge Question 2: EPA's review of epidemiological studies

We disagree with EPA's conclusion that "the association between glyphosate exposure and the risk of NHL [non-Hodgkins lymphoma] cannot be determined based on the available data" for many of the same reasons as laid out by Dr. Portier[7], Dr. Sass[8] and Bill Freese[9] in their comments to the SAP. EPA should not have given more weight to the Agriculture Health Study[10] (AHS), by classifying it as high quality, given the problems that: 1) the median follow-up time of 6.7 years may not be long enough to detect NHL[11], 2) only 61 of the 71 NHL cases with some exposure to glyphosate, were considered in the EPA analysis of cumulative exposure by tertiles,[12] making it more difficult to find a significant effect, and 3) the use of a 95% confidence interval (CI) rather than a 90% CI[13]. Use of a 90% CI would be more appropriate as it is more like conducting a one-tailed statistical test at a significance level of 0.05; a one-tailed statistical test is a more appropriate for a toxic chemical such as glyphosate which can be assumed to have only a harmful effect, and not a healthful effect, as a two-tailed statistical test implies.

As for the argument that the highest risk measures are coming from studies where there was a likely lower exposure to glyphosate, Bill Freese[14] presents compelling evidence of just the opposite, e.g., higher glyphosate usage rates (lbs/acre/year), and thus exposure to pesticide applicators, in the 1980s compared to the 1990s, which correlates with the higher estimates of

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[5] Pg. 3 in *Id.*
[6] Michalopoulos, S. 2016. EU agrees ban on glyphosate co-formulant. July 12, 2016, EurActiv.com. At.: https://www.euractiv.com/section/agriculture-food/news/eu-agrees-ban-on-glyphosate-co-formulant/
[7] Portier CJ. 2016. Submitted to USEPA (EPA-HQ-OPP-2016-0385-0094) Comments on the Glyphosate Issue Paper: Evaluation of Carcinogenic Potential October 4, 2016
[8] Sass J. 2016. Submitted to USEPA (EPA-HQ-OPP-2016-0385-0094) Comments on the Glyphosate Issue Paper: Evaluation of Carcinogenic Potential. November 4, 2016. At: https://www.nrdc.org/sites/default/files/comments-glyphosate-sap-20161103.pdf
[9] Freese B. 2016. Submitted to USEPA (EPA-HQ-OPP-2016-0385-0094) Comments on the Glyphosate Issue Paper: Evaluation of Carcinogenic Potential. October 12, 2016. At: http://www.centerforfoodsafety.org/files/sap-glyphosate-cancer-comments--cfs-20161_35863.pdf
[10] E.g., DeRoos AJ, Blair A, Rusiecki JA, Hoppin JA, Svec M, Dosemeci M, Sandler DP and MC Alavanja. 2005. Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. *Environmental Health Perspectives* 113(1): 49-54. At: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1253709/pdf/ehp0113-000049.pdf
[11] Portier CJ, Armstrong BK, Baguley BC, Baur X, Belyaev I et al. 2016. Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA). *Journal of Epidemiology and Community Health*, 70(8): 741-745. At: http://jech.bmj.com/content/70/8/741.full.pdf+html
[12] Portier CJ. 2016. *Op cit.*
[13] Sass J. 2016. *Op cit.*
[14] Freese B. 2016. *Op cit.*

NHL risk in the DeRoos et al. 2003 study[15], based on data from 1979 to 1986, compared to DeRoos et al. 2005[16], based on data from 1993 to 2001. The drastic increase in glyphosate use in late 1990s through 2000s comes as a result in drastic expansion in the acreage of corn, soybeans and cotton that are treated with glyphosate as a result of genetically engineered glyphosate tolerant crops.

The three meta-analyses that link glyphosate with NHL—(Schinasi and Leon 2014[17], IARC 2015[18], and Chang and Delzel 2016[19])—all have odds ratios of over 1.0, with lower-bound CIs at 1.0 or above, and all found at least one statistically significant association between glyphosate usage and NHL. Even the industry-sponsored meta-analysis characterized their finding as "marginally significant positive meta-RRs for the association between glyphosate use and risk of NHL and MM [multiple myeloma]."[20]

The EPA's 2005 Guidelines for Carcinogenic Risk Assessment define "suggestive evidence of carcinogenic potential" as, in part, "evidence of a positive response in studies whose power, design, or conduct limits the ability to draw a confident conclusion."[21] The data from the epidemiology studies are consistent (relative risks are positive, meta-analyses are positive), significant (in the meta-analyses), and consistent with the animal evidence (see charge question 3). However, chance, bias and/or confounding cannot be ruled out. IARC looked at the data and concluded there was "limited evidence of carcinogenicity in humans," which is defined as "a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence."[22] This would be consistent with EPA's "suggestive evidence of carcinogenic potential."

In conclusion, the SAP should recommend that EPA change their view of the epidemiological studies to "suggestive evidence of carcinogenic potential," since their present conclusion that "the association between glyphosate exposure and risk of NHL cannot be determined based on the available data," gives no weight to the human evidence at all in their final evaluation.

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[15] DeRoos AJ, Zahm SH, Cantor KP, Weisenburger DD, Holmes FF, Burmeister LF and A Blair. 2003. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. *Occupational and Environmental Medicine* 60: 1-9. At: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1740618/pdf/v060p00e11.pdf

[16] DeRoos et al. 2005. *Op cit.*

[17] Schinasi L and ME Leon. 2014. Non-Hodgkin lymphoma and occupational exposure to agricultural pesticide chemical groups and active ingredients: A systematic review and meta-analysis. *International Journal of Environmental Research and Public Health*, 11: 4449-4527. At: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4025008/pdf/ijerph-11-04449.pdf

[18] IARC. 2016. Monograph on glyphosate. At: http://monographs.iarc.fr/ENG/Monographs/vol112/mono112-09.pdf

[19] Chang ET and E Delzel. 2016. Systematic review and meta-analysis of glyphosate exposure and risk of lymphohematopoietic cancers. *Journal of environmental Science and Health, Part B*, 51(6): 402-428. At: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4866614/pdf/lesb-51-402.pdf

[20] Pg. 424 in Chang and Delzel, 2016, *Op cit.*

[21] Pg. 83 in US EPA. 2005. Guidelines for Carcinogenic Risk Assessment. Risk Assessment Forum. US EPA. March 2005. At: https://www3.epa.gov/airtoxics/cancer_guidelines_final_3-25-05.pdf

[22] Pg. 2 in IARC 2015: http://www.iarc.fr/en/media-centre/iarcnews/pdf/MonographVolume112.pdf

Charge Question 3: Evaluation of Animal carcinogenicity studies

There were 9 rat carcinogenicity studies and 6 mouse studies, with 4 of the rat studies showing treatment-related effects in various organs (including thyroid tumors) and 4 of the mice studies showing treatment effects in renal tumors, hemangiosarcomas and malignant lymphomas. In all the cases, EPA considered the data were not treatment related, in violation of their own 2005 Guidelines for the Carcinogenicity Risk Assessment (GCRA). For both the rat and mouse studies, EPA rejected positive findings "due to lack of pairwise statistical significance, lack of monotonic dose response, absence of preneoplastic or non-neoplastic leisons, no evidence of tumor progression, and/or historical control,"[23] or evidence found only at high doses in absence of evidence of excess toxicity. Each of the arguments EPA uses to dismiss positive findings are wrong.

First, the GCRA says that a significant trend test is sufficient for a positive finding; a significant pairwise test is not needed. Second, there is no mention in the GCRA of the need for a monotonic dose response relationship. The 2014 National Academy report on non-monotonic dose-response for endocrine disruptors recommends that EPA consider non-monotonic dose-response relationships.[24] Some *in vitro* and *in vivo* animal studies have suggested that glyphosate may interfere with hormonal activity and scientists, including endocrine experts, have stated that proper testing of glyphosate for endocrine activity is needed.[25]

Third, dismissing significant findings which lack preneoplastic or non-neoplastic leisons makes the assumption that all mechanisms by which chemical induce tumors in animals will involve enough stages such that there would be a historically identifiable preneoplastic lesion from which the final tumors are formed. As Dr. Portier has noted, this assumption has not been shown to be true.[26]

Fourth, EPA uses an outside historical control dataset to dismiss a positive finding in one study and fails to use an equally valid historical control data set to assess the importance of renal tumors in another study. EPA should use concurrent controls, where possible, as the GCRA notes.[27] In addition, as Dr. Portier notes, EPA used a historical control data set from animals that lived 24 months to compare to a response in a study that only lasted 18 months. If, as Dr. Portier notes, EPA had used the methodology used by the National Toxicology Program—the Poly-3 adjustment—to adjust the length of time an animal is in a study, allowing one to compare the 3

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[23] Pg. 95 in EPA Office of Pesticide Programs. 2016. Glyphosate Issue Paper: Evaluation of Carcinogenic Potential. At: https://www.epa.gov/sites/production/files/2016-09/documents/glyphosate_issue_paper_evaluation_of_carcincogenic_potential.pdf

[24] NRC. 2014. Review of the Environmental Protection Agency's State-of-the-Science Evaluation of Nonmonotonic Dose-Response Relationships as they Apply to Endocrine Disruptors. National Research Council. National Academies Press, Washington, D.C.

[25] Myers JP, Antoniou MN, Blumberg B, Carroll L, Colborn T, Everett LG, Hansen M, Landrigan PJ, Lanphear BP, Mesnage R, Vandenberg LN, Vom Saal FS, Welshons WV and CM Benbrook. 2016. Concerns over use of glyphosate-based herbicides and risks associated with exposures: a consensus statement. *Environmental Health* **15**:19 At: https://ehjournal.biomedcentral.com/articles/10.1186/s12940-016-0117-0

[26] Portier CJ. 2016. *Op cit.*

[27] "the standard for determining statistical significance of tumor incidence comes from a comparison of tumors in dosed animals with those in concurrent control animals" pp. 72-73 in EPA. 2005, *Op. cit.*

mouse studies which were only conducted for 18 months to a control population of 24 months (the standard length of time for a rodent carcinogenicity study), and used one-sided p-values (appropriate for studies of toxic chemicals that are expected to have negative health effects and not positive health effects), then statistically significant increases were found in renal tumors, malignant lymphomas and hemangiosarcomas in male mice.[28]

Fifth, EPA dismissed tumors at high doses despite no evidence of excess toxicity, which violates the CGRA.[29]

In sum, we urge the SAP to recommend that EPA reanalyze the animal carcinogenicity studies with strict adherence to its own CGRA, considering valid evidence from statistical trend tests, high doses in absence of evidence of excessive toxicity, and when compared to concurrent controls, and not requiring evidence of pre-neoplastic changes or monotonic dose response. We also urge the SAP to tell EPA to incorporate the Poly-3 adjustment, to adjust for lifetime exposure consistent with the practice of the NTP, in their analyses of the animal carcinogenicity studies, where appropriate. If the EPA does this reanalysis, we believe they will find evidence of carcinogenicity for glyphosate in both rats and mice.

Removal of Dr. Peter Infante

Finally, we would like to state that EPA's removal of Dr. Peter Infante[30], a world renowned epidemiologist, from the SAP, after EPA received a letter from industry lobby CropLife[31] urging them to dismiss Dr. Infante, undermines EPA's credibility and raises questions about EPA's independence and impartiality in this review. This was a most unfortunate action. At the very least, we urge EPA and the SAP to seriously consider his comments.

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[28] Portier, C. 2016 *Op. cit.*

[29] "effects seen at the highest doses are assumed to be appropriate for assessment … [unless] data demonstrate that the effects are solely the result of excessive toxicity rather than the carcinogenicity of the tested animal per se" pg. 40 in EPA, 2005. *Op. cit.*

[30] Dr. Infante has decades of experience in cancer research. In 24 years at the Occupational Safety and Health Administration (OSHA), his research played a major role in development of worker protection standards for carcinogens like benzene and asbestos. He has also served as an expert consultant on cancer for the National Toxicology Program (NTP), the World Health Organization (WHO) and the EPA.

[31] http://191hmt1pr08amfq62276etw2.wpengine.netdna-cdn.com/wp-content/uploads/2016/01/CLA-Comments-on-SAP-Disqualification-10-12-16.pdf