NATURAL RESOURCES DEFENSE COUNCIL

November 3, 2016

Comments from the Natural Resources Defense Council to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) on the Carcinogenic Potential of Glyphosate

Information at: https://www.epa.gov/sap/carcinogenic-potential-glyphosate
Comments submitted to Docket ID EPA-HQ-OPP-2016-0385

The following comments are being submitted on behalf of the Natural Resources Defense Council (NRDC). NRDC has no direct or indirect financial or fiduciary interest in the manufacture or sale of glyphosate or any chemical that would be the subject of the deliberations of this Committee.

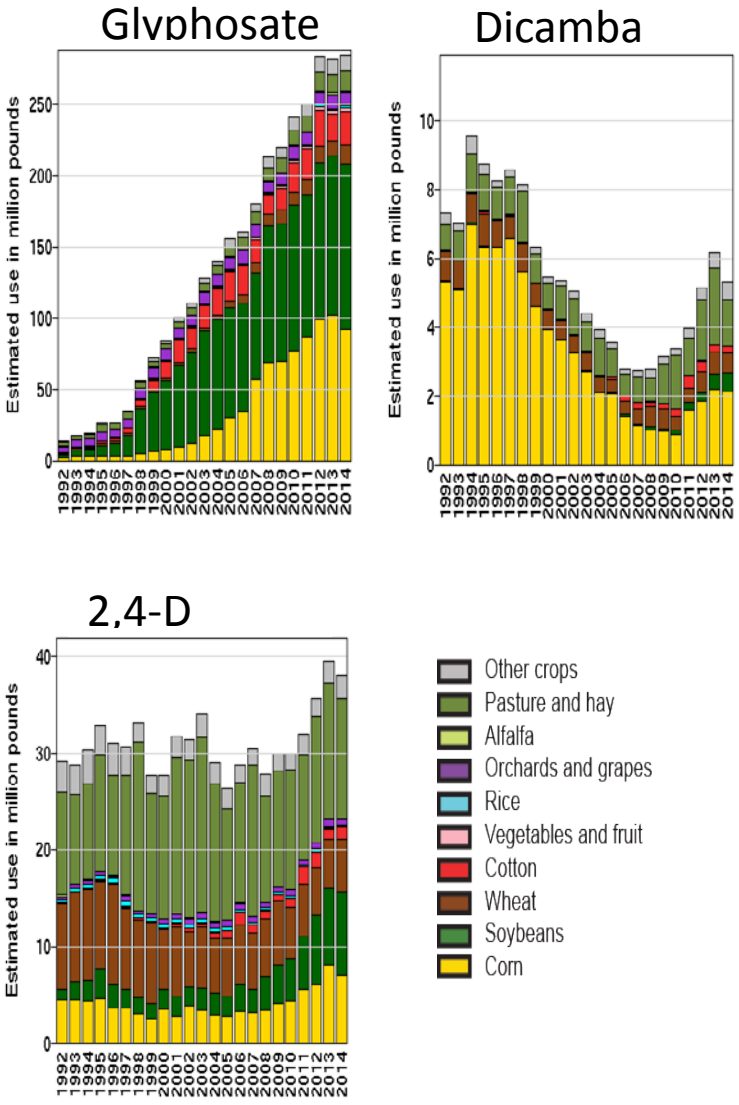
These comments reference the following documents:

EPA 2016. EPA Glyphosate Issue Paper: Evaluation of Carcinogenic Potential, September 12, 2016. Document ID: EPA-HQ-OPP-2016-0385-0094.

EPA 2005. EPA Guidelines for Carcinogen Risk Assessment, 2005.

Portier 2016. Comments of Christopher J. Portier, PhD. Submitted to USEPA on the Glyphosate Issue Paper: Evaluation of Carcinogenic Potential October 4, 2016. Document ID EPA-HQ-OPP-2016-0385-0371

INTRODUCTION



Glyphosate is used in over 750 herbicide products. Total annual use of glyphosate was estimated at 280-290 million pounds in 2014, with about 250 million pounds used in agriculture (Benbrook 2016; USGS 2012; EPA 2016 p. 16). Glyphosate's use in the US has increased 250-fold since 1974 when it was first introduced and 10-fold worldwide since US EPA last reviewed its risks in 1993 (Landrigan and Benbrook, 2015).[1] Corn and soybeans with genetically modified (GM) herbicide tolerance to glyphosate (Roundup) were first introduced in the mid-1990s, and now comprise over ninety percent of the corn and soybeans planted in the US (Landrigan and Benbrook, 2015).[2]

Herbicide overuse, misuse, and increased use

Ironically, because of massive glyphosate over-use leading to widespread weed resistance, its use is now thought to be in decline (EPA 2016, p. 16). But, this has unfortunately not led to a reconsideration of the agricultural practices that created the problem. Instead of replacing extensive use of herbicides on herbicide-tolerant GM engineered seeds with more integrated weed management approaches such as crop rotation and cover crops, Monsanto and other Agrochemical companies are simply pushing new chemical mixes.

For example, in 2014 EPA approved Dow AgroSciences' new Enlist Duo herbicide, which combines glyphosate and 2,4-D as active ingredients. However, in a subsequent lawsuit brought by NRDC and others challenging the registration of Enlist Duo,[3] EPA filed a motion asking the court to revoke (or

[1] http://www.nejm.org/doi/full/10.1056/NEJMp1505660#t=article

[2] http://www.nejm.org/doi/full/10.1056/NEJMp1505660#t=article

[3] *See* Br. of Pet'r Natural Resources Defense Council, *NRDC v. EPA*, Case Nos. 14-73353, 14-73359, 15-71207, 15-71213, ECF No. 106 (Oct. 23, 2015).

"vacate") EPA's approval of Enlist Duo. EPA argued that, in light of new information regarding the synergistic effects between glyphosate and 2,4-D, the agency could no longer be confident of its safety determination for Enlist Duo.[4] Specifically, in its court filing the agency wrote, "EPA cannot be sure, without a full analysis of the new information, that the current registration does not cause unreasonable effects to the environment." [5] In addition to not having fully considered the effects of Enlist Duo on public health and the environment, EPA was admitting that Enlist Duo may not be safe for yet another reason. Dow opposed EPA's request to the court, suggesting instead that the simply court "remand" the registration back to EPA for further evaluation rather than "vacate" the registration altogether; Dow's suggested approach would leave the registration in effect while EPA reconsidered it. In early 2016 the court denied EPA's request to vacate its registration of Enlist Duo, instead siding with Dow's request for a remand alone. As a result, Enlist Duo remained on the market, and in November of this year (2016), EPA proposed expanding its use on GE corn, soybean and cotton from the initial 15 states to an additional 19 states.[6]

In a similarly troubling debacle, Monsanto rushed to market its new "Xtend" herbicide-tolerant soybean seeds engineered to resist both glyphosate and dicamba. Monsanto began selling the new dicamba-resistant soybean seeds before the use of dicamba for those crops was approved by EPA, leading to illegal uses of the herbicide where farmers are desperate to fight the glyphosate-resistant 'pigweed' (Palmer amaranth).[7] Such uses led to many complaints of crop damage on neighboring farms: "*To date, the Missouri Department of Agriculture has received approximately 117 complaints alleging misuse of pesticide products containing dicamba. Missouri growers estimate that more than 42,000 acres of crops have been adversely affected. These growers have reported damage on a number of crops including peaches, tomatoes, cantaloupes, watermelons, rice, cotton, peas, peanuts, alfalfa, and soybeans. Similar complaints alleging misuse of dicamba products have been received by Alabama, Arkansas, Illinois, Kentucky, Minnesota, Mississippi, North Carolina, Tennessee and Texas*" (EPA Compliance Advisory, August 2016).[8]

The result of all this herbicide use, misuse, and overuse is an agricultural system that pads the corporate coffers of Monsanto and other heavily-invested agrochemical corporations, while leaving farmers economically challenged and woefully underprepared, with only one main tool in their toolbox - more toxic chemicals.[9]

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[4] http://www.chemweek.com/lab/EPA-asks-court-to-vacate-approval-of-Dows-Enlist-Duo-herbicide-updated_75467.html; *see* Resp'ts' Mot. for Voluntary Vacatur and Remand, *NRDC v. EPA*, Case Nos. 14-73353, 14-73359, 15-71207, 15-71213, ECF No. 121-1 (Nov. 24, 2015) [hereinafter EPA Mot. for Vacatur].

[5] https://www.nrdc.org/experts/sylvia-fallon/epa-should-cancel-dows-next-generation-herbicide-enlist-duo; EPA Mot. for Vacatur at 2.

[6] EPA Proposed Registration Decision of Enlist Duo Herbicide. November 2016. EPA-HQ-OPP-2016-0594. https://www.epa.gov/ingredients-used-pesticide-products/registration-enlist-duo

[7] http://www.npr.org/sections/thesalt/2016/08/01/487809643/crime-in-the-fields-how-monsanto-and-scofflaw-farmers-hurt-soybeans-in-arkansas

[8] US EPA Compliance Advisory August 2016. High number of complaints related to alleged misuse of dicamba raises concerns. https://www.epa.gov/sites/production/files/2016-08/documents/fifra-dicambacomplianceadvisory.pdf

[9] http://cjonline.com/news/business/2016-09-10/herbicide-resistant-weeds-challenge-farmers-bottom-lines

CHARGE QUESTIONS

#1 Comment on EPA's systematic review and any additional relevant studies.

NRDC agrees with EPA that more data and more scrutiny is required to fully evaluate formulated products containing glyphosate, particularly given the toxicity of surfactants like polyethoxylated (POE) tallowamine (EPA 2016, Section 7.0). In fact a report submitted under contract to USDA in 1997 – twenty years ago – warned that surfactants added to glyphosate products make them much more toxic, and that very little toxicity information is available about the formulated products.[10] Earlier this year, in July 2016, EU member states voted to ban POE-tallowamine from glyphosate-based products including Roundup. This followed the conclusions of the EFSA report (2015) noting that tallowamine ingredients are more toxic than glyphosate in terms of acute, short term, reproductive, and developmental toxicity, and that there is some evidence of DNA damage in vitro at high doses.[11] In contrast, in the US the EPA considers adjuvants such as the tallowamines to be "inerts", effectively treating them as if they were free of adverse effects. POE-tallow amine is approved by EPA for both food and non-food uses, at up to 25% in herbicide formulations, without any evaluation of its safety either alone or when combined with active ingredients.[12]

NRDC suggests that the SAP voice its support for EPA's research plans and call for more data,[13] and meanwhile recommend regulatory scrutiny and possible elimination of these toxic co-formulants in glyphosate and other pesticidal products.

#2 Comment on EPA's review of the epidemiologic studies

NRDC disagrees with EPA's conclusions, dismissal of evidence of risk, and failure to follow its own cancer guidelines. EPA dismissed the epidemiologic evidence because it did not rise to the level where EPA could not exclude chance and/or bias as an explanation for the observed associations (EPA CARC 2016, p. 68). However, the available epidemiologic evidence is certainly not negative, or no evidence (EPA 2005, p. 80). More realistically, the epidemiologic evidence provides "suggestive evidence of carcinogenic potential," which EPA's Cancer Guidelines describe as follows:

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[10] Diamond GL, Durkin PR. Effects of Surfactants on the Toxicitiy of Glyphosate, with Specific Reference to RODEO Report submitted to Leslie Rubin, COTR, Animal and Plant Health Inspection Service (APHIS). Biotechnology, Biologics and Environmental Protection, Environmental Analysis and Documentation, United States Department of Agriculture, February 6, 1997 http://www.fs.fed.us/foresthealth/pesticide/pdfs/Surfactants.pdf

[11] http://www.efsa.europa.eu/sites/default/files/4302_glyphosate_complementary.pdf

[12] Polyoxyethylene tallow amine (CAS No. 61791-26-2), is on the U.S. EPA List of Inert Ingredients of Pesticides, where it is classified as cleared for both food and nonfood uses.

Chemical Data Access Tool (CDAT):
https://java.epa.gov/oppt_chemical_search/?redirectFrom=InertFinder&casno=61791-26-2

EPA Inert Finder here: https://iaspub.epa.gov/apex/pesticides/f?p=INERTFINDER:3:::NO::P3_ID:6708

[13] Comments to EPA from Nichelle Harriot for Beyond Pesticides also makes the that the formulations are toxic and must be investigated, and until that happens, this should be considered a data gap that puts people at risk. October 2016. Document ID: EPA-HQ-OPP-2016-0385-0375

> *"Suggestive Evidence of Carcinogenic Potential" - This descriptor of the database is appropriate when the weight of evidence is suggestive of carcinogenicity; a concern for potential carcinogenic effects in humans is raised, but the data are judged not sufficient for a stronger conclusion . . . . such as evidence of a positive response in a study whose power, design, or conduct limits the ability to draw a confident conclusion (but does not make the study fatally flawed), but where the carcinogenic potential is strengthened by other lines of evidence (such as structure-activity relationships).*" (EPA 2005 p. 83)

A descriptor of the epidemiologic database as "suggestive evidence" would be reasonably consistent with IARC's conclusions that the epidemiology provided "limited" evidence, based mainly on, "case-control studies in the USA, Canada, and Sweden [that] reported increased risks for NHL [Non-Hodgkin Lymphoma] associated with exposure to glyphosate. The increased risk persisted in the studies that adjusted for exposure to other pesticides" (IARC Monograph, p. 75).[14] Such evidence, albeit suggestive or limited, is certainly not negative, and can strengthen other lines of evidence, as described in EPA's Cancer Guidelines.

EPA's own reporting (EPA CARC 2016, Table 3.3, p. 48-49) finds that when using the ever/never exposure metric, the study finds an association between glyphosate exposure and kidney cancer (OR 1.6, 95% CI 0.7-3.8), bladder cancer (1.5, 95% CI 0.7-3.2), melanoma (1.6, 95% CI 0.8-3.0), and colon cancer (1.4, 95% CI 0.8-2.2). An ever/never exposure metric is appropriate, and likely also more accurate than the tertile analysis, which is weakened by excluding some NHL cases (there are 92 NHL cases total, with 71 having some exposure; in contrast, the analysis of cumulative exposure by tertiles included only 61 cases, reducing the statistical power by excluding 14% of the NHL cases[15]).

EPA considers the Agriculture Health Study (AHS) study to be of high quality (EPA 2016, p. 30), but then dismissed the results as if they were negative (no cancer risk). All of the odds ratios in the AHS cancer findings are positive (increased cancer risk) (De Roos et al 2005). Although EPA applied 95% confidence intervals (CI) to the AHS study results – meaning that the agency did not consider risks statistically significant unless they exceeded a 95% confidence level – it is likely that, had 90% confidence intervals been used, they would have shown a significant elevated cancer risk. A 90% CI is more like conducting a one-tailed statistical test at a significance level of 0.5, instead of a two-tailed test at 0.5. A one-tailed test (or using a 90% CI) is more appropriate for a toxic chemical like glyphosate that can be expected to have only a harmful effect, and not also a healthful one. Two-tailed tests are used for substances like pharmaceutical agents, where both beneficial and potential harmful effects could be expected. While the study may not be 95% sure that glyphosate causes cancer, it can be 90% sure that glyphosate causes cancer. Moreover, the AHS study has less than ten years of follow up so far (median=7 years), making it likely that with more time there will be more cancer cases, and the statistical confidence will increase (Portier et al 2016; EPA CARC 2016, p. 67).

The cancer reported in the AHS report is supported by the industry-sponsored meta-analysis by Chang and Delzell (2016) that reported a positive statistically significant finding for the association between any versus no use of glyphosate and risk of NHL (meta-RR = 1.3, 95% confidence interval (CI) = 1.0–1.6,

[14] http://monographs.iarc.fr/ENG/Monographs/vol112/mono112-09.pdf

[15] Comments of Christopher J. Portier, PhD. Submitted to USEPA (EPA-HQ-OPP-2016-0385-0094) on the Glyphosate Issue Paper: Evaluation of Carcinogenic Potential October 4, 2016

based on six studies) and MM (meta-RR = 1.4, 95% CI = 1.0–1.9; four studies). IARC also conducted a meta-analysis that found elevated risks for glyphosate and NHL (IARC 2015).

NRDC suggests that the SAP recommend to EPA that it elevate the epidemiologic database to "*suggestive evidence of carcinogenic potential,*" consistent with EPA's Cancer Guidelines for "evidence of a positive response in studies whose power, design, or conduct limits the ability to draw a confident conclusion" (EPA 2005, p. 83).

#3 Comment on EPA's use of its 2005 EPA Cancer Guidelines for assessing the rodent carcinogenicity studies.

Failing to follow the Cancer Guidelines

EPA violated its own Cancer Guidelines (2005) when dismissing evidence of elevated cancer in rodent studies. Below I excerpt EPA's summary of its findings and reasons for dismissing the evidence, and then show how EPA failed to follow its Guidelines.

> "In 5 of the 9 rat studies conducted with glyphosate, no tumors were identified for detailed evaluation. Of the remaining 4 rat studies, a statistically significant trend was observed for tumor incidences in the testes, pancreas, liver, thyroid, or mammary gland; however, the agency determined that these tumor findings are not considered to be related to treatment, as described in Section 4.5, due to lack of pairwise statistical significance, lack of a monotonic dose response, absence of preneoplastic or non-neoplastic lesions, no evidence of tumor progression, and/or historical control information (in limited instances). Lastly, tumors seen in individual rat studies were not reproduced in other studies, including those conducted in the same animal species and strain at similar or higher doses." (EPA 2016, p. 95)
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> "In 2 of the 6 mouse studies, no tumors were identified for detailed evaluation. In the remaining 4 mouse studies, 3 observed a statistically significant trend in tumor incidences in the hemangiosarcomas, lung adenomas, malignant lymphomas or hemangiomas; however, the agency determined that none of the tumors observed in the mouse are treatment related, as described in Section 4.6, due to lack of pairwise statistical significance, lack of a monotonic dose response, absence of preneoplastic or non-neoplastic lesions, no evidence of tumor progression, and/or historical control information (in limited instances). Lastly, tumors seen in individual mouse studies were not reproduced in other studies, including those conducted in the same animal species and strain at similar or higher doses." (EPA 2016, p. 95)

EPA Cancer Guidelines say either a trend test or a pairwise test is sufficient to establish significance. EPA failed to adhere to its own Cancer Guidelines by rejecting cancer evidence in experimental rodents that was significant in a trend test. The Cancer Guidelines say that, "Trend tests and pairwise comparison tests are the recommended tests for determining whether chance, rather than a treatment-related effect, is a plausible explanation for an apparent increase in tumor incidence. . . . Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result" (EPA 2016, p. 72; EPA 2005 p.46).

EPA rejected trend test evidence if it was not also monotonic. EPA violated its Guidelines when it dismissed positive data that was significant in a trend test, with the following explanation, "If a trend

was found to be statistically significant, a closer examination of the tumor incidence was taken to determine whether the data demonstrate a monotonic [linear] dose-response where an increase in tumor incidence is expected with corresponding increase in dose." (EPA 2016, p. 72). This loophole for rejecting tumor evidence is not in the Cancer Guidelines. In fact, a search for the word 'monotonic' reveals that it does not appear at all in the Cancer Guidelines. The Guidelines do say in reference to the Bradford Hill criteria for epidemiologic information that "the absence of an exposure-response relationship does not exclude a causal relationship" (EPA 2005, p. 41). EPA should not have positive dismissed data for this reason. The Cancer Guidelines are consistent with the National Academies report on non-monotonic dose-response relationships for endocrine disruptors (NRC 2014), which recommended that EPA explicitly consider non-monotonic dose-response relationships.[16] Glyphosate in particular has raised red flags among scientific researchers and endocrine experts because it has not been properly tested for endocrine disruption activity, despite some in vitro and whole animal studies suggested that it may interfere with hormone activity.[17]

EPA dismissed tumors at high doses despite absence of evidence of excess toxicity. EPA also violated its Cancer Guidelines by dismissing tumor evidence at high doses. The Guidelines state that "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 carcinogenicity of the tested agent per se" (EPA 2005 p.140). The rodent studies do not report excessive toxicity at the high doses; these data do not support EPA's dismissal of tumor evidence at high doses.

EPA dismissed tumors by erroneous comparisons with historical controls. EPA violated its Cancer Guidelines when dismissing tumor evidence by claiming it was within the range of historical controls. As EPA correctly notes, the Guidelines are clear that "the standard for determining statistical significance of tumor incidence comes from a comparison of tumors in dosed animals with those in concurrent control animals." (EPA 2016, p. 72-73) EPA also acknowledges, but then disregards, the portion of the Guidelines that clearly direct, "Generally speaking, statistically significant increases in tumors should not be discounted simply because incidence rates in the treated groups are within the range of historical controls or because incidence rates in the concurrent controls are somewhat lower than average." (EPA 2005 p. 48; EPA 2016 p. 73).

EPA dismissed tumors if preneoplastic changes were not also reported. EPA violated its Cancer Guidelines by turning them upside down regarding the relevance of pre-neoplastic (pre-cancer) tumors. The Guidelines wisely note that the presence of pre-neoplastic tumors may "lend support to the significance of findings for animal carcinogenicity" (EPA 2005 p. 48), whereas EPA uses the lack of reported pre-neoplastic tumors as an excuse to disregard observed tumors.

NRDC suggests that the SAP recommend that EPA consider the rodent data with strict adherence to its own Cancer Guidelines, considering valid the evidence at high doses, from statistical trend tests, and when compared to concurrent controls. Arguments about requiring pre-neoplastic changes or

[16] 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 DC.

[17] 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,Benbrook CM. Concerns over use of glyphosate-based herbicides and risks associated with exposures: a consensus statement. Environ Health. 2016 Feb 17;15:19.

monotonic dose responses are not based on its Guidelines, are not common scientific practice, and will not support public health decisions.

The less-than-lifetime bioassay

Three of the mouse studies were conducted for only 18 months. In his comments submitted to this docket, Dr. Chris Portier presented the data adjusted with a Poly-3 test used by the National Toxicology Program at NIEHS to help evaluate the significance of less-than-lifetime bioassays (Portier 2016, p. 15). Adjusting the study lengths and combining the data for a pooled analysis yielded a highly significant trend for excess cancer risk for male mouse kidney cancer, male mouse malignant lymphoma, and hemangiosarcomas in male mice; in addition, trends remain even when high doses are removed from the analysis (see Portier 2016, Table 3).

Huff et al (2008) report that since about 80% of all human cancers occur in people over the age of 60, even a conventional 2 year bioassay does not have a sufficient latency period to detect tumors that will occur later in life.[18] Cadmium is an example of a chemical that was not shown to be carcinogenic in 2-year studies of Wistar rats (Löser 1980), but caused various tumors in the lung in a 31-month study of Wistar rats (Takenaka et al. 1983).[19] Toluene is another example, Soffritti et al. (2004).[20] NIEHS rejects the notion that an 18 month rodent bioassay (about 30-50 years in human age) is long enough to reliably predict cancer risks (Bucher 2002[21]; Haseman et al. 2001[22]; Kodell et al. 2000[23]). Instead, many scientists recommend extending the rodent bioassay to 30 months, and including pre-natal exposures (Haseman et al. 2001[24]; Huff 2002[25]; Huff et al. 2007[26]; Maltoni 1995[27]; Soffritti et al. 2002[28]).

[18] Huff J, Jacobson MF, Davis DL. The Limits of Two-Year Bioassay Exposure Regimens for Identifying Chemical Carcinogens. Environmental Health Perspectives. 2008;116(11):1439-1442.

[19] Löser E. A 2 year oral carcinogenicity study with cadmium on rats. Cancer Lett. 1980;9:191–198.

[20] Soffritti M, Belpoggi F, Padovani M, Lauriola M, Degli Esposti D, Minardi F. Life-time carcinogenicity bioassays of toluene given by stomach tube to Sprague-Dawley rats. Eur J Oncol. 2004;9:91–102.

[21] Bucher JR. The National Toxicology Program rodent bioassay: designs, interpretations, and scientific contributions. Ann NY Acad Sci.2002;982:198–207

[22] Haseman J, Melnick R, Tomatis L, Huff J. Carcinogenesis bioassays: study duration and biological relevance. Food Chem Toxicol. 2001;39:739–744

[23] Kodell RL, Lin KK, Thorn BT, Chen JJ. Bioassays of shortened duration for drugs: statistical implications. Toxicol Sci. 2000;55:415–432.

[24] Haseman J, Melnick R, Tomatis L, Huff J. Carcinogenesis bioassays: study duration and biological relevance. Food Chem Toxicol. 2001;39:739–744

[25] Huff J. Chemicals studied and evaluated in long-term carcinogenesis bioassays by both the Ramazzini Foundation and the National Toxicology Program: in tribute to Cesare Maltoni and David Rall. Ann NY Acad Sci.2002;982:208–230.

[26] Huff J, Lunn RM, Waalkes MP, Tomatis L, Infante PF. Cadmium-induced cancers in animals and in humans. Int J Occup Environ Health.2007;13:202–212

[27] Maltoni C. The contribution of experimental (animal) studies to the control of industrial carcinogenesis. Appl Occup Environ Hyg. 1995;10:749–760.

[28] Soffritti M, Belpoggi F, Minardi F, Maltoni C. Ramazzini Foundation cancer program: history and major projects, life-span carcinogenicity bioassay design, chemicals studied, and results. Ann NY Acad Sci. 2002;982:26–45

NRDC suggests that the SAP recommend that EPA incorporate the Portier (2016) analysis with the adjustment for lifetime exposure consistent with NIEHS standard practice, to more accurately represent realistic lifetime exposures to glyphosate in the general population as well as for workers and agricultural communities.

#4 Comment on EPA's use of the genotoxicity and mechanistic information

EPA included in its review published reports as well as information provided in recent international evaluations of glyphosate (IARC 2015, EFSA 2015, JMPR 2016). However, EPA also included evidence provided by industry-sponsored reviews of studies that were not available to EPA. This is very concerning. EPA acknowledges that sixteen studies for glyphosate technical (pure glyphosate) that were included in Kier and Kirkland (2013) were not available to the agency. Kier and Kirkland was sponsored by a consortium of glyphosate manufactures, including Monsanto.[29] The article declaration of interest says, "Larry Kier and David Kirkland were paid consultants of the Glyphosate Task Force for the preparation of this review. The Glyphosate Task Force is a consortium of 25 European glyphosate registrants, listed on http://www.glyphosatetaskforce.org/. Larry Kier is also a past employee of Monsanto Company" (Kier and Kirkland 2013).[30] The Kier and Kirkland review concludes that glyphosate and glyphosate-based formulations (GBFs) "tend to elicit DNA damage effects at high or toxic dose levels, but the data suggest that this is due to cytotoxicity rather than DNA interaction with GBF activity perhaps associated with the surfactants present in many GBFs. Glyphosate and typical GBFs do not appear to present significant genotoxic risk under normal conditions of human or environmental exposures."

Did EPA request the original data set in Kier and Kirkland (2013), instead of relying on an industry-sponsored review article? If not, why not? If so, why was it not provided? Without access to the original data set, the public cannot independently scrutinize EPA's review of the industry review.

EPA's conclusions and summary are as follows: "In the weight of evidence analysis, studies evaluating endpoints that measured gene mutations and chromosomal aberrations (i.e. permanent DNA damage) were given more weight than endpoints reflecting DNA events that may be transient or reversible such as primary DNA damage (e.g., comet assays). In vivo studies in mammals were given the greatest weight and more weight was given to doses and routes of administration that were considered relevant for evaluating genotoxic risk based on human exposure to glyphosate. Also, since the molecular mechanisms underlying the observation of SCEs are unclear and thus, the consequences of increased frequencies of SCEs are unclear, the data from this test were given low weight in the overall analysis" (EPA 2016 p. 126).

Unfortunately, EPA is very much in step with the May 2016 review by the Joint FAO-WHO Meeting on Pesticide Residues (JMPR), which also favored unpublished and guideline studies sponsored by industry, weighted some genotoxic endpoints higher than others based on a perception of severity, gave less

[29] Kier LD, Kirkland DJ. Review of genotoxicity studies of glyphosate and glyphosate-based formulations. Crit Rev Toxicol. 2013 Apr;43(4):283-315.

[30] Kier LD, Kirkland DJ. Review of genotoxicity studies of glyphosate and glyphosate-based formulations. Crit Rev Toxicol. 2013 Apr;43(4):283-315.

weight to intraperitoneal injection routes of exposure which it considered less physiologically relevant, and eliminated studies in non-mammalian species. These approaches are inappropriate for EPA, which must follow its Cancer Guidelines.

In contrast to the EPA and JMPR review, the earlier IARC assessment (March 2015) concluded that there was "strong" evidence from mechanistic studies showing that glyphosate caused damage to the cell's genetic information (genotoxicity), which can lead to abnormal cell function and ultimately a cancerous cell. IARC also identified cellular studies showing that glyphosate caused oxidative stress in cells, which can lead to cellular damage and elevate the risk of a cell becoming cancerous. This mechanistic evidence - both genotoxicity and oxidative stress - provides a plausible explanation for how glyphosate may cause cancer, and therefore IARC considered it as supportive evidence.

NRDC strongly disagrees with EPA's dismissal or reduced weighting of many of the positive studies, and its higher weighting of guideline studies which are most often the industry-sponsored studies generated to support regulatory approval. NRDC is especially concerned that EPA relied on a review article – particularly one sponsored by the industries whose products are the target of this assessment – instead of the original studies.

#5 Comment on EPA's use of the Bradford Hill criteria

The Bradford Hill criteria are included in the Cancer Guidelines to help evaluate the strength of an association, where the more criteria are fulfilled, the more likely that there is an association between exposure and outcome. However, neither Bradford Hill nor the EPA Cancer Guidelines ever meant them to be used as requirements. That is, if one or more of the Hill criteria are not fulfilled, that should not be taken as evidence that no association exists. As Bradford Hill (1965) wrote, and EPA emphasized in its 2005 Cancer Guidelines, "None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question — is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?" (Hill 1965 as quoted in the EPA Cancer Guidelines 2005, p. 39). In its assessment of whether or not glyphosate exposure is associated with an elevated cancer risk, EPA has not used the Hill criteria to weigh the strength of an association, but rather to hold each piece of data up against the criteria one at a time, and then to dismiss it piecemeal. Only by such inappropriate means could EPA take so much data that reports a link with cancer, and make an overall conclusion that glyphosate is "Not Likely to be Carcinogenic to Humans" (EPA 2016, p. 13 ;CARC 2015).

NRDC disagrees with the way EPA has used the Bradford Hill criteria. EPA has not the criteria as a guide to evaluate the strength of an association, but as a check list to dismiss evidence of harm. As Bradford Hill himself emphasized, putting of health-protective restrictions and regulations while we await stronger evidence of harm will only lead to continuing harm.

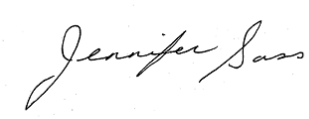
> "*All scientific work is incomplete - whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, to postpone action that it appears to demand at a given time. Who knows, asks Robert Browning, but the world may end tonight? True, but on available evidence most of us make ready to commute on the 8:30 next day*."
> - Austin Bradford Hill

CONCLUSION

EPA has classified glyphosate as "Not Likely" to cause cancer in humans, despite studies reporting elevated cancer risk in humans and laboratory animals, and a mechanism supporting a link with cancer. NRDC disagrees with EPA's conclusion. "Declaring a chemical as not hazardous, or reducing a level of health protection, should require validation, not speculation" (Melnick et al 2003).[31] It should be a much higher standard, requiring evidence of lack of carcinogenicity; see for example, the description by IARC of Group 4: Probably not carcinogenic to humans.[32] Dr. Ron Melnick, retired career NIEHS scientist, warned that serious public health consequences may follow if – as EPA has done here in its review of glyphosate – chemicals are misclassified as less toxic or non-toxic based on untested mechanistic hypotheses, poorly validated tests, or incomplete data sets.

Thank you for the opportunity to provide comments.

Respectfully,



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[31] Melnick RL, Kamel F, Huff J. Declaring chemicals "not carcinogenic to humans" requires validation, not speculation. Environ Health Perspect. 2003 Apr;111(4):A203-4.

[32] IARC Preamble. http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf

APPENDIX

IARC – Glyphosate is a probable (Group 2A) human carcinogen (March 2015)

In early 2015 The International Agency for Research on Cancer (IARC) - the cancer evaluation arm of the World Health Organization - convened a meeting of 17 scientific experts from 11 countries to review the cancer data regarding glyphosate, and published their findings in mid-2016.[33]

The IARC Working Group reviewed ten publicly-available laboratory studies, five on mice and five on rats, culled from the public literature and reports of the EPA (1991) and the WHO (2004). One mouse study reported a positive trend for hemangiosarcoma (WHO report) and another mouse study reported a rare tumor called a renal tubular carcinoma (EPA study) associated with glyphosate in long-term feeding studies. In both cases, effects were stronger in the males than females. Of the five rat studies, two reported significant increases in pancreatic islet-cell adenomas in male rats (EPA report); two studies did not find significant cancer increases; and one study did not last long enough to draw any conclusions about cancer risks. The Working Group determined that there was a statistically significant trend in the occurrence (incidence) of hemangiosarcoma in the male mice, but not the female mice.

The IARC experts also reviewed cellular studies and determined that there was "strong" evidence from mechanistic studies showing that glyphosate caused damage to the cell's genetic information (genotoxicity), which can lead to abnormal cell function and ultimately a cancerous cell. Studies also showed that glyphosate also caused oxidative stress in cells, which can lead to cellular damage and elevate the risk of a cell becoming cancerous. This mechanistic evidence - both genotoxicity and oxidative stress - provides a plausible explanation for how glyphosate may cause cancer, and therefore supports the evidence from the animal studies.

The IARC experts found that the epidemiologic studies provided some evidence of cancer, in particular elevated risk of non-Hodgkin lymphoma (NHL), but that the evidence was "limited" because the studies were either weakly positive or did not find a cancer risk at all.

The IARC experts unanimously voted to classify glyphosate as a probable (Group 2A) human carcinogen, based on three lines of evidence:

- "sufficient" evidence of cancer in mice and rats that were fed glyphosate over a several years;
- "strong" evidence of genotoxicity and oxidative stress from mechanistic or cellular studies; and
- "limited" evidence from epidemiologic studies (concerning NHL), particularly pesticide applicators and farmworkers.

IARC is specifically qualified to conduct such chemical cancer assessments like this one. IARC has been conducting such reviews for forty years, and has evaluated hundreds of chemicals. IARC is considered an authoritative body by governments around the world, and non-industry experts testify as to its integrity and scientific credibility, often in the face of harsh criticism from the industries whose products are being reviewed (Pearce et al 2015).[34]

[33] http://monographs.iarc.fr/ENG/Monographs/vol112/mono112-09.pdf

[34] http://ehp.niehs.nih.gov/1409149/

EFSA – Glyphosate unlikely to be carcinogenic or genotoxic (Nov 2015)

Meanwhile, another wing of the World Health Organization, the European Food Safety Agency (EFSA), reviewed glyphosate later in 2015 and found it unlikely to be carcinogenic or genotoxic.[35] Unlike IARC, the EFSA did not examine glyphosate formulations, but only considered studies on glyphosate alone. EFSA noted that adverse health effects reported in the epidemiologic studies could be related to glyphosate reactions with other constituents, or co-formulants, and noted in particular concerns with tallowamine. [36]

The EFSA report is based on findings of the German Federal Institute for Risk Assessment - the BfR[37] - which received a first draft of the science directly from the Glyphosate Task Force (GTF)[38], whose members include Monsanto and Syngenta and other agrochemical corporations. In terms of its assessment process, EFSA describes it as being standard procedure to have the agrochemical company supply the scientific information to the Member state (Germany and Croatia in this case), whose report then goes to EFSA to make a final evaluation.[39]

EFSA's report recommended not only re-approval of glyphosate, but also raising the acceptable daily intake (ADI) for people's everyday exposure to glyphosate (from 0.3 to 0.5 mg/kg-day), including through residues on food. The report recommended that an acute Reference Dose (aRfD) for glyphosate be established, but set it at the same level as the ADI, thereby supporting higher exposure limits and weaker health protections for both acute and chronic exposures.[40]

The dramatic inconsistency between the EFSA and IARC cancer reports spurred 96 prominent scientists from 25 countries to voice strong opposition to the EFSA report. Their letter to the European Commission states that the IARC decision is "by far the more credible," and urges the European Commission to "disregard the flawed EFSA finding on glyphosate" (Portier et al 2016).[41]

JMPR – unlikely to be carcinogenic to humans through dietary exposure (May 2016)

In May 2016, the Joint FAO-WHO Meeting on Pesticide Residues (JMPR) conducted a risk assessment of glyphosate, and concluded that through the dietary route of exposure, the genotoxic and carcinogenic risks of glyphosate were minimal.

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[35] https://www.nrdc.org/experts/jennifer-sass/glyphosate-iarc-got-it-right-efsa-got-it-monsanto

[36] http://www.bfr.bund.de/en/the_bfr_has_finalised_its_draft_report_for_the_re_evaluation_of_glyphosate-188632.html

[37] http://www.bfr.bund.de/en/the_bfr_has_finalised_its_draft_report_for_the_re_evaluation_of_glyphosate-188632.html

[38] http://www.glyphosatetaskforce.org/

[39] http://www.efsa.europa.eu/en/press/news/151112

[40] http://www.efsa.europa.eu/en/press/news/151112

[41] http://jech.bmj.com/content/early/2016/03/03/jech-2015-207005.full

Some of the differences between the JMPR and IARC review are as follows (as summarized by Dr. David Eastmond, a JMPR committee member):[42]

- JMPR reviewed both published and unpublished (mainly guideline) studies that were not publicly available, whereas IARC reviewed only publicly available studies.
- JMPR gave more weight to guideline studies from validated protocols. These are studies sponsored by the chemical manufacturer to support the chemical approval process.
- JMPR gave more weight to genotoxic studies of endpoints considered to be more serious (mutation, chromosomal alterations) than endpoints it considered less serious or possibly transient (DNA strand breaks, SCE's). However, there is no evidence that these are less indicative of cancer risks.
- JMPR gave less weight to intraperitoneal injection routes of exposure, which it considers to be less physiologically relevant. Giving it less weight may be appropriate for JMPR, which only considers dietary exposures, but not for US EPA that must consider the inherent carcinogenicity of glyphosate.
- JMPR considered the results of the human biomonitoring studies to be equivocal whereas IARC considered them to be significant supportive data.

JMPR claimed that there was no evidence of immune toxicity, which it would have considered supportive of NHL in humans, despite one rat study JMPR reviewed that reported elevated risk of thyroid C-cell carcinomas.

JMPR heavily weighted the Agriculture Health Study (AHS; DeRoos et al 2005) on glyphosate pesticide applicators, because it is a large well-conducted cohort study of high quality. However, JMPR (and EPA) reported that it did not find a link with cancer. EPA also ranked the AHS study highly, and also described the results as negative. This is inaccurate. I discuss this in more detail in Charge Question #2, but in a nutshell the AHS study reports elevated risks for bladder, kidney melanoma, and colon cancers in an ever/never exposure metric comparison. This is supported by the industry-sponsored meta-analysis by Chang and Delzell (2016) that reported a positive and marginally statistically significant association between any versus no use of glyphosate and risk of NHL (meta-RR = 1.3, 95% confidence interval (CI) = 1.0–1.6, based on six studies) and MM (meta-RR = 1.4, 95% CI = 1.0–1.9; four studies). IARC considered the epidemiology data to provide "limited" evidence of cancer, which is a more accurate and defensible reporting of the data.

JMPR considered "incidental" the significantly increased incidence of tumors in ten rat studies:

- Interstitial cell tumors of the testes (1 study)
- Pancreatic islet cell adenoma (1 study)
- Thyroid C-cell tumors (1 study)
- Skin keratoma (2 studies, males only; no dose-response in one study; only the trend test, not pairwise test, was statistically positive in the other study)

JMPR dismissed evidence from seven mouse studies of lymphoma (positive trend in 3 studies; negative trend in 1 study; possible increase in 1 study), because the increased risk was significant in a trend test but not in a pairwise statistical comparison, and JMPR felt that the incidences in the high dose animals

[42] The differences in the JMPR and IARC reviews is well presented by Dr. David Eastmond, a member of the JMPR review committee, at the Toxicology Forum meeting in July, 2016. I have summarized some of the main points of his presentation. http://dialogue.toxforum.org/p/cm/ld/fid=26

were within the range of historical control data. While EPA drew similar conclusions, EPA violated its own Cancer Guidelines in doing so; the Guidelines are clear that either statistical test can be used.

JMPR dismissed evidence from four mouse studies of kidney adenomas (positive trend in 4 studies) for much the same reasons as with the lymphomas. The trend test was significant but thepairwise comparisons were not. Adenomas were of greatest significance at the highest doses (shouldn't this be expected?), which JMPR felt exceeded the recommended dose limit (up to 50,000 ppm in the diet, which is 7,500 mg/kg in males and 8,700 mg/kg in females). EPA made similar arguments, again violating its own Cancer Guidelines which state that: "significance in either kind of test is sufficient" (EPA Cancer Guidelines, p. 140), and that "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 carcinogenicity of the tested agent per se" (EPA Cancer Guidelines p.140).

JMPR's final conclusions are that, "The Meeting concluded that glyphosate is not carcinogenic in rats but could not exclude the possibility that it is carcinogenic in mice at very high doses. In view of the absence of carcinogenic potential in rodents at human-relevant doses and the absence of genotoxicity by the oral route in mammals, and considering the epidemiological evidence from occupational exposures, the Meeting concluded that glyphosate is unlikely to pose a carcinogenic risk to humans from exposure through the diet."[43] This is a strangely hamstrung statement, acknowledging that it cannot exclude the possibility of cancer risk, but then drawing distinctions between risk at high and low doses directly from the studies, which is never appropriate (too few animals per dose, not the purpose or design of the studies, fails to consider pharmacokinetic differences between species, etc.), and disregarding the epidemiologic evidence of cancers from real-world exposures in real-world people. Lastly, restricting its conclusions to the oral route of exposure would be inappropriate for EPA, which by law must consider all routes of exposures as well as occupational scenarios.

In advance of the JMPR meeting on glyphosate, NRDC wrote a letter[44] raising concerns about three committee members who have close financial ties with the global food and chemical industry trade group International Life Sciences Institute (ILSI) and its scientific arm, Health and Environmental Sciences Institute (HESI). In its 2014 Annual Report, ILSI stated that financial support for its North American programs is primarily funded by its industry membership, which includes glyphosate producers such as Monsanto Company and DuPont. Our concerns were acknowledged but disregarded.[45]

[43] http://www.who.int/foodsafety/jmprsummary2016.pdf

[44] NRDC letter to JMPR. June 2015. https://www.nrdc.org/sites/default/files/hea_15061501a.pdf

[45] JMPR response to NRDC. August 2015. https://www.nrdc.org/sites/default/files/hea_15091301a.pdf