Submitted via E-mail

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RE: Comments on Proposed No Significant Risk Level for Glyphosate

Dear Ms. Barajas-Ochoa:

These comments are submitted on behalf of the Center for Biological Diversity, the Center for Environmental Health, Center for Food Safety, Pesticide Action Network, Environmental Working Group, CALPIRG, Safe Ag Safe Schools, Beyond Toxics, As You Sow, California Environmental Health Initiative, Farmworker Association of Florida, California Rural Legal Assistance Foundation, Californians for Pesticide Reform, Friends of the Earth and San Francisco Baykeeper. Our organizations support the Office of Environmental Health Hazard Assessment (OEHHA)'s proposal to adopt a No Significant Risk Level (NSRL) for exposure to glyphosate under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Prop 65).

The proposed NSRL of 1100 micrograms per day is based on a mouse study by Atkinson et al. However, other quality studies discussed in these comments provide a more scientifically sound and health protective basis for calculating the NSRL. We therefore request that OEHHA assess these studies, and recommend in particular that OEHHA base a revised NSRL on the Lankas study.[1]

I. OVERVIEW

Glyphosate is the most widely used pesticide in the United States and in the world. It is also the most widely used pesticide in the state of California as measured by acreage treated.[2]

[1] Cal. Health & Safety Code Sec. 25249.5 *et seq.*; *see* People ex. rel. Lungren v. Super. Ct. (American Standard, Inc.), 14 Cal. 4th 294, 307, 314 (1996) (Cal. Supreme Court upholds that the protective purposes of Prop 65 are to be broadly construed).
[2] Calif. Dept. of Pesticide Regulation. Summary of Pesticide Use Report Data – 2015. Available at: http://www.cdpr.ca.gov/docs/pur/pur15rep/15sum.htm

The massive use of glyphosate is especially concerning in light of its potential health impacts. The World Health Organization's International Agency for Research on Cancer (IARC) conducted an exhaustive review of the publically available scientific literature in 2015 and concluded that glyphosate is "probably carcinogenic to humans" (Group 2A).[3] IARC carefully weighed evidence in three areas, and found that: 1) There was sufficient evidence to conclude that glyphosate causes cancer in animal studies; 2) There was limited evidence that exposure to glyphosate causes cancer (non-Hodgkin lymphoma) in humans; and 3) There was strong evidence that glyphosate can damage DNA and induce oxidative stress,[4] two well characterized pathways that can lead to cancer.[5,6]

IARC's finding that glyphosate causes cancer in animals prompted OEHHA to announce that it will list glyphosate as a known carcinogen under California's Proposition 65 law.[7] The agency is now taking public comment on its suggested NSRL for glyphosate of 1100 micrograms per day.

As a leader in environmental and public health protection, California has undergone a recent paradigm shift in the management of toxic chemicals. Now over 30 years old, Prop 65 has been applied to afford broad protections for the public from toxic chemical exposure.[8] In 2007, the California EPA and other agencies established the California Green Chemistry Initiative to stimulate the design, use, and disposal of "green" or less hazardous chemical substances.[9] In 2013, the Safer Consumer Products regulations were passed that require manufacturers or other responsible parties to seek safer alternatives to harmful chemical ingredients in widely used products.[10] Once it is listed under Prop 65, glyphosate will automatically become a candidate chemical and potentially be selected for the alternative assessment process.[11] There is clear public and political momentum toward stricter regulatory standards for chemicals in general based on the health hazards

[3] WHO. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 112: Some Organophosphate Insecticides and Herbicides. Glyphosate. 2017. Available at: http://monographs.iarc.fr/ENG/Monographs/vol112/mono112.pdf
[4] *Id.*
[5] Klaunig, J.E., et al., The role of oxidative stress in chemical carcinogenesis. Environ Health Perspect, 1998. 106 Suppl 1: p. 289-95.
[6] Lee, S.J., et al., Distinguishing between genotoxic and non-genotoxic hepatocarcinogens by gene expression profiling and bioinformatic pathway analysis. Sci Rep, 2013. 3: p. 2783.
[7] OEHHA. The California Environmental Protection Agency's Office of Environmental Health Hazard Assessment. Glyphosate to be Listed under Proposition 65 as Known to the State to Cause Cancer. Available at: https://oehha.ca.gov/proposition-65/crnr/glyphosate-be-listed-under-proposition-65-known-state-cause-cancer
[8] People ex. rel. Lungren v. Super. Ct. (American Standard, Inc.) (1996) 14 Cal. 4th 294, 307, 314 (Cal. Supreme Court upholds that the protective purposes of Prop 65 are to be broadly construed.) .
[9] State of California, California EPA. California Green Chemistry Initiative Final Report. Dec. 2008. Available at: http://www.sehn.org/pdf/GREEN_Chem.pdf.
[10] Safe Consumer Products regulations were enacted pursuant to Health and Safety Code Sections 25252 & 25253. *See* Final Statement of Reasons Safe Consumer Products. Sec. 2. Available at: https://www.dtsc.ca.gov/LawsRegsPolicies/Regs/upload/Final-Statement-of-Reasons-corrected-Table-of-Contents.pdf.
[11] 22 C.F.R. Div. 4.5 Ch. 55 Sec. 69502.2(a)(1)(A); Cal. Dept. of Toxic Substances Control. Safer Consumer Products. Authoritative Lists. Available at: http://www.dtsc.ca.gov/SCP/SourceLists.cfm.

caused by chronic exposures to toxic environmental chemicals, including glyphosate, for which concerns over the risks of exposure have rapidly expanded over the past several years.[12]

We strongly urge OEHHA to uphold its statutory purpose to protect humans from the harmful impacts of glyphosate and lower the NSRL to account for studies demonstrating cancer-causing effects at concentrations more than an order of magnitude lower than 1000 mg/kg/day.[13]

II. OEHHA'S PROPOSED NSRL DOES NOT RELY ON THE MOST SENSITIVE STUDY OF ACCEPTABLE SCIENTIFIC QUALITY

The IARC used multiple lines of evidence to identify glyphosate as a Group 2A "probable" human carcinogen, which ultimately led OEHHA to list this chemical under the "Labor Code" mechanism of Prop 65. OEHHA has identified the Atkinson et al. 1993 study[14] as the most sensitive study of sufficient quality to guide the suggested NSRL. We disagree with this conclusion.

The IARC's guidance prohibits the agency from relying on information that is not publicly available or where limited data are provided. We fully agree with the importance of transparency in science, especially when coming to a hazard classification. The IARC followed its own guidelines in the cancer assessment of glyphosate and this is one reason the analysis was so rigorous, robust and scientifically defensible.

OEHHA has already concurred with the IARC's cancer hazard determination and is now undertaking a different process to determine a NSRL. Once a cancer hazard has been identified it is absolutely necessary to use the most sensitive study of acceptable quality to identify a safety threshold dose. We believe that, for this process, it is important that OEHHA take into account all scientific studies on the carcinogenicity of glyphosate and not just the studies that IARC assessed in its analysis. Once a hazard is identified, it is extremely important to ensure that people will not potentially be exposed to levels that can cause harm.

Since IARC's determination, additional tumor data have come to light – both in studies not available to IARC's Glyphosate Working Group, as well as previously undisclosed

[12] Myers, J.P., Antoniou, M.N., Blumberg, B., Carroll L., Colborn, T., Everett, L.G., Hansen, M., et al. "Concerns over Use of Glyphosate-Based Herbicides and Risks Associated with Exposures: A Consensus Statement." *Environmental Health* 15, no. 1 (December 2016). doi:10.1186/s12940-016-0117-0.

[13] OEHHA. Initial statement of reasons title 27, California code of regulations. Proposed amendment to: section 25705(b) specific regulatory levels posing no significant risk. Glyphosate. Safe drinking water and toxic enforcement act of 1986 proposition 65. Available at: https://oehha.ca.gov/media/downloads/crnr/glyphosate032917isor.pdf.

[14] Atkinson, C., Martin, T., Hudson, P., and Robb, D. (1993). Glyphosate: 104 week dietary carcinogenicity study in mice. Inveresk Research International, Tranent, EH33 2NE, Scotland. IRI Project No. 438618. April 7, 1993. MRID 49631702. Also identified as: Cheminova. Glyphosate: 104 week dietary carcinogenicity study in mice. Tranent, UK: Inveresk Research International, Ltd; (1993) in Greim et al. (2015).

tumor findings in studies that IARC did evaluate.[15] Some of these additional tumor data were also assessed in EPA's most recent evaluation of glyphosate's carcinogenic potential, and reviewed in Greim et al.[16]

We have identified three findings from studies reviewed by EPA that show statistically significant increases in tumor incidence with oral administration of glyphosate at doses far below 1000 mg/kg/day. These studies are listed in section III below.

III. OEHHA MUST CONSIDER ALL AVAILABLE SCIENCE THAT DEMONSTRATES A LOWER NSRL IS NECESSARY TO PROTECT HUMAN AND ENVIRONMENTAL HEALTH

We have identified three studies demonstrating that exposure to glyphosate below 1000 mg/kg/day leads to a statistically significant increase in the development of multiple tumors. Each of these studies was deemed of high enough scientific quality to be included in the EPA's evaluation of glyphosate's carcinogenic potential.[17] OEHHA often relies on EPA's study inclusion criteria as a guide for what studies the agency will rely on for threshold dose.[18]

These studies are as follows:

1. Wood et al. 2009[19]

   This study found a highly statistically significant trend in malignant lymphomas at doses of 71.4, 234.2 and 810 mg/kg/day in CD-1 mice.

[15] Portier, C. Open letter re: Review of the Carcinogenicity of Glyphoate by EChA, EFSA and BfR, to Jean Claude Juncker, President, European Commission, May 28, 2017.
[16] Greim, H., Saltmiras, D., Mostert, V., & Strupp, C. (2015). Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies. *Critical Reviews in Toxicology*, *45*(3), 185–208. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4819582/#CIT0024.
[17] EPA. Office of Pesticides Programs. Glyphosate Issue Paper: Evaluation of Carcinogenic Potential. September 12, 2016. Available at: https://www.epa.gov/sites/production/files/2016-09/documents/glyphosate_issue_paper_evaluation_of_carcincogenic_potential.pdf.
[18] For an example refer to "Proposed MADL for Atrazine, Propazine, Simazine, 2,3-Diamino-6-Chloro-S-Triazine (DACT), Des-Ethyl Atrazine (DEA), and Des-Isopropyl Atrazine (DIA)." OEHHA used an unpublished GLP-compliant study used by EPA to designate the MADL for atrazine (Morseth, 1996). Available at: https://oehha.ca.gov/media/downloads/crnr/isortriazines2006122015.pdf.
[19] Wood, E., Dunster, J., Watson, P., and Brooks, P. (2009b) Glyphosate Technical: Dietary Carcinogenicity Study in the Mouse. Harlan Laboratories Limited, Shardlow Business Park, Shardlow, Derbyshire DE72 2GD, UK. Study No. 2060-011. April, 22, 2009. MRID 49957402. Also referred to as Nufarm. (2009a). Glyphosate Technical: Dietary Carcinogenicity Study in the Mouse. Derbyshire, UK: Harlan Laboratories Ltd. in Greim et al. (2015).

Table 4.16. Malignant Lymphomas in Male CD-1 Mice (Wood et al., 2009b) Fisher's Exact Test and Cochran-Armitage Trend Test Results.				
Dose (mg/kg/day)	0	71.4	234.2	810
Malignant Lymphoma Incidence (%)	0/51 (0)	1/51 (2)	2/51 (4)	5/51 (10)
Raw p-value =	0.007**	0.500	0.248	0.028*
Sidak p-value =	--	0.875	0.574	0.082

Note: Trend test results denoted at control; * denotes significance at p=0.05; ** denotes significance at p=0.01. a= Number of tumor bearing animals/Number of animals examined.

Table adapted from EPA, 2016[20]

2. Lankas 1981[21]

This study found a highly statistically significant trend in testicular interstitial cell tumors in male Sprague-Dawley rats at doses of 3.05, 10.3 and 31.49 mg/kg/day, as well as a highly significant difference in tumor incidence between high-dose and control groups.

Table 4.1. Testicular Interstitial Cell Tumors in Male Sprague-Dawley Rats (Lankas, 1981) Cochran-Armitage Trend Test & Fisher's Exact Test Results				
Dose (mg/kg/day)	0	3.05	10.3	31.49
Incidence (%)	0/50 (0)	3/47 (6)	1/49 (2)	6/44 (12)
Raw p-value =	0.009**	0.121	0.500	0.013*
Sidak p-value =	--	0.321	0.875	0.039*

Note: Trend test results denoted at control; * denotes significance at p=0.05; ** denotes significance at p=0.001.

Table adapted from EPA, 2016[22]

3. Stout and Ruecker, 1990[23]

[20] EPA. Office of Pesticides Programs. Glyphosate Issue Paper: Evaluation of Carcinogenic Potential. September 12, 2016. Pg. 89. Available at: https://www.epa.gov/sites/production/files/2016-09/documents/glyphosate_issue_paper_evaluation_of_carcincogenic_potential.pdf.

[21] Lankas, G, P. (1981) A Lifetime Study of Glyphosate in Rats. Report No. 77-2062 prepared by Bio Dynamics, Inc. EPA Accession. No. 247617 – 247621. December 23, 1981. MRID 00093879. Also referred to as Monsanto. (1981). A Lifetime Feeding Study of Glyphosate (ROUNDUP Technical) in Rats. East Millstone, New Jersey, USA: Bio/dynamics Inc in Greim et al.

[22] EPA. Office of Pesticides Programs. Glyphosate Issue Paper: Evaluation of Carcinogenic Potential. September 12, 2016. Pg. 74-75. Available at: https://www.epa.gov/sites/production/files/2016-09/documents/glyphosate_issue_paper_evaluation_of_carcincogenic_potential.pdf.

[23] Stout, L. D. and Ruecker, P.A. (1990). Chronic Study of Glyphosate Administered in Feed to Albino Rats. MRID No. 41643801; Historical Controls. MRID 41728700. Also referred to as Monsanto. (1990). Chronic Study of Glyphosate Administered in Feed to Albino Rats. St. Louis, MO, USA: Monsanto Agricultural Company in Greim et al.

In this study, statistically significant trends were observed for both thyroid adenomas and combined thyroid adenomas/carcinomas in female Sprague-Dawley rats at the dose levels indicated in the table below.[24]

Table 4.7. Thyroid C-Cell Tumors in Female Sprague Dawley Rats Cochran-Armitage Trend Test & Fisher's Exact Test Results (Stout and Ruecker, 1990).

Tumor Type	0 mg/kg/day	113 mg/kg/day	457 mg/kg/day	1183 mg/kg/day
Adenoma				
Incidence	2/57[a]	2/60	6/59[b]	6/55
(%)	(4)	(7)	(10)	(11)
Raw p-value =	0.040*	0.710	0.147	0.124
Sidak p-value =	--	0.976	0.380	0.328
Carcinoma				
Incidence	0/57	0/60	1/59[c]	0/55
(%)	(0)	(0)	(2)	(0)
Raw p-value =	0.494	1.000	0.509	1.000
Sidak p-value =	--	1.000	0.509	1.000
Adenoma/Carcinoma				
Incidence	2/57	2/60	7/59	6/55
(%)	(4)	(3)	(12)	(11)
Raw p-value =	0.042*	0.710	0.090	0.124
Sidak p-value =	--	0.976	0.246	0.328

Note: Trend test results denoted at control; * denotes significant at p=0.05.
a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55.

Table adapted from EPA, 2016[25]

This study also found a statistically significant increase in pancreatic islet cell adenomas in male Sprague-Dawley rats at the low dose of 89 mg/kg/day.

IV. OEHHA MUST DO AN INDEPENDENT ANALYSIS OF THESE STUDIES AND NOT RELY ON EPA'S FLAWED CONCLUSIONS

These three studies clearly indicate that oral exposure to glyphosate at concentrations much lower than 1000 mg/kg/day can result in treatment-related increases in tumor incidence. One reason for the relatively high NSRL based on the Atkinson et al. study is that the result depends on tumor incidence in the high-dose group. In contrast, the three studies we describe above have a more consistent dose-response pattern, as do others OEHHA might consider.[26] Technical comments and analysis submitted by Dr. Chris Portier, former director of the National Center for Environmental Health at the Centers for Disease Control and Prevention and former associate director of the National Institute of Environmental Health Sciences, to the glyphosate Scientific Advisory Panel (SAP) also concluded that glyphosate exhibited strong evidence of carcinogenicity in studies

[24] EPA. Office of Pesticides Programs. Glyphosate Issue Paper: Evaluation of Carcinogenic Potential. September 12, 2016. Pg. 77-78. Available at: https://www.epa.gov/sites/production/files/2016-09/documents/glyphosate_issue_paper_evaluation_of_carcincogenic_potential.pdf.
[25] *Id.* at 78.
[26] See e.g. Portier, C. Open letter re: Review of the Carcinogenicity of Glyphoate by EChA, EFSA and BfR, to Jean Claude Juncker, President, European Commission, May 28, 2017.

involving dose levels below 1000 mg/kg/day (a copy of this letter was submitted with these comments).[27]

After analyzing these studies, the EPA concluded in its evaluation of the carcinogenic potential of glyphosate that the tumors were not treatment related. Of note is the fact that the EPA did not follow its own guidelines[28] or internationally recognized Organisation for Economic Co-operation and Development (OECD) guidelines[29] used by IARC when analyzing each of these three studies. This simple fact was agreed upon unanimously by the SAP that analyzed EPA's glyphosate assessment[30] and was summarized very nicely in comments to the SAP by Dr. Portier.[31]

EPA's conclusion on these and other studies is flawed for multiple reasons.

1. The agency repeatedly used a lack of monotonic dose response in tumor incidence as justification to discount statistically significant findings. Nowhere in EPA's or OECD's guidelines are there any mention of carcinogens needing to follow a monotonic dose response pattern, and the recent glyphosate SAP rejected this as an invalid criterion. In fact, comments were made during the SAP meeting that throwing out dose responses that are non-monotonic "should not be a criterion at all."[32] The valid criterion for dose-response is a statistically significant result from a trend test, and statistically significant trends are quite often found even when the dose-response pattern is not monotonic. In addition, we know that endocrine disruptors, which can be involved in carcinogenesis, often have effects at low but not higher doses, highlighting the importance of putting protections in place to

[27] Comments of Christopher J. Portier, PhD on the Glyphosate Issue Paper: Evaluation of Carcinogenic Potential. October 4, 2016. Document ID EPA-HQ-OPP-2016-0385-0371. Available at: https://www.regulations.gov/document?D=EPA-HQ-OPP-2016-0385-0371

[28] EPA. Guidelines for Carcinogen Risk Assessment. March 2005. Pgs 2-20 and 2-21. Available at: https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf

[29] OECD. 2012. Guidance Document 116 On The Conduct And Design Of Chronic Toxicity And Carcinogenicity Studies, Supporting Test Guidelines 451, 452 And 453 2nd Edition. Series on Testing and Assessment No. 116. Available at: http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2011)47&doclanguage=en

[30] FIFRA Scientific Advisory Panel Meeting Minutes and Final Report No. 2017-01. (2017). A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: EPA's Evaluation of the Carcinogenic Potential of Glyphosate. Pg 18. Available at https://www.epa.gov/sites/production/files/2017-03/documents/december_13-16_2016_final_report_03162017.pdf

[31] Comments of Christopher J. Portier, PhD on the Glyphosate Issue Paper: Evaluation of Carcinogenic Potential. October 4, 2016. Document ID EPA-HQ-OPP-2016-0385-0371. Available at: https://www.regulations.gov/document?D=EPA-HQ-OPP-2016-0385-0371.

[32] FIFRA Scientific Advisory Panel (SAP) Open Meeting Federal Insecticide, Fungicide, and Rodenticide Act December 13-16, 2016. Meeting transcript, line 14, pg. 993. Document ID EPA-HQ-OPP-2016-0385-0500. Available at: https://www.regulations.gov/document?D=EPA-HQ-OPP-2016-0385-0500

protect the public from chemicals that do not follow the typical "dose makes the poison" paradigm.[33]

2. The agency uses non-significance in one statistical test to discount significance in another. For some of the tumors in these studies, there was a statistically significant finding in the Cochran-Armitage Trend Test or in the Fisher's Exact Test for pairwise comparisons but not in both. The EPA erroneously used this as justification to discount the statistical significance that was present. EPA's Guidelines for Carcinogen Risk Assessment state that, in reference to the trend test and pairwise test, "[s]ignificance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result."[34] Therefore, using the results of one test to cancel out the results of the other test is a violation of the agency's own guidelines and is not a scientifically appropriate course of action for study analysis.

3. The agency improperly used historical control data to discount significant differences between treated animals and the concurrent control cohort for tumors in all three studies. EPA's guidelines caution against the use of historical controls except in very extreme circumstances, stating "[g]enerally 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. Random assignment of animals to groups and proper statistical procedures provide assurance that statistically significant results are unlikely to be due to chance alone."[35] The guidance further goes on to recommend caution for relying solely on concurrent control data when "…incidence rates in concurrent controls are unusually low in comparison with historical controls."[36]

   In the case of the Stout and Ruecker, 1990 study, the EPA uses historical control data from 7 earlier studies indicating a range of 1.8 - 8.3 % spontaneous pancreatic adenoma formation in male Sprague-Dawley rats as a means to cast doubt on the concurrent control value of 2%.[37] The concurrent control spontaneous tumor formation is on the low end, but well within the range of historical controls. It is certainly not "unusually low," which is the bar that must be met using EPA guidance.

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[33] Vandenberg LN, Colborn T, Hayes TB, et al. Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses.*Endocrine Reviews*. 2012;33(3):378-455. doi:10.1210/er.2011-1050.
[34] EPA. Guidelines for Carcinogen Risk Assessment. March 2005. Pg 2-19. Available at: https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf
[35] *Id.* at 2-21
[36] *Id.*
[37] EPA. Office of Pesticides Programs. Glyphosate Issue Paper: Evaluation of Carcinogenic Potential. September 12, 2016. Pg 76. Available at: https://www.epa.gov/sites/production/files/2016-09/documents/glyphosate_issue_paper_evaluation_of_carcincogenic_potential.pdf.

Further, EPA guidance also states that "[w]hen historical control data are used, the discussion should address several issues that affect comparability of historical and concurrent control data, such as genetic drift in the laboratory strains, differences in pathology examination at different times and in different laboratories (e.g., in criteria for evaluating lesions; variations in the techniques for the preparation or reading of tissue samples among laboratories), and comparability of animals from different suppliers. The most relevant historical data come from the same laboratory and the same supplier and are gathered within 2 or 3 years one way or the other of the study under review; other data should be used only with ***extreme*** caution."[38]

The historical control data EPA utilized were from studies up to 7 years older than the Stout and Ruecker, 1990 study.[39] EPA's analysis of Wood et al., 2009 used historical control data from other labs from experiments that took place more than 20 years prior. The data were also not correctly presented as summed up in Dr. Portier's comments.[40] In addition, there was no discussion of possible genetic drift, pathological differences and what suppliers the animals came from. Without these data, it is impossible to know whether these are acceptable historical control cohorts. And the age of many of the studies certainly indicate that they are not.

4. In two of the three studies, there was no indication of preneoplastic lesions to indicate a progressive disease. Dr. Portier chastises EPA for use of this criterion in its analysis, stating in his comments to the FIFRA SAP: "This presumes that all mechanisms by which chemicals induce tumors in animals will involve enough stages that there would be a histologically identifiable preneoplastic lesion from which final tumors are formed. This simply is not the case and this criteria is applied without any concern for its validity by the EPA."[41] Cancer is a progressive disease, but that does not mean that every stage will be readily identifiable on a visual level or even a molecular level given the limited number of tools pathologists currently have. Lack of identifiable pre-neoplastic lesions is simply not a justifiable reason to discount significant data.

5. EPA utilizes two-sided P values to test for significance in pairwise comparisons, when one-sided P tests are more appropriate and should be used in this context.[42]

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[38] EPA. Guidelines for Carcinogen Risk Assessment. March 2005. Pg 2-21. Emphasis added. Available at: https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf
[39] EPA. Office of Pesticides Programs. Glyphosate Issue Paper: Evaluation of Carcinogenic Potential. September 12, 2016. Pg 76, Table 4-3.
[40] Comments of Christopher J. Portier, PhD on the Glyphosate Issue Paper: Evaluation of Carcinogenic Potential. October 4, 2016. Pg 13. Document ID EPA-HQ-OPP-2016-0385-0371. Available at: https://www.regulations.gov/document?D=EPA-HQ-OPP-2016-0385-0371,
[41] *Id.* at 2.
[42] Ludbrook, J. 2013. Should we use one-sided or two-sided P values in tests of significance? Clinical and Experimental Pharmacology and Physiology 40(6): 357-361.

We caution against using these scientifically indefensible excuses to explain away real data. OEHHA should conduct an independent analysis of these studies using the current internationally accepted guidelines for carcinogen risk assessment that IARC uses and EPA's guidance is based on.[43]

V. REQUESTS THAT OEHHA CONSIDER AN INFINITE GLYHPOSATE NSRL ARE BASELESS AND SHOULD BE DENIED

During the public hearing that OEHHA held on June 7th, 2017, a lawyer representing Monsanto cited the 2004 court case Baxter Healthcare Corporation v. Denton as precedent for why OEHHA should make the glyphosate NSRL infinite (effectively exempting all products from the labeling mandate). We believe it is necessary to rebut this claim as the two cases differ significantly in many ways as to not be relevant to one another.

In 1988, di(2-ethylhexyl)phthalate (DEHP) was listed as a carcinogen under Prop 65 using the state's qualified experts (SQE) mechanism, which took into account IARC's classification of DEHP as a Group 2B carcinogen. Years later, after California had listed DEHP as a carcinogen on prop 65, the IARC reclassified the chemical from "possibly carcinogenic" Group 2B to "not classifiable" Group 3 due to the carcinogenic mechanism not being relevant to humans. While there have been some instances of Group 2B carcinogens being reclassified into Groups 3 or 4, there has never been a single instance in the 50 years IARC has been in existence of a Group 2A (which is what glyphosate is classified as) being downgraded to Groups 3 or 4.[44] That is because the burden of proof for an agent to be classified as Group 2A is very high and hard to contradict with a preponderance of evidence. Group 2B has a lower standard, which makes it more susceptible to changes based on new evidence.

Following the change in classification by IARC, Baxter Healthcare Corporation brought suit against OEHHA challenging its determination that IV bags containing DEHP need to be labeled as containing a known human carcinogen, arguing that, since the mechanism of carcinogenesis is not relevant to humans, there was no significant risk to humans based on exposure. The court sided with Baxter and concluded that DEHP could remain on the Prop 65 list because it met the listing criteria, but that IV bags containing DEHP would not need to carry a warning label and the NSRL would, in effect, be infinite.

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[43] OECD. 2012. Guidance Document 116 On The Conduct And Design Of Chronic Toxicity And Carcinogenicity Studies, Supporting Test Guidelines 451, 452 And 453 2nd Edition. Series on Testing and Assessment No. 116. Available at: http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2011)47&doclanguage=en

[44] Huff, J. IARC Monographs, Industry lnfluence, and upgrading, Downgrading, and Under-grading Chemicals: A Personal Point of View." *International Journal of Occupational and Environmental Health*, 8(3), pp. 249–270

So, in the case of DEHP, not only was the initial evidence for carcinogenicity in humans less strong (Group 2B), but the actual mechanism by which carcinogenicity is initiated was later found to be not relevant in humans. Contrast that with glyphosate, where there is a Group 2A classification based on sufficient evidence of carcinogenicity in animals with limited evidence of carcinogenicity in humans. In addition, the IARC has found strong evidence that glyphosate is a genotoxin and an inducer of oxidative stress.[45] And this is undeniably relevant to humans.

IARC found that, in the case of glyphosate formulations, DNA double strand breaks and micronuclei formation correlated with human exposure *in vivo*. Glyphosate and its metabolites can induce DNA strand breaks, chromosomal aberrations, and sister chromatid exchange in multiple human cell lines *in vitro*. Addition of antioxidants to human cells *in vitro* reduced cytotoxicity following glyphosate exposure, and treatment of human cells with a sublethal dose of glyphosate induced production of hydrogen peroxide, a known oxidant. Other assays used to determine reactive oxygen species (ROS) levels indicate that glyphosate, AMPA and glyphosate formulations can induce ROS in human cells *in vitro*.

Clearly the evidence that glyphosate can cause cancer in humans is in a completely different category as DEHP ever was. The court ruled that Baxter Healthcare Corporation provided proof by a preponderance of evidence that IV bags containing DEHP posed no significant cancer risk to humans because it was demonstrated that the mechanism of carcinogenesis in animals was not relevant to humans. No such finding has been made in the case of glyphosate, where carcinogenesis in animals is buttressed by human epidemiology studies showing increased incidence of non-Hodgkin lymphoma and DNA damage, as well as by genotoxicity in *in vitro* in human cells.

There is disagreement among IARC and some governmental agencies about the cancer causing effects of glyphosate, yet that in no way rises to the level of industry having a preponderance of evidence that OEHHA came to a faulty conclusion with its NSRL. The IARC is the most reputable cancer research agency in the world. In fact, a major factor in OEHHA losing the Baxter case was the fact that IARC had reversed its position and concluded that DEHP was likely to act through a mechanism that is *not* relevant in humans. That has not, nor is it likely to happen in the case of glyphosate – as mentioned above, a Group 2A classification is not as easily reversed by new evidence as a 2B classification. The current evidence is simply too strong.

Because of ethical strictures against experimentation on human beings, it is widely accepted in the scientific and regulatory communities that development of cancer in animal model organisms is an effective surrogate for carcinogenicity in humans. In its cancer assessment guidelines, EPA states: "…tumors observed in animals are generally assumed to indicate that an agent may produce tumors in humans."[46] The DEHP case is

[45] IARC Working Group. Glyphosate. In: *Some organophosphate insecticides and herbicides: diazinon, glyphosate, malathion, parathion, and tetrachlorvinphos*. Vol **112**. IARC Monogr Prog, 2015.
[46] EPA. Guidelines for Carcinogen Risk Assessment. March 2005, op. cit., p. 2-22.

one of the rare examples where the mechanism of carcinogenicity in animals was found to be not relevant to humans, and that was the entire basis that the judge used to determine that there was no significant risk of humans developing cancer from exposure to DEHP through IV bags. That fundamental issue is not true in the case of glyphosate or formulations containing glyphosate. There is sufficient animal evidence and limited human evidence of carcinogenicity as well as strong mechanistic evidence of carcinogenicity in human cells. Therefore, the animal study that OEHHA uses to determine the NSRL will effectively indicate the level of glyphosate that will result in a significant risk of a human developing cancer.

CONCLUSION

The State of California has taken an important step in listing glyphosate as a known human carcinogen, but the listing is only as effective as the NSRL will allow. We identified three studies of sufficient quality that found glyphosate exposures below 1000 mg/kg/day were positively associated with cancer development.

As mentioned previously, in its evaluation of glyphosate's carcinogenic potential, the EPA deemed each of these studies of sufficient quality for use. Historically, this has been sufficient to meet OEHHA's study quality criteria. These studies have met the exact same guideline criteria mandated by the EPA as the Atkinson et al., 1993 study that is currently being used as a basis for the NSRL. Therefore, these studies are of sufficient quality for use in NSRL determination.

To be clear, the Atkinson et al. 1993 study is of acceptable scientific quality to base the NSRL on – but that NSRL would not be sufficiently health protective, in light of other quality studies showing carcinogenic effects at lower doses. But if OEHHA decides not to lower the NSRL, then it should absolutely refrain from raising it. The experimental design of the Atkinson et al. 1993 study and significance in the trend test has effectively ruled out that the outcome is a result of chance alone. There have already been efforts by speakers at the public hearing to discredit this study in ways that are not in alignment with current, internationally accepted guidelines. We sincerely hope that OEHHA will not get dragged into nitpicking every tiny detail of the study design and outcome in an effort to cast doubt on its scientific findings.

The US EPA's recent analysis of the carcinogenic potential of glyphosate is very troubling, and the agency's conclusions on these three studies are fundamentally flawed. EPA's own Scientific Advisory Panel, and numerous public commenters,[47] documented serious scientific flaws in the agency's evaluation. Most striking was EPA's blatant violations of its own Guidelines for Carcinogen Risk Assessment, violations all tending to exonerate glyphosate from the strong evidence of its carcinogenicity. Bias of this sort is unacceptable for a regulatory agency. We sincerely hope that OEHHA will see the

[47] For instance, see Center for Food Safety's comments to the Glyphosate SAP, October 12, 2016, at http://www.centerforfoodsafety.org/reports/4537/cfs-comments-to-epa-science-advisory-panel-on-the-carcinogenicity-of-glyphosate#.

value in identifying a set of guidelines first, then following those guidelines when independently analyzing the studies outlined in these comments.

We strongly urge OEHHA to base the glyphosate NSRL on any one of the three studies referenced above. Of the three studies, the Lankas study appears to us to be the most sensitive study of sufficient scientific quality and the most suitable for use in calculating an NSRL.

Sincerely,

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