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Subject: GLYPHOSATE NSRL
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Attachments: [image004.png](#)
[NSRL Public Comment.pdf](#)
[Exh. 1.pdf](#)
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Madam/Sir, please find attached a public comment (and attached exhibits referenced throughout the comment) regarding the proposed NSRL for glyphosate.

Sincerely,

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Dear Madam/Sir,

I write with regard to the proposed amendment to Section 25705(b) of the California Code of Regulations. The Office of Environmental Health Hazard Assessment (OEHHA) seeks to impose a No Significant Risk Level (NSRL) of 1100 micrograms for glyphosate, the active chemical in the widely used herbicide, Roundup. There are several scientific, legal, and public health issues raised by the proposed NSRL which provides a Safe Harbor exemption from the warning requirement of the Safe Water and Toxic Enforcement Act (Proposition 65). We respectfully request that the agency carefully consider the issues raised herein before imposing a potentially unsafe Safe Harbor NSRL.

Analyze and Incorporate Results from Animal Bioassays Using Lower Exposure Doses than the Cheminova Study Relied Upon in the Initial Statement of Reasons

First, it is questionable whether the proposed Safe Harbor has considered a sufficient number of animal bioassays and accounted for the variable exposure doses used in studies which observed tumor incidence and lymphomagenesis at significantly lower doses than the study cited by the Initial Statement of Reasons. OEHHA reviewed a two year rodent carcinogenicity study where 50 male CD-1 mice were fed a diet containing glyphosate at concentrations intended to achieve dose rates of 0, 100, 300, or 1000 milligrams of glyphosate per kilogram of body weight per day.¹ Tumor incidence was observed in the 1000 milligrams per day dose group. However, other rodent studies examining exposure to both mice and rats have found the development of tumors at much lower doses, including:

¹ Initial Statement of Reasons at 2, available at:
<https://oehha.ca.gov/media/downloads/cnrn/glyphosate032917isor.pdf>.

1. Wood et al. found Lymphoid hyperplasia at low and mid doses in male mice at 71.4 and 234.2 mg/kg-bw/day in a study where malignant lymphomas were significantly induced at 810 mg/kg-bw/day.²
2. Lankas in a 1981 study where Lymphocytic hyperplasia was observed at 11 mg/kg-bw/day in Sprague-Dawley rats.³
3. Lankas observed Testicular interstitial tumors in male Sprague-Dawley rats which demonstrated a significant trend and a significant pairwise comparison between control and the high dose of 31.49 mg/kgbw/ day.⁴
4. Stout and Ruecker observed Pancreatic islet cell adenoma in male Sprague-Dawley rats demonstrating a significant pairwise comparison relative to controls at the low dose, 89 mg/kg-bw/day in 1990.⁵

Indeed, all of the above bioassays were noted by the EPA's Scientific Advisory Panel (SAP) in the SAP's evaluation of the 2016 EPA glyphosate issue paper.⁶

Specifically, the 2009 study of Wood et al.⁷, where malignant lymphomas were observed in CD-1 mice using 810mg/kg/day dose rate, achieved a clear dose-response and was supported by findings in another 18 month study. There was a monotonic increase in lung adenocarcinomas (10%, 10%, 14%, 22%) and a monotonic increase in malignant lymphomas (0%, 2%, 4%, 10%). Son and Gopinath (2004) saw 21 animals out of 1453 examined prior to 80 weeks with lung adenocarcinomas (1.4%).⁸ Giknis and Clifford (2005) observed a mean rate of 4.5% with a range of 0% to 21.7% in 52 studies which included mostly 78 week controls (26 studies) and 104 week controls (21 studies).⁹ Including only studies of 80 weeks or less, the rate in Giknis and Clifford (2005) is 37/1372 = 2.7% with a range of 0% to 14%. Giknis and Clifford (2000)

² Wood, E., J. Dunster, P. Watson, and P. Brooks, *Glyphosate Technical: Dietary Carcinogenicity Study in the Mouse*. 2009: Harlan Laboratories Limited, Shardlow Business Park, Shardlow, Derbyshire DE72 2GD, UK. Study No. 2060-011. April, 22, 2009.

³ Lankas, G.P, *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.

⁴ *Id.*

⁵ Stout, L.D. and P.A. Ruecker, *Chronic Study of Glyphosate Administered in Feed to Albino Rats*. MRID No. 41643801; Historical Controls. MRID 41728700.

⁶ See SAP Final Report at 88, available at: https://www.epa.gov/sites/production/files/2017-03/documents/december_13-16_2016_final_report_03162017.pdf.

⁷ Wood, E., J. Dunster, P. Watson, and P. Brooks, *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.

⁸ Son, W.C. and C.Gopinath, *Early occurrence of spontaneous tumors in CD-1 mice and Sprague-Dawley rats*. *Toxicol Pathol*, 2004. 32(4): 371-4.

⁹ Giknis, M. and C. Clifford, *Spontaneous Neoplastic Lesions in the CrI:CD-1(ICR)BR Mouse in Control Groups from 18 Month to 2 year Studies*. Charles River Laboratories.

conducted a similar evaluation, using mostly the same data as their 2005 paper and saw an average tumor incidence before 80 weeks of 2.6% with a range of 0% to 14%.¹⁰

A lower NSRL would thus be reached using data from such studies which found carcinogenesis and lymphomagenesis at lower doses than the bioassay considered by OEHHA in determining the Safe Harbor.

Pursuant to a California Public Records Act request, documents were obtained from OEHHA which demonstrate that representatives from Monsanto met with OEHHA on October 7, 2015 in light of glyphosate being listed under Proposition 65. Exh. 1. The memo notes by two OEHHA employees present at the meeting indicate that Monsanto made a formal presentation and supplied materials to OEHHA regarding specific rodent carcinogenicity studies to review and consider in support of Monsanto's assertion that a Safe Harbor NSRL was needed in light of IARC's findings likely requiring a Proposition 65 probable human carcinogenicity listing for glyphosate. Exh. 2 at *1-2. Moreover, both notes reference the Greim et. al. (2015)¹¹ publication, co-authored by a Monsanto employee, which omitted one animal bioassay from analysis because of Monsanto's fears that "the original mouse data suggested some carcinogenic potential." Exh. 3 at *1¹²; see Exh. 2 at *2; Exh. 4. OEHHA should be presented with an impartial and comprehensive scope of data in determining the NSRL, and the animal bioassays listed above, which observed tumor incidence at lower doses than the study cited in the Initial Statement of Reasons, provide additional information for OEHHA to review before making a final decision.

OEHHA should also consider incorporating into its NSRL analysis the recent disclosure of eight additional tumor sites found in previously unavailable data in several of the key animal studies related to glyphosate carcinogenicity. Dr. Christopher J. Portier (former Director of the Environmental Toxicology Program at the NIEHS, Associate Director of the National Toxicology Program, and collaborator on IARC monographs) noted in his May 28, 2017 letter to the President of the European Commission, Jean Claude Juncker, regarding the Review of the Carcinogenicity of Glyphosate by EChA, EFSA and BfR:

On March 15, 2016, members of the European Parliament requested public access to the complete records of animal laboratory data from chronic carcinogenicity studies of glyphosate; these data were previously deemed to be confidential business information. The presence of this new information along with what was already available in the Supplemental Material from Greim et al. (2015) allowed me to evaluate the data for any additional significant increases in tumor incidence that have not been reported in the evaluations by both EFSA and EChA. In these additional analyses, I found eight significant increases in tumor incidence that do

¹⁰ Giknis, M. and C., Clifford, *Spontaneous Neoplastic Lesions in the CrI: CD-1(ICR) BR Mouse*. Charles River Laboratories.

¹¹ Greim, H., et al., *Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies*. Crit. Rev. Toxicol, 2015. 45(3): 185-208.

¹² MONGLY01009950, available at: <https://usrtk.org/wp-content/uploads/2017/03/187series.pdf>. All internal Monsanto documents cited in this Comment as exhibits are publicly available at: <https://usrtk.org/pesticides/mdl-monsanto-glyphosate-cancer-case-key-documents-analysis/>.

not appear in any of the publications or government evaluations presented by both EFSA and ECHA.¹³

These additional tumor sites' data were not available to IARC when IARC issued its glyphosate probable carcinogen findings in 2015. They further bolster IARC's original carcinogenicity findings. We therefore urge OEHHA to conduct an exhaustive review of the eight studies which concluded significant ($p < 0.05$) tumor increases due to glyphosate exposure.¹⁴

Study Species	Tumor type Sex; Incidences	P-value ¹⁵ (one-sided)
Wood et al. (2009) CD-1 Mouse	Lung adenocarcinomas Males; 5/51, 5/51, 7/51, 11/51	0.028
Sugimoto et al. (1997) CD-1 Mouse	Hemangioma (any tissue) Female: 0/50, 0/50, 2/50, 5/50*	0.002
Atkinson et al. (1993) Sprague-Dawley Rat	Thyroid follicular cell adenomas and carcinomas Males: 0/50, 0/50, 0/50, 2/50, 2/49	0.034
Lankas (1981) Sprague-Dawley Rats	Thyroid c-cell Carcinomas Females; 1/47, 0/49, 2/50, 6/47	0.003
Enomoto (1997) Sprague-Dawley Rat	Kidney adenoma Male; 0/50, 0/50, 0/50, 4/50	0.004
Brammer (2001) Wistar Rat	Hepatocellular Adenoma Males; 0/53, 2/53, 0/53, 5/52*	0.008
Wood et al. (2009) Wistar Rat	Skin Keratocanthoma Males; 2/51, 3/51, 0/51, 6/51	0.03
these groups have a significantly increased ($p < 0.05$) incidence of tumors relative to the controls by the Fisher Exact Test in addition to a significantly positive trend test finding.	Mammary gland adenomas and adenocarcinomas females; 2/51, 3/51, 1/51, 8/51	0.007

¹³ Portier Letter at 2, available at: <https://www.nrdc.org/sites/default/files/open-letter-from-dr-christopher-portier.pdf>.

¹⁴ Data from Portier Letter at 3.

¹⁵ The p-values presented here are from the exact Cochran-Armitage linear trend test in proportions.

Epidemiological Data Should be Appraised

Second, California Code of Regulations Section 25703(a)(2) requires that a quantitative risk assessment appraise the “quality and suitability of available epidemiologic data... to determine whether the study is appropriate as the basis of a quantitative risk assessment, considering such factors as the selection of the exposed and reference groups, reliable ascertainment of exposure, and completeness of follow-up. Biases and confounding factors shall be identified and quantified.” *Id.* OEHHA reviewed “data from the rodent carcinogenicity studies of glyphosate discussed by IARC [the International Agency for Research on Cancer], and determined that the two-year study conducted in male CD-1 mice fed glyphosate (purity, 98.6%) in the diet met the criterion in Section 25703 as the most sensitive study of sufficient quality.”¹⁶ Although Section 25703 does indeed require a quantitative risk assessment to consider animal bioassays, OEHHA has not thoroughly complied with the statute by overlooking the abundant epidemiological literature on glyphosate carcinogenicity.

For example, a number of epidemiological studies, such as Orsi et al. (2009)¹⁷ and a recent study by Morton et al. (2014)¹⁸ demonstrate a significantly elevated risk of NHL among farmers. Also, Hardell et al. (2002) indicated an RR of 1.85 (95% CI 0.55 – 6.27) with multivariate analysis, while univariate analysis indicated a RR = 3.04 (95% CI 1.08-8.52).¹⁹

De Roos et al. (2003), in a case-control study, reported that the use of glyphosate was associated with increased incidence of NHL.²⁰ In the logistic regression model based on 36 cases, the odds ratios for association between exposure to glyphosate and NHL were 2.1 (95% CI: 1.1-4.0) and 1.6 (95% CI: 0.9-2.8) in hierarchical regression models.

Eriksson et al. (2008), in another case-control study, reported that exposure to glyphosate was associated with increased odds for lymphoma subtypes and elevated odds of B-cell lymphoma (OR=1.87, 95% CI: 0.998-3.51) and the subcategory of small lymphocytic lymphoma/chronic lymphocytic leukemia (OR=3.35, 95% CI: 1.42-7.89).²¹ Indeed, this study demonstrated elevated risk for glyphosate exposure in relation to several categories of NHL and evaluated the risk of NHL related to latency period (see below).

Pahwa et al. (2016), in an abstract consisting of pooled analysis of North American and Canadian epidemiological studies (NAPP) (analyzing 1690 cases and 5131 controls), reported elevated risk of all NHL types with any glyphosate use (OR=1.51, 95% CI 1.18-1.95); a dose-

¹⁶ Initial Statement of Reasons at 2, available at:

<https://oehha.ca.gov/media/downloads/crn/glyphosate032917isor.pdf>.

¹⁷ Orsi, L., et al., *Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study*, Occupational and environmental medicine 2009, 66: 291-298.

¹⁸ Morton LM et al., *Heterogeneity among non- Hodgkin lymphoma subtypes: The Inter Lymph non-Hodgkin lymphoma subtypes project*. J. Natl. Cancer Inst 2014, 48: 130-144.

¹⁹ Hardell, L., et al., *Exposure to pesticides as risk factor for non- Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies*. Leuk Lymphoma. 2002 May; 43(5):1043-1049.

²⁰ De Roos, A.J., et al., *Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men*. Occu. & environ. medicine (2005) 60. 1-9.

²¹ Eriksson, M., et al., *Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis*. International journal of cancer 123, 1657-1663.

response effect was observed with greater use (>2 days/year, OR=2.66, 1.61-4.40).²² With regards to NHL subtypes, increases were observed for small lymphocytic lymphoma (SLL; 2.58, 95% CI 1.03-6.48, among those using for more than 5 years), and for follicular lymphoma (OR=2.36, 95% CI 1.06-5.29), diffuse large B-cell lymphoma (DLBCL; OR=3.11, 95% CI 1.61-6.00), and other subtypes (OR=2.99, 95% CI 1.10-8.09) for use more than 2 days per year.

Moreover, a meta-analysis conducted by Schinasi et al. (2014) on glyphosate and Non-Hodgkin's Lymphoma reported increases in NHL risk with any glyphosate exposure (with a meta-RR of 1.5, 95% CI 1.1-2.0).²³ Stronger increases were reported for B-cell lymphoma (meta-RR: 2.0, 95% CI 1.1-3.6). The heterogeneity of study results was low, indicating consistent results observed in multiple studies across different settings. IARC conducted its own meta-analysis using solely the most highly adjusted estimates from the same studies reviewed by Schinasi et al. (2014) and reported a meta risk-ratio of 1.3 (95% CI, 1.03–1.65), with consistent findings across studies (low heterogeneity).²⁴

²² Pahwa M., et al., *A detailed assessment of glyphosate use and the risks of non-Hodgkin lymphoma overall and by major histological sub-types: Findings from the North American Project*. Abstr. Book of Abstracts. IARC 50th Anniversary Meeting, May 2016 Lyon, France.

²³ Schinasi, L and M.E. Leon, *Non-Hodgkin lymphoma and occupational exposure to agricultural pesticide chemical groups and active ingredients: a systematic review and meta-analysis*. Int. J. Environ Res Public Health. 2014 Apr 23; 11(4):4449-527.

²⁴ Recently, IARC was criticized for not considering an unpublished 2013 manuscript by Blair et al. ("*Lymphoma Risk and Pesticide Use in the Agricultural Health Study*") before classifying glyphosate as a "2A Probable Human Carcinogen". An article published in Reuters (<http://www.reuters.com/investigates/special-report/glyphosate-cancer-data/>) conjectured that IARC would probably not have classified glyphosate as a carcinogen if the IARC working group had access to the unpublished Blair et al. (2013) manuscript, part of the Agricultural Health Study. However, there are several problems with the AHS, also referred to as De Roos, A.J, et al. (2005). *Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study*. Env. Health Perspect. 113, 49-54. Study flaws include the inability to determine the latency period for NHL, the control group having an elevated risk of NHL, and exposure misclassification. See Infante P., *A Review of the Epidemiological Literature Related to the Development of Non-Hodgkin Lymphoma*, Presented before the FIFRA, US Environmental Protection Agency Scientific Advisory Panel regarding EPA's Evaluation of the Carcinogenic Potential of Glyphosate, Arlington, Virginia December 15, 2016, available at: http://gmwatch.org/files/Infante_Glyphosate_paper_010617_Tables.pdf. Importantly, the draft manuscript by Blair et al. (2013) is an attempt to update the AHS data to include exposures between 1998 and 2004 (the time the AHS cohort was approached for a second interview/follow-up), and diagnosis occurring throughout December 2008. There was a 63% response rate among AHS cohort members contacted in 1998-2004 when exposures were updated from the period after enrollment. This means that one third of all subjects *did not* report their exposures during a time when glyphosate use increased tremendously (after 1995). In order to not lose these participants, and possibly generate a very strong selection bias, the authors conducted "data driven imputations of exposures" for those who did not respond. While data driven imputation is often used in epidemiology, it is usually not considered acceptable to use for something as critically important as exposure to the studied substance. See Blair, et al., *Using multiple imputation to assign pesticide use for non-responders in the follow-up questionnaire in the Agricultural Health Study*, J Expo Sci. Environ Epidemiol. 2012 July; 22(4): 409–416. Even if it were acceptable to impute exposure, one must assume that it is sufficient to use the data at hand to predict data from those AHS subjects who did not respond, and possibly also assume that those who did not respond had similar pesticide use and exposure patterns as those who did respond, both in NHL and non NHL-cases. At the very least, this assumption may cause enough exposure misclassification which would bias any moderate size effect estimates towards the null. Thus, rather than risk being criticized for a significant selection bias (having lost one third of subjects to follow-up) the authors chose to impute/guess what the use would have been for the non-responders, based on originally reported use. This is generally not acceptable, but it is particularly inappropriate when the use of glyphosate changed dramatically over the relevant years, rendering dubious the use of prior

Chang and Delzel, (2016) provided four separate meta-analyses, all of which are reported as having a meta-RR of 1.3 with associated confidence bounds ranging from (1.0-1.6) to (1.0-1.8).²⁵ Chang and Delzel presented only 1 significant digit for the lower confidence bounds and since their model is exactly the same as the IARC model, they also had at least one significant finding, characterizing their findings accordingly: “we found marginally significant positive meta-RRs for the association between glyphosate use and risk of NHL.”

The European Scientific Committee on Health and Environmental Risks (SCHER), the Scientific Committee on Consumer Products (SCCP), and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) have jointly agreed: “it is generally recognized that dose-response information from epidemiological studies is preferred as the starting point for *quantitative risk analysis* of carcinogens instead of data from experimental *animal studies*.” (emphasis added).²⁶ Indeed, there are three high quality studies containing dose-response information for glyphosate use. Pahwa et al. (2016) (discussed above) demonstrates that handling glyphosate for >2 days/year was associated with a significantly increased risk of NHL.²⁷ McDuffie (2001) also demonstrates that handling glyphosate for >2 days/year was associated with a significantly increased risk of NHL (OR=2.12 95% CI: 1.2-3.73).²⁸ Eriksson et al. (2008) (discussed above) demonstrates that handling glyphosate for more than 10 years was associated with a significantly increased risk of NHL (OR= 2.36 95% 1.04-5.37).²⁹

Prioritizing animal bioassays over epidemiological data when assessing the carcinogenic potential of glyphosate overlooks the risk to individuals exposed to glyphosate via application. California Code of Regulations Section 25703(a)(1) requires that OEHHA consider the “degree to which dosing resembles the expected manner of *human exposure*” and “*the route of exposure*.” (emphasis added).

The dietary ingestion of glyphosate, as evaluated in the animal bioassay considered by OEHHA in the Initial Statement of Reasons, does not resemble the expected manner of human exposure to

responses to impute/guess exposure data. There would only have to be 2-3 cases of “wrong imputation/guesses” to lose significance, and the chance of such error is particularly high where the use has changed so significantly. This is the major problem with the AHS study and likely explains why a manuscript written in 2013 (Blair et al.) has not yet been published. IARC only considers published, peer-reviewed research. Lastly, the AHS seems to suffer from a very high frequency of co-exposures to other potentially carcinogenic pesticides even for those subjects listed as unexposed to glyphosate. For example, exposures to 2, 4 D, Lachlan and atrazine were very high among the glyphosate unexposed (50-60% exposed); this may increase the baseline rate of NHL such that an incremental increase due to glyphosate exposure is not as strong or even impossible to estimate.

²⁵ Chang, E.T and E. Delzell., *Systematic review and meta-analysis of glyphosate exposure and risk of lymphohematopoietic cancers*. Journal of environmental science and health Part B, Pesticides, food contaminants, and agricultural wastes 51, 402-434.

²⁶ Risk Assessment Methodologies and Approaches for Genotoxic and Carcinogenic Substances at 18, available at: http://ec.europa.eu/health/ph_risk/committees/04_scher/docs/scher_o_113.pdf

²⁷ Pahwa, M, et al., *A detailed assessment of glyphosate use and the risks of non-Hodgkin lymphoma overall and by major histological sub-types: Findings from the North American Project*. Abstr. Book of Abstracts. IARC 50th Anniversary Meeting, May 2016 Lyon, France.

²⁸ McDuffie, H.H, et al., *Non-Hodgkin's lymphoma and specific pesticide exposures in men: Cross-Canada study of pesticides and health*. Cancer Epidemiol Biomarkers Prev 10, 1155-1163.

²⁹ Eriksson, M, et al., *Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis*. International journal of cancer 123, 1657-1663.

glyphosate through application. Significantly, when glyphosate is applied in agriculture or domestically, it is mixed with several toxic surfactants and humectants, which not only increase the absorption of glyphosate through the skin, but also work synergistically with glyphosate to increase genotoxicity. As explained by Monsanto in an internal memo:

Surfactants are able to increase glyphosate absorption through the skin by (1) removal of lipids (sebum) from the epidermal surface due to surfactant action, (2) increase of the hydration state of the skin (under closed exposure conditions), (3) increase of skin contact (spreading of water droplets by surfactant action), (4) increase of contact time with the skin due to decrease of evaporation of water from the droplets containing surfactant (surfactant monolayer at surface of droplets slows down passage to vapour phase,) increase of sub epidermal blood flow due to irritant action of surfactant, (6) intra-epidermal and sub epidermal intercellular water accumulation due to the irritant action of the surfactant.

Exh. 5 at *3.³⁰

Epidemiological data (including a review of the available meta-analyses) would thus provide robust and comprehensive evaluation of a chemical which most users absorb via cutaneous and respirational contact and which has been positively associated with cancers such as Non-Hodgkin's Lymphoma. OEHHA should reconsider the proposed NSRL of 1100µg after a thorough review of the epidemiological data in accordance with the requirements of Section 25703 and the principles of sound science.

Distinguishable Legal Authority Relied upon by Monsanto

Third, during the June 7, 2017 OEHHA public hearing regarding the proposed NSRL for glyphosate, Monsanto's outside counsel presented a statement which cited a single California Appellate Court decision in support of Monsanto's contention that the NSRL should be "infinite". The case cited by Monsanto, *Baxter Healthcare Corp. v. Denton*, 120 Cal. App. 4th 333, 15 Cal. Rptr. 3d 430 (2004), is distinguishable if not entirely inapposite to the current matter. *Baxter* concerned a writ of mandate by a medical device manufacturer forcing OEHHA "to promulgate a regulation that prescription medical devices containing [a] certain substance [DEHP] posed no significant risk of cancer in humans, and a warning was not required." *Id.* As an initial matter, Monsanto's rote mantra during the June 7 public hearing was that OEHHA has the authority to issue exemptions from Prop 65, a central matter in *Baxter*. Nobody is challenging OEHHA's statutory discretion to impose an "infinite" Safe Harbor, it is rather the circumstances under which OEHHA has proposed a glyphosate NSRL of 1100 micrograms that are contested.

Ironically, in *Baxter*, the device manufacturer requesting an exemption from Prop 65 "pointed out that the International Agency for Research on Cancer, which is recognized by pertinent regulations as an authoritative body on the identification of chemicals causing cancer (Regs., §

³⁰ MONGLY01839477, available at: <https://usrtk.org/wpcontent/uploads/2017/03/192series.pdf>.

12306, subd. (m)), had recently determined that the biological mechanism by which DEHP increases the incidence of liver tumors in rats and mice is not relevant to, and does not operate in, humans.” *Id.* at 438.³¹ Both the Superior and Appellate Courts recognized the pertinence of IARC’s conclusion. Indeed, this aspect of *Baxter* compels the opposite finding to Monsanto’s desire for an “infinite” NSRL, given that IARC has classified glyphosate as a “2A probable human carcinogen”, resolving significant doubts—unlike the chemical in *Baxter*— regarding glyphosate’s carcinogenic properties in humans.

Of substantial consideration in *Baxter* was OEHHA’s inability to establish that “DEHP is listed for *any reason other than* that it is known to cause liver cancer in rats and mice.” 120 Cal. App. 4th at 370. (emphasis added). Here, glyphosate is listed *precisely because* regulators, international research organizations, and scientists have determined that glyphosate is capable of causing cancer in humans.³² Moreover, “[i]f DEHP has been shown to cause only liver cancer in rats and mice, then it logically follows that *Baxter* did not have to show there was no significant risk of DEHP causing innumerable other types of cancer in every conceivable part of the human body... If the scientific evidence demonstrated that DEHP exposure is not likely to cause humans to develop the only type of cancer DEHP is known to cause, then there is no significant risk that exposure to DEHP will cause cancer in humans.” *Id.* at 455. However, glyphosate is known to cause a host of cancers in humans based upon the abundant adverse data obtained from epidemiological studies and animal bioassays— *none* of which limit tumor incidence to isolated body parts of animals other than humans. In that regard, the conclusions of IARC are unequivocal regarding the potential for glyphosate to cause cancer in humans, and Monsanto cannot justifiably rely on *Baxter* where the incidence of carcinogenesis associated with DEHP was limited to liver cancer in rats and mice. The factual circumstances of *Baxter* render it inappropriate to the current matter, particularly since the proposed 1100 micrograms Safe Harbor for glyphosate has not faced any legal challenges which require individualized determinations of burdens of proof and assessments of scientific data subject to the rules of evidence. OEHHA should not be led astray by Monsanto’s deployment of distinguishable legal authority.

Glyphosate Bio-Accumulation and Effect on Human Microbiota

Fourth, the animal bioassay considered by OEHHA only entailed dietary exposure to glyphosate. As such, it failed to account for lymphomagenesis that may be precipitated by the recognized pathways of oxidative stress and genotoxicity via cutaneous and respirational exposure *as well* as a third mechanism which operates through digestion. It is undisputed that glyphosate interferes with 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase enzyme.

³¹ IARC’s glyphosate classification is essentially the opposite of its classification of DEHP—the chemical in *Baxter*—where the court lent great weight to the IARC conclusion (“The court also noted that the International Agency for Research on Cancer (IARC) has concluded that the mechanism of carcinogenesis operating in rats and mice does not operate in humans and, on this basis, IARC has reclassified DEHP from “possibly carcinogenic to humans” to “not classifiable as to its carcinogenicity to humans.”) *Id.* at 439.

³² Indeed, a central contention regarding the scientific evidence in *Baxter* was whether the carcinogenic properties of DEHP were limited to rats and mice; no such issues are relevant in the question over the proper NSRL for glyphosate (“The superior court found that “*Baxter*’s experts presented a detailed, coherent and persuasive theory explaining the mechanism by which DEHP exposure leads to cancer in laboratory animals and further explaining why that mechanism does not operate in humans.”) *Id.* at 456.

Glyphosate kills plants by inhibiting this enzyme, disrupting the fifth of six enzymatic steps in the shikimate pathway, which processes aromatic amino acids.³³ However, the same enzyme—the EPSP synthase that glyphosate “targets”—is present in many beneficial bacteria that inhabit the human and other mammalian mucous membranes, skin and gut.³⁴

As noted by Scofield (2014), “[o]ver the first several years of life each of us establishes a community of microorganisms that are commensal and inhabit niches on skin and mucous membranes. These microorganisms are collectively known as the microbiome, or microbiota, and are predominately obtained from one’s mother...gut-associated organisms are critical to the development and activation of the immune system, especially with regard to cell types intimately associated with autoimmunity.”³⁵ Studies demonstrate that the health of beneficial gut bacteria is essential to the overall health of humans and other mammals.³⁶ Moreover, unstable microbiota and bacterial inflammation, including dysbiosis (imbalance of bacterial populations) has been associated with lymphomagenesis: “Whether microbes influence immune cells directly, indirectly, or a combination of both, increased lymphocyte proliferation can lead to a higher chance of aberrant DNA replication particularly in some B lymphocytes which are innately vulnerable to genetic instability and activation. Oxidative stress caused by intestinal microbiota either directly or indirectly through the immune system, can also affect carcinogenesis. Therefore, the microbiota can affect several pathways associated with lymphomagenesis.”³⁷ A comparison of the available data has led investigators to correlate “differences in the microbiota with systemic oxidation state, inflammation and genotoxicity.”³⁸

Studies examining low doses of glyphosate-based biocides at levels that are generally considered “safe” for humans show that these compounds can nevertheless cause liver and kidney damage.³⁹

³³ Hermann K.M., *The Shikimate Pathway as an Entry to Aromatic Secondary Metabolism*, 107 *Plant Physiology* 7 (1995), available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC161158/pdf/1070007.pdf>; Hollander H. and N. Amrhein. *The Site of the Inhibition of the Shikimate Pathway by Glyphosate*, 66 *Plant Physiology* 823, (1980), available at: <http://www.plantphysiol.org/content/66/5/823.full.pdf>; Industry Task Force on Glyphosate, *Glyphosate: Mechanism of Action*, Glyphosate Facts (June 19, 2013), available at: <http://www.glyphosate.eu/glyphosate-mechanism-action>.

³⁴ Samsel A. and S. Seneff, *Glyphosate’s Suppression of Cytochrome P450 Enzymes and Amino Acid Biosynthesis by the Gut Microbiome: Pathways to Modern Diseases*, 15(4) *Entropy* 1416 (2013), available at: <http://www.mdpi.com/1099-4300/15/4/1416/htm>.

³⁵ Scofield R.H., *Rheumatic Diseases and the Microbiome*. *International Journal of Rheumatic Diseases* 2014; 17: 489–492

³⁶ Jandhyala S.M., et al., *Role of the Normal Gut Microbiota*, 21 *World J. of Gastroenterology* 8787 (2015), available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4528021/>

³⁷ Yamamoto, M.L. and R.H. Schiestl, *Intestinal Microbiome and Lymphoma Development*, *Cancer J.* 2014; 20(3): 190–194.

³⁸ Lou, K., *B cell Lymphoma and the Microbiome*, *SciBX* 6(31) 2013.

³⁹ Myers, J.P., et al., *Concerns over use of glyphosate-based herbicides and risks associated with exposures: a consensus statement*, 15 *Environ. Health* 9 (2016), available at: <https://ehjournal.biomedcentral.com/articles/10.1186/s12940-016-0117-0>; see also Seralini, G.E., et al., *Republished study: long-term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize*, 26 *Environ. Sci. Europe* 14 (2014), available at: <http://enveurope.springeropen.com/articles/10.1186/s12302-014-0014-5>; Benedetti, A.L., et al., *The effects of sub-chronic exposure of Wistar rats to the herbicide Glyphosate-Biocarb*, 153(2) *Toxicol. Lett.* 227-32 (2004), available at: <http://www.ncbi.nlm.nih.gov/pubmed/15451553>; Larsen, K., et al., *Effects of Sublethal Exposure to a Glyphosate-Based Herbicide Formulation on Metabolic Activities of Different Xenobiotic-Metabolizing Enzymes in Rats*, 33(4) *Int. J. Toxicol.* 307-18 (Jul. 2014), available at:

Shehata et al. (2014) found that: “A reduction of beneficial bacteria in the gastrointestinal tract microbiota by ingestion of glyphosate could disturb the normal gut bacterial community. Also, the toxicity of glyphosate to the most prevalent *Enterococcus* spp. could be a significant predisposing factor that is associated with the increase in *C. botulinum*-mediated diseases by suppressing the antagonistic effect of these bacteria on clostridia.”⁴⁰ In another study, Shehata et al. (2014) observed further adverse effects of glyphosate on microbiota: “It is worthy to mention that glyphosate also has an inhibitory effect on microbial growth and antibiotics effect at lower concentrations than those found in agriculture (Clair et al., 2012b). Glyphosate could disrupt the bacterial community due to differences in sensitivity between microorganisms.”⁴¹

Furthermore, OEHHA did not consider the potential for glyphosate to bio-accumulate in human and animal bodies. This additional feature should be considered as part of a comprehensive review of the data in determining an NSRL. It has been demonstrated that glyphosate is capable of bio-accumulating and metabolizing in mammals.⁴² Significantly, “[s]ince Monsanto found bioaccumulation of glyphosate in all animal tissues, with the highest levels in the bones and marrow [35, 36], one would expect that all tissues derived from animals fed a diet containing glyphosate residues and used for food by people around the globe would be contaminated.”⁴³ Given that glyphosate may act as a non-coding amino acid in identical terms to that of the naturally occurring chemical, glycine⁴⁴, the erroneous integration of glyphosate into enzyme and protein synthesis may occur, “producing a defective product that resists proteolysis.”⁴⁵ Although the precise adverse effects of this mechanism are not conclusive, it behooves OEHHA to review the available literature for indications of how glyphosate may subtly effect biochemical changes that should be considered in calculating an appropriate NSRL. It is within the scope of scientific prudence and a cautionary approach to public health to examine such peripheral effects of glyphosate given the diverse mechanisms by which this chemical is known to cause cancer.

<http://www.ncbi.nlm.nih.gov/pubmed/24985121>; Mesnage, R., et al., *Transcriptome profile analysis reflects rat liver and kidney damage following chronic ultra-low dose Roundup exposure*, 14 *Environ. Health* 70 (2015), available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4549093>.

⁴⁰ Shehata A., et al., *The effect of glyphosate on potential pathogens and beneficial members of poultry microbiota in vitro*, *Curr. Microbiol.* 2013 Apr; 66(4):350-8, available at: <https://www.ncbi.nlm.nih.gov/pubmed/23224412>.

⁴¹ Shehata A. et al., *Neutralization of the Antimicrobial Effect of Glyphosate by Humic Acid In Vitro*. *Chemosphere* 104 (2014) 258-261, available at:

https://www.researchgate.net/profile/Awad_Shehata/publication/258852349_Neutralization_of_the_antimicrobial_effect_of_glyphosate_by_humic_acid_in_vitro/links/5502b19f0cf231de076f4a2c/Neutralization-of-the-antimicrobial-effect-of-glyphosate-by-humic-acid-in-vitro.pdf.

⁴² Howe, R.K., et al., *The Metabolism of Glyphosate in Sprague Dawley Rats. Part II. Identification, Characterization and Quantification of Glyphosate and its Metabolites after Intravenous and Oral Administration* (unpublished study MSL-7206 conducted by Monsanto and submitted to the EPA July 1988). MRID#407671-02 (1988).

⁴³ Samsel, A. and S. Seneff, *Glyphosate pathways to modern diseases VI: Prions, amyloidoses and autoimmune neurological diseases*. *Journal of Biological Physics and Chemistry* 17(March 2017): 8-32 (“Glyphosate integration into and inhibition of lipase could induce excessive bioaccumulation of fatty material in the blood vessels, gut, liver, spleen and other organs, as well as mimic lysosomal acid lipase deficiency.”) at 15.

⁴⁴ See Cattani, D., et al., *Mechanisms underlying the neurotoxicity induced by glyphosate-based herbicide in immature rat hippocampus: involvement of glutamate excitotoxicity*. *Toxicology* 320 (2014) 34–45. 13. Beecham, J.E. and S. Seneff, *The possible link between autism and glyphosate acting as glycine mimetic—A review of evidence from the literature with analysis*. *J. Molec. Genet. Med.* 9 (2015) 4.

⁴⁵ *Id.* at 8.

Lastly, we ask that OEHHA consider the subtle but imperative difference between glyphosate exposure and exposure to Roundup, which contains glyphosate as well as a cocktail of “inert” ingredients, adjuvants and surfactants— all carrying potential health risks. Indeed, the surfactant POEA has been banned in several countries⁴⁶ and certain co-formulants like the harmful humectant, ethylene glycol, is toxic to children as found in a 70 cc of Roundup containing 5% ethylene glycol. 1, 4 dioxane, one of the impurities of POEA, has been listed by OEHHA under Proposition 65 as known to the State of California to cause cancer. Monsanto itself is well aware of the dangers of 1, 4 dioxane, but still chose to increase the amount of 1, 4 dioxane in the formulated Roundup product, as illustrated by this internal email:

1, 4-dioxane was once included on the FAO specification with a limit of 1 ppm, but since this is an impurity in the ethoxylated surfactants and not in the glyphosate manufacturing process itself, the specification was later dropped from the FAO specification. The 1 ppm limit in the formulation was retained by Monsanto as a specification managed via the raw material specification since it was considered to be reasonably attainable and a level that was considered to be below any health risk level. However, it is my understanding that the Monsanto CSWG had later increased the level of 1,4- dioxane up to 10 ppm in final formulated products. The other thing is that we have to be very careful before we go slinging mud about 1,4-dioxane in Chinese glyphosate in public, because whether it is 1 ppm or 10 ppm, we most likely have it on our products too, and the general public does not understand the difference between 1 ppm and a bucket full...if there is a chemical that is considered to be a cancer-causing, it don't matter how much is in there, just that it is in there!

Exh. 6 at *1.⁴⁷

Another chemical, N-Nitroso-Glyphosate (“NNG”), is found in glyphosate-based formulations such as Roundup, but not necessarily in glyphosate evaluated in animal bioassays. The public will not find any reference to NNG on the Roundup® label. NNG is part of a family of carcinogenic chemicals known as “nitroso compounds”. Nitroso compounds have consistently been identified as carcinogenic following analysis.⁴⁸ NNG forms whenever glyphosate interacts with nitrites, whether outside or inside the body. Exh. 7 at *2-5.⁴⁹ Monsanto is aware of this problem with NNG and has attempted to downplay the issue. Exh. 8 at *1 (“I would suggest we agree in writing that ‘bad results’ of NNG due to accelerated ageing can be caused by the heat level and is therefore not representative for “normal ageing”).⁵⁰ Indeed, Monsanto acknowledges that NNG is toxic. Exh. 9 at *2 (“If you talk to Kerry, [Liefer, an EPA employee], I wouldn't push the NNG issue too hard --- don't want to draw attention to the toxicity of our

⁴⁶ See http://europa.eu/rapid/press-release_MEMO-16-2012_en.htm.

⁴⁷ MONGLY01041300, available at: <https://usrtk.org/wp-content/uploads/2017/03/192series.pdf>

⁴⁸ Loh, et al., *N-nitroso compounds and cancer incidence: the European Prospective Investigation into Cancer and Nutrition (EPIC)–Norfolk Study*. *Am J Clin Nutr* May 2011, vol. 93 no. 5 1053-061.

⁴⁹ MONGLY00925905, available at: <https://usrtk.org/wp-content/uploads/2017/03/192series.pdf>

⁵⁰ MONGLY0675873, available at: *Id.*

product...”).⁵¹ Furthermore, Monsanto acknowledges in internal memos that oral ingestion of pure glyphosate does not resemble dermal exposure by workers:

To me all this discussion continues to show that we still need solid data for ADME arising from dermal exposure. Our dermal absorption end point is based on the literature and, as I recall, we failed to get the original data to support the results. The movement of glyphosate in the blood flow from dermal contact, is different: to that through oral or intravenous exposure. The little data we have suggests that the excretion is significantly more through the faeces than the urine. Dermal exposure is the greatest risk of exposure for operators. Therefore, we need to be secure on the ADME of such exposure.” Unfortunately, Monsanto decided not to investigate the issue further due to cost and due to fear of finding an additional mammalian metabolite created by glyphosate.

Exh. 10 at *2.⁵²

In light of the above, the proper Absorption, Distribution, Metabolism, and Excretion (ADME) of Roundup, the toxicity of the various surfactants and humectants, and the bioaccumulation of Roundup⁵³ at low doses must also be factored into the determination of a realistic NSRL. All users of Roundup are ultimately users of glyphosate, and OEHHA should not gloss over this important distinction when determining the appropriate exposure level at which Roundup may be deemed “safe”.

Concluding Remarks

Monsanto’s withholding of important information regarding glyphosate carcinogenicity, in addition to collusion with regulatory officials, are the subject of many documents that have been obtained and unsealed *In Re: Roundup Products Liability Litigation*, 3:16-md-02741, currently pending in United States District Court for the Northern District of California. Many of the issues raised in this Comment are derived from Monsanto’s own documents referenced here as exhibits. EU Parliament Members and the US EPA Office of the Inspector General are conducting investigations based on some of these documents. Such documents illustrate the lack of information available to regulators and researchers to properly assess and classify glyphosate in a transparent manner.⁵⁴ Regulators such as OEHHA require comprehensive data in order to make informed and safe regulatory decisions. Additional documents pertinent to the Safe Harbor NSRL and Roundup/glyphosate carcinogenicity are presently still under seal and it is strongly

⁵¹ MONGLY03549275, available at: *Id.*

⁵² MONGLY02155826, available at: *Id.*

⁵³ See Peluso M., et al., *32P-postlabeling detection of DNA adducts in mice treated with the herbicide Roundup*. *Environ Mol. Mutagen* (1998) 31:55–59.

⁵⁴ Indeed, Dr. Christopher Portier, in his letter to the President of the European Commission regarding the glyphosate review by EChA, EFSA and BfR (discussed above), also reflected on the importance of transparency for the scientific process in addressing serious public health issues: “The glyphosate hazard classification appears to have been a good example of how lack of transparency regarding the scientific evidence that underlies important public health decisions can erode public trust and raise concerns.” at 5. We sincerely hope that OEHHA will lend due weight to information overlooked or not considered by other regulatory agencies.

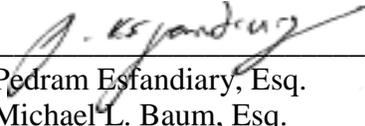
recommended that OEHHA obtain access to such documents before OEHHA takes the potentially precarious step of issuing an NSRL of 1100 micrograms.

At a minimum, OEHHA should reconsider the proposed amendment to Section 25705(b) and postpone imposing an NSRL for glyphosate until a thorough evaluation of the available epidemiological literature (in conformity with Section 25703(a)(2)), review of animal bioassays demonstrating lymphomagenesis at lower doses than the study cited by the Initial Statement of Reasons, and the potential for glyphosate to cause cancer by disrupting bacterial populations, has been conducted. The known dangers of glyphosate warrant extensive investigation before Californians are exposed to *any* amount, as recognized by the judicious decision to list glyphosate under Proposition 65. There are numerous explicit health concerns associated with glyphosate that render it inappropriate for a consumer to be deprived of the opportunity to exercise informed choice when contemplating purchasing and using this product, or a product containing glyphosate. A label warning would thus ensure the presence of a modest protective moat before the gates of public health. A Safe Harbor with an unsafe NSRL circumvents that protection. Please continue to protect the health and welfare of Californians and all those who emulate California as a standard bearer.

Sincerely,

BAUM HEDLUND ARISTEI & GOLDMAN, P.C.

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