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MONSANTO COMPANY

SUPERIOR COURT OF THE STATE OF CALIFORNIA

COUNTY OF SAN FRANCISCO

DEWAYNE JOHNSON,

Plaintiff,

vs.

MONSANTO COMPANY,

Defendant.

Case No. CGC-16-550128

DECLARATION OF SANDRA A. EDWARDS IN SUPPORT OF DEFENDANT MONSANTO COMPANY'S TRIAL BRIEF TO EXCLUDE TESTIMONY FROM DR. SAWYER REGARDING CALIFORNIA NSRL

Honorable Judge Suzanne R. Bolanos

Department: 504
Trial Date: June 18, 2018

I, Sandra A. Edwards, declare as follows:

1. I am an attorney duly admitted to practice before this Court. I am a partner with Farella Braun + Martel LLP, attorneys of record for Defendant Monsanto Company ("Monsanto"). I submit this Declaration in support of Monsanto's Trial Brief To Exclude Testimony From Dr. Sawyer Regarding California NSRL.

2. Attached hereto as **Exhibit 1** is a true and correct copy of an email from Jeff Travers to Kirby Griffis dated July 20, 2018.

3. Attached hereto as **Exhibit 2** is a true and correct copy of the Office of Environmental Hazard Assessment's "Final Statement of Reasons Title 27, California Code of Regulations, Section 25705(b) Specific Regulatory Levels Posing No Significant Risk, No Significant Risk Level: Glyphosate" (April 10, 2018), available at https://oehha.ca.gov/media/downloads/crnr/glyphosatensrlfsor041018.pdf.

4. Attached hereto as **Exhibit 3** is a true and correct copy of the Office of Environmental Hazard Assessment's "Initial Statement of Reasons Title 27, California Code of Regulations, Proposed Amendment to: Section 25705(b) Specific Regulatory Levels Posing No Significant Risk, Glyphosate" (March 29, 2017), available at https://oehha.ca.gov/media/downloads/crnr/glyphosate032917isor.pdf.

5. Attached hereto as **Exhibit 4** is a true and correct copy of an excerpt from the deposition of William Sawyer on February 26, 2018.

6. Attached hereto as **Exhibit 5** is a true and correct copy of William Sawyer's Expert Report (Dec. 21, 2017).

7. Attached hereto as **Exhibit 6** is a true and correct copy of William Sawyer's Affidavit (March 30, 2018).

8. Attached hereto as **Exhibit 7** is a true and correct copy of an email from Jeff Travers to Josh Malone dated May 25, 2018.

9. Attached hereto as **Exhibit 8** is a true and correct copy from the June 28, 2018 trial transcript in this case.

10. Attached hereto as **Exhibit 9** is a true and correct copy from the July 10, 2018 trial

transcript in this case.

11. Attached hereto as **Exhibit 10** is a true and correct copy from the July 11, 2018 trial transcript in this case.

12. Attached hereto as **Exhibit 11** is a true and correct copy from the July 17, 2018 trial transcript in this case.

13. Attached hereto as **Exhibit 12** is a true and correct copy of the Office of Environmental Hazard Assessment's "Response to Comments Concerning the Notice of Intent to List Glyphosate as Causing Cancer Under Proposition 65" (March 2017), available at https://oehha.ca.gov/media/downloads/crnr/0317responsetocomments.pdf.

14. Attached hereto as **Exhibit 13** is a true and correct copy of an excerpt from the deposition of William Sawyer on February 27, 2018.

I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct, and that this declaration was executed on July 23, 2018, at San Francisco, California.

Sandra A. Edwards

Farella Braun + Martel LLP
235 Montgomery Street, 17th Floor
San Francisco, California 94104
(415) 954-4400

Exhibit 1

From: Hilmert, James M.
To: Krajewski, Sarah A.
Subject: Fwd: Sawyer"s Reliance on California NSRL documents
Date: Sunday, July 22, 2018 2:43:39 PM

Sent from my iPhone

Begin forwarded message:

From: "Griffis, Kirby T." <KGriffis@Hollingsworthllp.com>
Date: July 21, 2018 at 1:13:48 PM PDT
To: "Hilmert, James M." <jhilmert@winston.com>
Subject: Fwd: Sawyer's Reliance on California NSRL documents

Hollingsworth LLP

Kirby T. Griffis
Partner

D 202.898.5828 | KGriffis@Hollingsworthllp.com1350 I Street NW | Washington, DC 20005
www.hollingsworthllp.com

Begin forwarded message:

From: "Griffis, Kirby T." <KGriffis@Hollingsworthllp.com>
Date: July 21, 2018 at 10:47:24 AM PDT
To: 'Jeffrey Travers' <JTravers@millerfirmllc.com>
Cc: "Edwards, Sandra" <sedwards@fbm.com>, "Lombardi, George C." <glombard@winston.com>, David Dickens <DDickens@millerfirmllc.com>, "rbwisner@baumhedlundlaw.com" <rbwisner@baumhedlundlaw.com>
Subject:RE: Sawyer's Reliance on California NSRL documents

This is an inaccurate description of the history in every respect. We oppose the use of these materials and consider it barred.

<HollingsworthLLP_34a84990-3d9e-4b28-a044-cd21af3f95ee.jpg>

From: Jeffrey Travers [mailto:JTravers@millerfirmllc.com]
Sent: Saturday, July 21, 2018 1:46 PM
To: Griffis, Kirby T.
Cc: Edwards, Sandra; Lombardi, George C.; David Dickens;

rbwisner@baumhedlundlaw.com
Subject: RE: Sawyer's Reliance on California NSRL documents

Kirby,

Judge Bolanos actually excluded the NSRL because it was not disclosed in Dr. Portier's supplemental reliance lists. 1686:10-25. Dr. Sawyer has timely disclosed his reliance on these materials. Monsanto had an opportunity to depose him on June 4th on these materials, but James Hilmert decided to postpone the deposition. This will be the second opportunity to depose Dr. Sawyer on these materials that you are declining, so we will assume that you do not deem it necessary to depose Dr. Sawyer in order to be adequately prepared at trial to cross him on these materials. We will plan on using these documents during his direct testimony.

-Jeff

From: Griffis, Kirby T. [mailto:KGriffis@Hollingsworthllp.com]
Sent: Friday, July 20, 2018 9:32 PM
To: Jeffrey Travers <JTravers@millerfirmllc.com>
Cc: Edwards, Sandra <sedwards@fbm.com>; Lombardi, George C. <glombard@winston.com>; David Dickens <DDickens@millerfirmllc.com>; rbwisner@baumhedlundlaw.com
Subject: Re: Sawyer's Reliance on California NSRL documents

Per Judge Bolanos' rulings on Prop 65, Dr. Sawyer may not testify about the NSRL. If you disagree, you should raise that with the Court for reargument.

On Jul 20, 2018, at 5:27 PM, Jeffrey Travers <JTravers@millerfirmllc.com> wrote:

Counsel,

Dr. Sawyer relied upon California's Initial Statement of Reasons for setting the NSRL in his affidavit attached to Plaintiff's Sargon opposition, and California's Final Statement of Reasons for the NSRL was on his 5/25/2018 reliance list. We can make him available for a deposition for an hour on Wednesday, July 25, 2018 if you feel the need to question him on the documents.

-Jeffrey Travers

Exhibit 2

FINAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

SECTION 25705(b) SPECIFIC REGULATORY LEVELS POSING NO SIGNIFICANT RISK

NO SIGNIFICANT RISK LEVEL: GLYPHOSATE

This is the Final Statement of Reasons for the adoption of a No Significant Risk Level (NSRL)[1] for glyphosate. On June 26, 2017, the Office of Environmental Health Hazard Assessment (OEHHA) announced the listing of glyphosate, effective July 7, 2017, as a chemical known to the state to cause cancer for purposes of Proposition 65[2]. OEHHA issued a Notice of Proposed Rulemaking to adopt a proposed amendment to Section 25705, Specific Regulatory Levels Posing No Significant Risk, identifying an NSRL of 1100 micrograms per day (µg/day) for glyphosate under Title 27, California Code of Regulations, section 25705(b)[3]. The Initial Statement of Reasons sets forth the grounds for the amendment to the regulation.

Briefly, in developing the NSRL for glyphosate, OEHHA relied on Volume 112 in the series of International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans, entitled "Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos"[4], which summarizes the available data from rodent carcinogenicity studies of glyphosate, as well as other information relevant to the carcinogenic activity of this chemical. The NSRL is based upon the results of the most sensitive scientific study deemed to be of sufficient quality[5]. OEHHA agrees with IARC's determination that the increased incidence of hemangiosarcomas observed in a study of male CD-1 mice is treatment-related and is using that study as the basis for the NSRL.

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[1] No Significant Risk Levels (NSRLs) for cancer-causing chemicals have been established for many of the chemicals listed under Proposition 65. A business would not be required to provide a Proposition 65 warning for an exposure to a listed carcinogen that is at or below the NSRL.

[2] The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code section 25249.5 *et. seq.*, hereafter referred to as "Proposition 65" or "The Act".

[3] All further regulatory references are to sections of Title 27 of the Cal. Code of Regs., unless otherwise indicated.

[4] International Agency for Research on Cancer (IARC, 2015). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112, Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France. Available from: http://monographs.iarc.fr/ENG/Monographs/vol112/index.php

[5] Section 25703(a)(4)

The Notice of Proposed Rulemaking was published in the California Regulatory Notice Register on April 7, 2017 (Register 2017, No. 14-Z) and initiated a 45-day public comment period that was scheduled to close on May 22, 2017. OEHHA received several requests to extend the public comment period and it was extended until June 21, 2017. OEHHA received over 1,300 oral and written public comments on the proposed rulemaking from several organizations and numerous individuals.

PEER REVIEW

As required by Section 25302(e) of the regulations, on May 17, 2017, OEHHA provided the notice of proposed rulemaking and the initial statement of reasons for the proposed NSRL for glyphosate to the members of the Carcinogen Identification Committee for their individual review and comment. OEHHA received peer-review comments from committee members Thomas McDonald, M.P.H., Ph.D., Luoping Zhang, PhD, Shanaz Dairkee, PhD, and Jason Bush, Ph.D.

UPDATED INFORMATION

There are no updates to the information contained in the ISOR, and no new documents were relied upon or added to the rulemaking file. Non-substantive revisions were made to the final regulation text to align the text with the text currently printed in the California Code of Regulations.

SUMMARY AND RESPONSE TO RELEVANT COMMENTS RECEIVED

OEHHA's responses to the oral and written comments received throughout this rulemaking process are incorporated in this Final Statement of Reasons (FSOR). Some commenters analyzed IARC's scientific conclusions, supporting or disagreeing with IARC's classification of glyphosate as a Group 2A carcinogen and providing their own scientific analyses and conclusions, cited the conclusions of other international regulatory or scientific bodies that were contrary to IARC's, or expressed or reiterated general disagreement with the addition of glyphosate to the Proposition 65 list; such comments are not directed to the subject of this rulemaking, which is the establishment of an NSRL for glyphosate. OEHHA responded to these types of comments in the listing documents for glyphosate and does not respond to them again here.

Other commenters discussed the US Environmental Protection Agency's (US EPA's) report entitled 'Glyphosate Issue Paper: Evaluation of Carcinogenic Potential'[6],

[6] US EPA (2016). Glyphosate Issue Paper: Evaluation of Carcinogenic Potential. Office of Pesticide Programs, US Environmental Protection Agency. September 12, 2016. Available from: https://www.epa.gov/sites/production/files/2016-09/documents/glyphosate_issue_paper_evaluation_of_carcincogenic_potential.pdf

critiquing the analysis and conclusions therein, including comments that US EPA did not follow good laboratory practices in its weight of the evidence evaluation by omitting relevant studies[7], as well as concerns that the cancer-related data provided by the US EPA has been brought into question based on allegations of collusion with Monsanto. These comments are not directed to the subject of this rulemaking and are not responded to here.

OEHHA additionally received many comments during the regulatory process that included observations or opinions regarding the use of glyphosate; suggestions that OEHHA conduct further studies into the health effects of glyphosate; statements that the NSRL does not consider impacts other than carcinogenicity; concerns of increased chronic illness among children and the lack of studies of the effects of pesticides on children[8]; opinions that glyphosate is safe, regulated, and effective; statements of support for other actions that are not the subject of this rulemaking (such as banning or restricting use of the chemical); and recommendations to use methods of clinical testing of 0.5 parts per billion or lower, and much lower for urine and water testing[9]. Some commenters expressed concern over the negative effects of genetically modified organisms (GMOs), that all GMOs should be banned, or that the US Food and Drug Administration should adopt mandatory regulations concerning genetically engineered plants and animals[10]. Some commenters also stated that Monsanto is greedy, corrupt, or withholding scientific evidence of glyphosate's toxicity to humans and animals[11]. Such remarks do not constitute an objection or recommendation specifically directed at the proposed action, or the procedures followed in this rulemaking action. Accordingly, OEHHA is not required under the Administrative Procedure Act to respond to such comments in this FSOR. Because OEHHA is constrained by limitations upon its time and resources, and is not obligated by law to respond to irrelevant comments[12], OEHHA does not provide responses to all of these remarks in this FSOR. However, the absence of responses to such remarks should not be construed to mean that OEHHA agrees with them.

Many commenters made the same or similar comments, and this document does not provide an exhaustive accounting of all commenters addressing the same point. A summary of the comments relevant to this rulemaking is provided below, along with OEHHA's responses to those comments. As explained in detail in the responses to comments, OEHHA declines to change the proposed NSRL based on the comments.

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[7] Comment from Kurt Wallace.
[8] Comment from Michelle Perro
[9] Comment from Diane Rude
[10] Comment from Stephanie Easton
[11] Comment from Kathleen Furey
[12] California Government Code section 11346.9(a)(3)

Comment 1 (Baum, Hedlund, Aristei & Goldman, P.C., A Voice for Choice, Donna R. Farmer, Ph.D., on behalf of Monsanto and others): The potency estimate for the NSRL should be based on cancer findings from human epidemiological studies, rather than on findings from animal carcinogenicity studies. Many commenters assert that in failing to consider epidemiologic studies, the proposed safe harbor level does not conform to "quantitative risk assessment" and that OEHHA did not follow Section 25703 of the regulations.

Some of these commenters went on to state that prioritizing animal bioassays over epidemiological data overlooks the risk to individuals exposed to glyphosate during its application as a pesticide. They further argue that use of epidemiological data would provide a more robust and comprehensive evaluation of a chemical which most users absorb via cutaneous and respirational contact.

Paul Eusey, Tricia Brooks, and several other commenters stated that OEHHA should review the lowest levels of glyphosate in the epidemiological studies, but should always err on the side of caution and public health (see also Response #29 and discussion of precautionary principle).

Response 1: As stated in Section 25703 of the regulations, the assessment used to derive the NSRL "shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer"[13]. Glyphosate was listed pursuant to the Labor Code listing mechanism[14] as a result of IARC's classification of glyphosate in Group 2A ("probably carcinogenic to humans"), with a finding of sufficient evidence of carcinogenicity in experimental animals[15,16]. IARC also found "there is *limited evidence* in humans for the carcinogenicity of glyphosate", noting "[a] positive association has been observed for non-Hodgkin lymphoma." Given that the listing of glyphosate is based on findings of limited evidence in humans and sufficient evidence in animals, basing the potency estimate for the NSRL on animal studies is both appropriate and consistent with Section 25703.

Animal bioassays are more frequently used than epidemiological data in quantitatively assessing the health risks of chemicals, including carcinogens. The epidemiological

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[13] Section 25703(a)(4)
[14] Section 25249.8(a) of the Act
[15] OEHHA (2015). Notice of Intent to List - Tetrachlorvinphos, Parathion, Malathion, Glyphosate. https://oehha.ca.gov/media/downloads/crnr/090415noillcset27.pdf
[16] IARC (2015). Full citation provided in footnote 3.

studies evaluated by IARC, like many human studies, do not provide the type of information on levels of exposure that is needed for dose-response analysis. Specifically, these studies broadly characterized glyphosate exposure to individuals as either 'never' or 'ever' exposed, or as 'duration' of exposure, and were unable to quantify the individuals' specific levels of exposure to the chemical. Since the epidemiology studies did not measure or estimate the dose level to which participants were exposed, a cancer potency cannot be calculated using these studies.

OEHHA disagrees with the commenters' assertions that the use of animal cancer bioassay data to estimate cancer potency results in a less robust or comprehensive risk assessment than would the use of epidemiologic data, or that the use of animal data in some way overlooks risks to workers or other individuals exposed to glyphosate. As noted above, the epidemiologic studies available to date on glyphosate only provide limited evidence of a causal relationship between exposure and cancer risk, and they do not provide the type of information on levels of exposure needed in order to estimate cancer potency. Thus, OEHHA's use of animal cancer bioassay data from the most sensitive study of sufficient quality to estimate human cancer potency for this chemical is appropriate and consistent with the Proposition 65 regulations[17], other cancer risk assessment guidance from OEHHA[18], and guidance from US EPA[19]. The estimate of human cancer potency is equally valid for estimating risks to occupationally exposed workers and to other individuals exposed to glyphosate, and the NSRL for glyphosate is not limited to a specific route of exposure[20,21]. No change to the regulatory proposal was made based on these comments.

Comment 2 (Moms Across America, Marty Eustis, Majorie Golden, Gloria Anderson and other commenters): Glyphosate induces breast cancer in humans. Marty Eustis commented that the NSRL should be "substantially lower" than the proposed 1100 micrograms/day in order to actually be safe to Californians. Majorie Golden, Gloria Anderson, and Marty Eustis commented that until a comprehensive independent study is done, the NSRL should be at or "well below 0.0001 mg/day" (Thongprakisang et al.), the concentration where it stimulated breast cancer cells in vitro.

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[17] Section 25703

[18] OEHHA (2009). Technical Support Document for Cancer Potency Factors. https://oehha.ca.gov/media/downloads/crnr/tsdcancerpotency.pdf

[19] US EPA (2005). Guidelines for Carcinogen Risk Assessment. March, 2005. Risk Assessment Forum, US Environmental Protection Agency, Washington, DC.

[20] OEHHA (2017). Initial Statement of Reasons, Title 27, California Code of Regulations, Proposed Amendment to: Section 25705(b) Specific Regulatory Levels Posing No Significant Risk. Glyphosate. Available at https://oehha.ca.gov/media/downloads/crnr/glyphosate032917isor.pdf

[21] Section 25703(a)(4)

Response 2: These comments all appear to be based on an *in vitro* study by Thongprakaisang et al. (2013)[22], in which glyphosate was shown to induce proliferation in a hormone-dependent human breast cancer cell line (T47D cells derived from ductal carcinoma cells), but not in a hormone-independent human breast cancer cell line (MDA-MB231 breast adenocarcinoma cells). This study is not a human epidemiology study and thus it does not provide evidence that glyphosate induces breast cancer in humans. Rather, it is a study of the effect of glyphosate on the proliferation of cultured cells, and it does not provide information that can be used to derive the NSRL for glyphosate. No changes were made to the regulatory proposal based on this comment.

Comment 3 (Monsanto, Ramboll Environ on behalf of The Scotts Company LLC, and others): Reviews by others have concluded that there are no treatment-related tumors in animal cancer bioassays of glyphosate, nor are there other datasets that provide evidence of a strong dose-response relationship of carcinogenicity that could be relied upon to estimate the potential for health effects in humans following exposure to expected concentrations and that the lack of an adequate dataset is consistent with conclusions reached by JMPR (2006) and US EPA (2016) that any tumor findings are not treatment-related. OEHHA has no basis to quantify an NSRL using experimental animal studies.

Response 3: Glyphosate was listed under Proposition 65 via the "Labor Code" listing mechanism, based on IARC's classification[23] of glyphosate as *probably carcinogenic to humans* (Group 2A), and its conclusion that there is *sufficient evidence* of carcinogenicity in experimental animals for glyphosate. IARC's conclusion of sufficient evidence in experimental animals is based on findings from two studies in male mice. Specifically, IARC cited "a significant positive trend in the incidence of haemangiosarcoma [a malignant neoplasm] in male CD-1 mice" in a two-year diet study[24], and "a positive trend in the incidence of renal tubule carcinoma [a malignant neoplasm] and of renal tubule adenoma and carcinoma (combined) [an appropriate combination of benign and malignant neoplasms]" in male CD-1 mice in a different

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[22] Thongprakaisang S, Thiantanawat A, Rangkadilok N, Suriyo T, Satayavivad J., 2013. Glyphosate induces human breast cancer cells growth via estrogen receptors. *Food Chem Toxicol* **59**:129-36.
[23] IARC (2015). Full citation provided in footnote 3.
[24] As noted in the Initial Statement of Reasons, this study of glyphosate (purity 98.6%) met the criterion in Section 25703 as the most sensitive study of sufficient quality, and was used to derive the NSRL. This study was performed by Inveresk Research International and summarized in the 2006 Joint FAO/WHO Meeting on Pesticide Residues report (JMPR, 2006. Glyphosate. In: Joint FAO/WHO Meeting on Pesticide Residues. Pesticide residues in food – 2004: toxicological evaluations. Report No. WHO/PCS/06.1. Geneva: World Health Organization; pp. 95 – 169.) and by IARC (IARC, 2015, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112. Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France).

two-year diet study[25], with IARC noting that these malignant kidney tumors are rare in this strain of mice. OEHHA agrees with IARC's determination that these tumor findings are treatment-related and demonstrate statistically significant dose-response relationships.

In developing the NSRL for glyphosate, OEHHA followed the guidance set forth in Section 25703 that the assessment "be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer", and based the NSRL on the results of the most sensitive scientific study deemed to be of sufficient quality. OEHHA determined that the two-year study conducted in male CD-1 mice fed glyphosate (purity 98.6%) in the diet, in which a significant positive trend in the incidence of hemangiosarcomas was observed, met the criteria in 25703 as the most sensitive study of sufficient quality. OEHHA used this data to derive the NSRL for glyphosate. No changes were made to the regulatory proposal based on this comment.

Comment 4 (Monsanto): The commenter cited the decision in *Baxter Healthcare Corp. v. Denton,* 120 Cal. App. 4th 333, 15 Cal. Rptr. 3d 430 (2004) to support its assertion that OEHHA is required to determine that a glyphosate exposure at any level does not pose a "significant risk", and as such requires OEHHA to establish an "infinite" NSRL. Baum, Hedlund, Aristei & Goldman, P.C. and others stated that Monsanto's reliance on *Baxter v. Denton* is inappropriate.

Response 4: OEHHA disagrees that the *Baxter* decision mandates the establishment of an infinite NSRL. The decision in *Baxter* is factually distinguishable from the proposed NSRL for glyphosate[26]. The commenter provides no evidence that the mechanism of action for glyphosate does not operate in humans, which was the pivotal issue in that case. In *Baxter*, the Appellate Court focused on evidence that the mechanism by which DEHP increased the incidence of liver tumors in animals was not relevant to humans[27]. This notably included evidence regarding the classification of DEHP by IARC[28]. At the time of the *Baxter* decision, IARC had downgraded its earlier classification of DEHP as Group 2B ("possibly carcinogenic to humans") to Group 3 ("not classifiable as to its carcinogenicity to humans"). Glyphosate, on the other hand,

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[25] In summarizing this study of glyphosate (purity 99.7%), IARC cited four US EPA documents (US EPA 1985a, b, 1986, 1991a) (IARC, 2015, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112. Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France).
[26] See comment letters from Baum, Hedlund, Aristei & Goldman, P.C., (Comment #9945) and Center for Biological Diversity, et al. (Comment #9974)]
[27] Baxter Healthcare Corp. v. Denton, 120 Cal. App. 4th 333, 15 Cal. Rptr. 3d 430 (2004), at 438.
[28] *Id.*

has received a higher Group 2A classification from IARC[29]. IARC's Group 2A classification of glyphosate is based on "sufficient evidence" in animal studies and "limited evidence" in human (epidemiological) studies. IARC found that mechanistic and other relevant data support the Group 2A classification of glyphosate (e.g., "strong" evidence for genotoxicity, both for "pure" glyphosate and for glyphosate formulations) and concluded, "[t]here is evidence that these effects can operate in humans". IARC has not reclassified glyphosate, or modified its findings that animal studies provided sufficient evidence of carcinogenicity and human studies provided limited evidence of carcinogenicity. No changes to the regulatory proposal were made based on this comment.

Comment 5 (Monsanto, Chris Portier, SafeAgSafeSchools, Anthony Samsel, Baum, Hedlund, Aristei & Goldman, P.C., and others): Monsanto commented that according to Section 25703, OEHHA's assessment is not limited to the specific studies used as the basis for listing the chemical, but instead OEHHA's "assessment shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for listing the chemical as known to the state to cause cancer." Monsanto went on to say that OEHHA's basis for listing is IARC's classification of glyphosate as a category 2A chemical on the basis of sufficient evidence in animals and that OEHHA should consider all available rodent studies and not just the select few that IARC chose to evaluate. The other studies contradict the conclusions reached by IARC's working group with respect to the four referenced animal studies.

Additionally, Chris Portier, Safe Ag Safe Schools, Anthony Samsel, Baum, Hedlund, Aristei & Goldman, P.C., Sonoma County Conservation Action[30] and others requested that OEHHA analyze and incorporate additional bioassay data in the derivation of an NSRL for glyphosate, not just studies reviewed by IARC. This includes the studies discussed in the review article by Greim et al. (2015). Some of these studies, including Wood et al. (2009), Lankas (1981), and Stout and Ruecker (1990), as cited by Baum, Hedlund, Aristei & Goldman, P.C. and Safe Ag Safe Schools, observed tumors or lymphomas at much lower doses than the study used to derive the NSRL. Baum, Hedlund, Aristei & Goldman, P.C, stated that if the data from these studies were used, a significantly lower NSRL would have been reached. Safe Ag Safe Schools stated that the NSRL is not based on the most sensitive study of acceptable quality and should be based on a dose of 31.49 mg/kg/day. Chris Portier and the Center for Biological Diversity commented that the Atkinson study is not the most sensitive study of sufficient

[29] IARC (2015). Full citation provided in footnote 3.
[30] The commenter suggested a revised NSRL based on a dose of 31.39/mg/kg/day, which is related to the Lankas study discussed in Greim et al.

quality to guide the suggested NSRL, and that other studies provide a more scientifically sound and health- protective basis for calculating the NSRL (i.e., Wood et al. [2009], Lankas [1981], and Stout and Ruecker [1990]), and that OEHHA must do an independent analysis of these studies and not rely on US EPA's conclusions.

During the public hearing for this rulemaking, Dr. Donna Farmer, senior toxicologist at Monsanto's Regulatory Product Safety Center, commented that OEHHA's reliance on male mouse hemangiosarcomas is not justified for the derivation of a NSRL.

Seosamh Devine commented that OEHHA relied too much on Monsanto's scientific opinions.

Response 5: As noted by the commenters, Section 25703 of the regulations states that the assessment used to derive the cancer potency "shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer"[31]. Glyphosate was listed under Proposition 65 via the "Labor Code" listing mechanism, based on IARC's classification[32] of glyphosate as *probably carcinogenic to humans* (Group 2A), and its conclusion that there is *sufficient evidence* of carcinogenicity in experimental animals for glyphosate. As discussed in response to comment 3, IARC's conclusion of sufficient evidence in experimental animals is based on findings from two studies in male mice. Specifically, IARC cited "a significant positive trend in the incidence of haemangiosarcoma in male CD-1 mice" in a two-year diet study[33], and "a positive trend in the incidence of renal tubule carcinoma and of renal tubule adenoma and carcinoma (combined)" in male CD-1 mice in a different two-year diet study[34], with IARC noting that these malignant kidney tumors are rare in this strain of mice.

In contrast to the commenters implication that IARC only evaluated a select few studies in its monograph on glyphosate, IARC[35] discussed each of the 14 sets of animal cancer

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[31] Section 25703(a)(4)

[32] IARC (2015). Full citation provided in footnote 3.

[33] As noted in the Initial Statement of Reasons, this study of glyphosate (purity 98.6%) met the criterion in Section 25703 as the most sensitive study of sufficient quality, and was used to derive the NSRL. This study was performed by Inveresk Research International and summarized in the 2006 Joint FAO/WHO Meeting on Pesticide Residues report (JMPR, 2006. Glyphosate. In: Joint FAO/WHO Meeting on Pesticide Residues. Pesticide residues in food – 2004: toxicological evaluations. Report No. WHO/PCS/06.1. Geneva: World Health Organization; pp. 95 – 169.) and by IARC (IARC, 2015, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112. Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France).

[34] In summarizing this study of glyphosate (purity 99.7%), IARC cited four US EPA documents (US EPA 1985a, b, 1986, 1991a) (IARC, 2015, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112. Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France).

[35] IARC (2015). Full citation provided in footnote 3

studies (five in mice and nine in rats)[36] included in the review by Greim *et al.* (2015)[37], as well as two additional sets of studies in rats, for a total of 16 sets of animal cancer studies. IARC noted in particular that the information reported in the article by Greim *et al.* and provided in the supplemental materials lacked sufficient detail regarding "statistical methods, choice of doses, body-weight gain, survival data, details of histopathological examination, and/or stability of dosed feed mixture" to be evaluated[38]. IARC evaluations "rely only on data that are in the public domain and available for independent scientific review"[39]. Utilizing additional sources in the public domain, IARC was able to conduct independent scientific review of two of the five sets of mouse studies included in Greim *et al.*, five of the nine sets of rat studies included in Greim *et al.*, and two additional sets of rat studies not included in Greim *et al.*

OEHHA is not aware of any additional animal cancer studies of glyphosate, other than the 16 sets of studies discussed by IARC. Of those 16 sets, IARC found that two sets of studies in mice and six sets of studies in rats were *adequate* for the evaluation of glyphosate carcinogenicity (emphasis added).

Of those eight sets of rodent studies, treatment-related increases in the incidence of malignant tumors were observed in one study in male mice, and treatment-related increases in the incidence of combined malignant and benign tumors were observed in a second male mouse study. Treatment-related increases in benign tumors were observed in two male rat studies and one female rat study; in each case, IARC noted there was no apparent progression of the benign tumors to malignancy.

Thus, OEHHA reviewed the available data from the rodent carcinogenicity studies of glyphosate in light of the requirement of Section 25703 that the assessment "be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause 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. OEHHA agrees with IARC's determination that the increased incidence of hemangiosarcomas observed in this study of male CD-1 mice is treatment-related.

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[36] Each set of studies consists of two experiments, one in males and one in females.

[37] 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. *Crit Rev Toxicol* 45(3):185-208.

[38] IARC (2015). Full citation provided in footnote 3.

[39] IARC (2015). IARC monograph Volume 112, General Remarks. p. 35.

OEHHA used this data to derive the NSRL for glyphosate. OEHHA did not rely on US EPA's conclusions to derive the NSRL for glyphosate; nor did OEHHA rely on Monsanto's scientific opinions to derive the NSRL (see also Response #3).

No changes were made to the regulatory proposal based on this comment.

Comment 6 (Valerie Noble and several commenters): The proposed NSRL does not account for bioaccumulation of glyphosate. Food Democracy Now further stated that a 2004 joint report from the United Nations Food and Agriculture [Organization] Program [*sic*] and the World Health Organization determined that glyphosate accumulates in the bones of lab animals.

Response 6: Valerie Noble did not provide a citation for the finding she attributed to Kruger et al. regarding bioaccumulation of glyphosate. OEHHA performed a literature search and identified one publication authored by Monika Kruger[40] . Contrary to the commenter's assertion, this publication provides no data indicating that glyphosate bioaccumulates. OEHHA is not aware of any evidence from studies in humans that demonstrate that glyphosate bioaccumulates. Similarly, there is no evidence that glyphosate bioaccumulates in non-human primates, or other mammals. For example, in rhesus monkeys, nearly all of an intravenous dose of glyphosate was eliminated within 24 hours[41], and in Fischer 344 rats greater than 90% of an oral dose of glyphosate was eliminated within 72 hours[42]. In another rat study, the total body burden of radiolabeled glyphosate residues measured 7 days after a single oral dose was approximately 1% of the administered dose. Further, no evidence of glyphosate bioaccumulation was observed in two repeated dosing studies conducted in rats[43].

The report referred to by the commenters appears to be the 2006 Joint FAO/WHO Meeting on Pesticide Residues (JMPR) report. However, the report does not conclude that glyphosate accumulates in the bones of lab animals. The report states that, after reviewing studies in mammals, there is no evidence of accumulation of glyphosate in

[40] Krüger M, Shehata AA, Schrödl W, and Rodloff A (2013). Glyphosate suppresses the antagonistic effect of Enterococcus spp. on Clostridium botulinum. Anaerobe 20: 74–78. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23396248
[41] IARC (2015) p. 45, full citation provided in footnote 3.
[42] IARC (2015) p. 44, full citation provided in footnote 3.
[43] IARC (2015) p. 43, full citation provided in footnote 3.

mammals[44][45]. No changes were made to the regulatory proposal based on this comment.

Comment 7 (Meghan Lawler, Pesticide Free Zone, and Laura Hayes, Linda Causey, Zen Honeycutt and other commenters): OEHHA should consider effects other than carcinogenicity in setting the NSRL, such as evidence of induction of liver disease at 4 nanograms/kg, teratogenicity, breakdown of the blood-brain barrier, and evidence of destruction of gut bacteria at 0.1 ppm. Meghan Lawler and Laura Hayes stated that glyphosate is a neurotoxin, endocrine disruptor, mineral chelator, and antibiotic, and that it causes liver disease.

Some commenters stated that the NSRL fails to account for the potential transgenerational effects of endocrine disruptors, and asserted that an appropriate study to determine the NSRL should involve mice studies for three generations. Pesticide Free Zone commented that by excluding low dose studies from consideration, OEHHA may not be accounting for harmful endocrine-disrupting chemical actions. Laura Hayes commented that the most serious negative health consequences result when glyphosate substitutes for glycine during protein synthesis.

Response 7: Proposition 65 requires the maintenance and updating of a list of chemicals that cause cancer or reproductive toxicity, and requires businesses that knowingly cause exposures to listed chemicals to provide warnings. Other health effects – including liver disease, breakdown of the blood-brain barrier and destruction of gut bacteria – are outside the scope of the law. Following the guidance set forth in Section 25703, OEHHA bases NSRLs on cancer dose-response assessments, which are conducted using data from the most sensitive scientific studies deemed to be of sufficient quality. Observations of liver disease, teratogenicity, breakdown of the blood-brain barrier, destruction of gut bacteria, and endocrine disruption are not observations of cancer, and thus studies relating to such health effects do not provide data that can be used in a cancer dose-response assessment. The NSRL for glyphosate is based on animal carcinogenicity studies, and dose-response analysis of tumor incidence data from these studies.

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[44] JMPR (2006). Glyphosate. In: Pesticide residues in food – 2004. Evaluations 2004 Part II – Toxicological evaluations, Joint Meeting of the FAO Panel of Experts on Pesticides Residues in Food and the Environment and the WHO Core Assessment Group, Rome, Italy, 20-29 September 2004, p. 95–116, 172. Available from: whqlibdoc.who.int/publications/2006/9241665203_eng.pdf

[45] JMPR (2016). Glyphosate. In: Joint FAO/WHO Meeting on Pesticide Residues. Pesticide residues in food 2016. Special Session of the Joint FAO/WHO Meeting on Pesticide Residues, Geneva, 9 to 13 May 2016. Rome: Food and Agriculture Organization of the United Nations/Geneva, World Health Organization (WHO) (FAO Plant Production and Protection Paper No. 227), p. 19–28, 45, 72–82. Available from: http://www.fao.org/3/a-i5693e.pdf

In reviewing the mechanistic data available for glyphosate, IARC did not conclude that glyphosate is carcinogenic via endocrine disruption. Rather, IARC concluded that there was strong evidence for genotoxicity and oxidative stress, and weak evidence for receptor-mediated effects. There are no data to suggest that glyphosate acts as a carcinogen via a transgenerational mechanism. OEHHA is not aware of any multi-generational cancer studies of glyphosate.

No changes were made to the regulatory proposal based on these comments.

Comment 8 (K. Paul Stoller, MD, Nancy O'Mara, MPH, Mei-Ling Stefan, Anthony Samsel and others): Urge consideration of the possible human health effects of other chemicals present in commercial formulations of glyphosate, e.g. adjuvants, surfactants, and inert ingredients, as well as consideration of possible synergism of glyphosate with other xenobiotic chemicals. There are no safe levels of the N-nitrosamines of glyphosate that are found in every glyphosate product.

Response 8: The Proposition 65 warning requirement applies only to chemicals listed for causing cancer or reproductive toxicity. In this case, the substance listed as causing cancer is glyphosate[46], not commercial formulations of glyphosate. Analysis of possible effects (*e.g.,* additive, synergistic, or antagonistic) of other exposures that may co-occur with glyphosate is outside the scope of Proposition 65 and is not relevant to the derivation of the NSRL for glyphosate. Thus, the NSRL is based on the results of the most sensitive scientific study of *glyphosate* deemed to be of sufficient quality. No changes were made to the regulatory proposal based on this comment.

Comment 9 (Dr. Stephen C. Frantz, Nancy O'Mara, MPH, and others): Urge consideration of a non-linear dose-response relationship, stating that endocrine disrupting chemicals, such as glyphosate, do not demonstrate the common default monotonic dose-response relationship.

Response 9: No data were provided to support the assertions that a non-monotonic cancer dose-response relationship exists for glyphosate.

[46] As noted in the Notice of Intent to List Glyphosate (https://oehha.ca.gov/proposition-65/crnr/notice-intent-list-tetrachlorvinphos-parathion-malathion-glyphosate) and the Notice of Listing (https://oehha.ca.gov/proposition-65/crnr/glyphosate-listed-effective-july-7-2017-known-state-california-cause-cancer), the 2015 IARC monograph on glyphosate indicates the following chemicals are "also relevant: 38641-94-0 (glyphosate-isopropylamine salt) 40465-66-5 (monoammonium salt) 69254-40-6 (diammonium salt) 34494-03-6 (glyphosate-sodium) 81591-81-3 (glyphosate-trimesium)" (IARC, 2015b), because these salts dissociate to free glyphosate.

As discussed in the Initial Statement of Reasons (ISOR)[47] for this action, OEHHA reviewed the available data from the rodent carcinogenicity studies of glyphosate discussed by IARC and determined that the most sensitive scientific study of sufficient quality for the cancer dose-response assessment was a study in male mice in which a statistically significant increasing trend in hemangiosarcoma was observed. The data from this study exhibited a monotonic dose-response relationship. Based upon consideration of the available mechanistic and other relevant data, OEHHA fit a multistage polynomial cancer model to the dose-response data to estimate cancer potency and derive the NSRL for glyphosate. This is consistent with the guidance set forth in Section 25703. No changes were made to the regulatory proposal based on this comment.

Comment 10 (Anthony Samsel): Glyphosate is a synthetic amino acid and an analogue of glycine. Glyphosate ligates with lysozyme, which may impact fibrocystic cytokines and human and animal immune systems. Glyphosate inhibits several enzymes, including protease, lipase, and pepsins, which can have effects on human health.

The commenter submitted three publications that were not included in IARC's review (Table 1).

Response 10: This comment is essentially a summary of Samsel and Seneff's 2016 article, entitled "Glyphosate pathways to modern disease V: Amino acid analogue of glycine in diverse proteins"[48]. This paper proposes a number of hypotheses regarding possible mechanisms by which glyphosate may effect human health. However, these hypotheses are not supported by experimental data and the relevance of the hypothesized health effects to cancer induction is unclear.

OEHHA reviewed each of the three publications in the context of the guidance set forth in Section 25703, which provides that "the assessment shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer"[49] and determined that none of the studies provide data that would affect the cancer dose-response analysis (See Table 1). No changes were made to the regulation based on this comment.

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[47] OEHHA (2017). Initial Statement of Reasons, Title 27, California Code of Regulations, Proposed Amendment to: Section 25705(b) Specific Regulatory Levels Posing No Significant Risk. Glyphosate. Available at https://oehha.ca.gov/media/downloads/crnr/glyphosate032917isor.pdf

[48] Samsel A and Seneff S (2016). Glyphosate pathways to modern disease V: Amino acid analogue of glycine in diverse proteins. *J Biol Phys Chem* **16**:9-46.

[49] Section 25703(a)(4)

Table 1. Publications submitted by Anthony Samsel

Reference	Comments
Samsel A and Seneff S (2015). Glyphosate pathways to modern disease IV: Cancer and related pathologies. *Journal of Biological Physics and Chemistry* **15**:121-159.	This article reviews epidemiological evidence of cancers in humans exposed to glyphosate and mechanistic information on glyphosate, and discusses possible carcinogenic mechanisms. "Glyphosate has a large number of tumorigenic effects on biological systems, including direct damage to DNA in sensitive cells, disruption of glycine homeostasis, succinate dehydrogenase inhibition, chelation of manganese, modification to more carcinogenic molecules such as N-nitrosoglyphosate and glyoxylate, disruption of fructose metabolism, etc." This article does not provide data that would affect the cancer dose-response analysis that forms the basis for the NSRL.
Samsel A and Seneff S (2016). Glyphosate pathways to modern disease V: Amino acid analogue of glycine in diverse proteins. *Journal of Biological Physics and Chemistry* **16**:9-46.	This article proposes that glyphosate is a synthetic amino acid and analogue of glycine, which can be incorporated into peptides, affect various enzymes, and lead to numerous diseases. "Glyphosate, acting as a glycine analogue, may be mistakenly incorporated into peptides during protein synthesis." "…the combination of activation of kinases and suppression of phosphatases that can plausibly be induced through glyphosate's displacement of conserved glycines in the enzymes can be predicted to lead to an overabundance of phosphorylated molecules, systemically." "Phosphorylation is a widespread modification with profound effects on affected molecules, which can increase risk to both Alzheimer's disease and cancer."

	"VLA-4 [very late antigen-4] is required for normal development of both T- and B-cells in the bone marrow, in part by regulating the balance between proliferation and differentiation of haematopoietic progenitors [291]. It can therefore be expected that impaired function would lead to pathologies such as immune dysfunction and cancer. Two conserved glycine residues at positions 130 and 190 are essential for its adhesive activity [292]. Glyphosate's link to NHL may therefore be explained through substitution of glyphosate for glycine at one or both of these conserved residues." This paper proposes a number of theories regarding disease mechanisms. However, these theories are not supported by experimental data. This article does not provide data that would affect the cancer dose-response analysis that forms the basis for the NSRL.
Samsel A and Seneff S (2017). Glyphosate pathways to modern disease VI: Prions, amyloidoses and autoimmune neurological diseases. *Journal of Biological Physics and Chemistry* **17**:8-32.	This article is a review of glyphosate and autism, multiple sclerosis, and other autoimmune disorders. The only reference to cancer is the reporting of a correlation between the incidence of thyroid cancer in the US and an increase in glyphosate usage on corn and soy crops. However, statistical correlations of cancer incidence with usage/exposure are not enough to presume causation. This article does not provide data that would affect the cancer dose-response analysis that forms the basis for the NSRL.

Comment 11 (Dr. Stephen C. Frantz): "Developing an NSRL that relies on 'acceptable calculated reference doses' supplied by the USEPA and its international counterparts is generally troublesome. That is, the EU 'standard' for daily chronic exposure to [glyphosate] is 0.5 mg/kg body weight, a level that is 3.5 fold *lower* than the U.S. 'standard' of 1.75 mg/kg body weight. Obviously, both levels cannot be acceptable and safe; and the EU version is already less than half of the proposed 1.1 mg by OEHHA."

Response 11: The NSRL for glyphosate does not rely on "acceptable calculated reference doses" or other values calculated by other agencies. Following the guidance

set forth in Section 25703, NSRLs are based on cancer dose-response assessments, which are conducted using data from the most sensitive scientific studies deemed to be of sufficient quality. As discussed in the ISOR for this rulemaking[50], OEHHA determined that the two-year study conducted in male CD-1 mice fed glyphosate (purity, 98.6%) in the diet met this criterion. OEHHA used this data to derive the NSRL for glyphosate.

Furthermore, as stated in Section 25703, an NSRL is defined as "[the level] which is calculated to result in one excess case of cancer in an exposed population of 100,000, assuming lifetime exposure at the level in question." NSRLs are intended to aid businesses in determining if they must comply with the warning and discharge provisions of Proposition 65; NRSLs are not intended to establish exposure or risk levels for other regulatory purposes (Section 25701(d)).

While reference doses set by other agencies are not relevant to this rulemaking, OEHHA notes that the European Union has set the *acceptable daily intake* (ADI) for glyphosate at 0.5 mg/kg[51], and US EPA has set the *chronic reference dose* (cRfD) for glyphosate at 1.00 mg/kg-day[52]; each of these values was developed by applying an uncertainty factor to a No Observed Adverse Effect Level (NOAEL) derived from developmental toxicity studies in rabbits. Neither value was based on cancer dose-response assessment and neither was developed specifically to protect against cancer. And finally, the ADI set by the European Union is not less than half of the proposed NSRL for glyphosate. The NSRL is expressed as an intake of µg/day, while the ADI (and cRfD) are expressed as mg/kg-day. Normalized to body weight, the NSRL would be less than the ADI or cRfD, not greater. No changes were made to the regulatory proposal based on this comment.

Comment 12 (The California League of Food Processors): Establishing an NSRL conflicts with tolerances set by US EPA for residues in food.

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[50] OEHHA (2017). Initial Statement of Reasons, Title 27, California Code of Regulations, Proposed Amendment to: Section 25705(b) Specific Regulatory Levels Posing No Significant Risk. Glyphosate. Available at https://oehha.ca.gov/media/downloads/crnr/glyphosate032917isor.pdf

[51] European Food Safety Authority (EFSA, 2015). Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate. EFSA Journal 2015;13 (11):4302. doi:10.2903/j.efsa.2015.4302. Available from: http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2015.4302/epdf, page 13

[52] The commenter refers to the former cRfD set by US EPA. The value has been updated since the comment was submitted, as shown in US EPA (2017). Glyphosate. Dietary Exposure Analysis in Support of Registration Review. Office of Chemical Safety and Pollution Prevention. Available from: https://www.epa.gov/sites/production/files/2017-12/documents/glyphosate_dietary_exposure_analysis_in_support_of_registration_review.pdf

Response 12: There is no direct correlation between a tolerance level set by US EPA and an NSRL adopted for purposes of Proposition 65. The two standards are developed under different laws and have different purposes. Whereas tolerances are mandatory maximum allowable pesticide residues on foods, NSRLs identify levels of exposure to listed carcinogens associated with a 1 in 100,000 cancer risk. If a food exposure to a pesticide listed as a carcinogen results in a cancer risk greater than 1 in 100,000, Proposition 65 requires a warning even if the food complies with US EPA's tolerances and can be legally sold in California. In such an instance, Proposition 65 gives Californians the right to be informed of the exposure and to make their own decision as to whether they wish to purchase or consume the food. No changes were made to the regulatory proposal based on this comment.

Comment 13 (K. Paul Stoller, MD): Regulators should not rely on just one study to determine acceptable daily intake.

Response 13: No Significant Risk Levels (NSRLs) are distinct from Acceptable Daily Intakes (ADIs). The NSRL is defined in the Proposition 65 regulations as "[the level] which is calculated to result in one excess case of cancer in an exposed population of 100,000, assuming lifetime exposure at the level in question." ADI values, on the other hand, are based on non-cancer health effects, and are neither defined nor used under Proposition 65.

In developing the NSRL for glyphosate, OEHHA followed the guidance set forth in Section 25703 and based the NSRL on the results of the most sensitive scientific study deemed to be of sufficient quality. No changes were made to the regulatory proposal based on this comment.

Comment 14 (Anthony Samsel): A thorough consideration cannot be had without a deep investigation and understanding of the nitrosamines of glyphosate which are carcinogens.

Response 14: Nitrosamines of glyphosate are not listed under Proposition 65 as causing cancer, nor are they the subject of this rulemaking. As discussed in response to comment 8, an NSRL applies specifically to the particular substance or chemical that has been listed as known to the state to cause cancer[53]. Therefore, studies of other chemicals, such as nitrosamines of glyphosate, do not provide information relevant to the derivation of the NSRL for glyphosate. No changes were made to the regulatory proposal based on this comment.

[53] Health and Safety Code section 25249.10(c) and Title 27, Cal. Code of Regs. section 25701.

Comment 15 (Ramboll Environ, on behalf of The Scotts Company, LLC): OEHHA and IARC failed to consider additional conclusions from the 2006 JMPR report on the study used to derive the NSRL, namely the lack of a dose-response relationship, the lack of statistically significant comparisons between treated animals and control animals, and the fact that the incidences were within the historical ranges for controls, and thus improperly reached conclusions regarding use of this data. Dr. Thomas McDonald, a peer reviewer and member of the Carcinogen Identification Committee, also stated that the dataset selected as the basis for the NSRL does not appear to be well supported as a treatment-related effect.

Response 15: As discussed in response to comment 5, IARC conducted an independent scientific review of the two-year study conducted in male CD-1 mice fed glyphosate (purity, 98.6%) in the diet, which OEHHA used to derive the NSRL. IARC concluded that a treatment-related increase in hemangiosarcomas was observed in this study, with a statistically significant positive trend. The tumor incidence data and positive trend test results, shown in Table 1 of the ISOR[54], demonstrate the dose-response relationship observed for hemangiosarcoma in this study.

While the pairwise comparison between the tumor incidence in animals in the high dose group and those in the control group did not rise to the $p < 0.05$ level of statistical significance, data from Charles River Laboratories indicate that hemangiosarcomas are infrequently observed in untreated male CD-1 mice, with a mean incidence of 1.13% (range 0% – 12.00%) reported in 2000[55], and 0.56% (range 0% - 4.55%) in 2010[56]. More specifically, no hemangiosarcomas were observed in untreated controls in 38 of the 46 studies summarized in 2000[57], or in 13 of the 14 studies summarized in 2010[58].

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[54] OEHHA (2017). Initial Statement of Reasons, Title 27, California Code of Regulations, Proposed Amendment to: Section 25705(b) Specific Regulatory Levels Posing No Significant Risk. Glyphosate. Available at https://oehha.ca.gov/media/downloads/crnr/glyphosate032917isor.pdf

[55] Giknis MLA and Clifford CB (2000). Spontaneous Neoplastic Lesions in the Crl:CD-1®(ICR)BR Mouse. Charles River Laboratories, Wilmington, MA.

[56] Giknis MLA and Clifford CB (2010). Spontaneous Neoplastic Lesions in the Crl:CD1 (ICR) Mouse in Control Groups from 18 Month to 2 Year Studies. Charles River Laboratories, Wilmington, MA. Available from: http://animalab.eu/sites/all/pliki/produkty-dopobrania/spontaneous-neoplastic-lesions-in-the-crlcd1icr-mouse-in-control-groups-from-18-month-to-2-year-studies-march-2010.pdf

[57] Giknis MLA and Clifford CB (2000). Spontaneous Neoplastic Lesions in the Crl:CD-1®(ICR)BR Mouse. Charles River Laboratories, Wilmington, MA.

[58] Giknis MLA and Clifford CB (2010). Spontaneous Neoplastic Lesions in the Crl:CD1 (ICR) Mouse in Control Groups from 18 Month to 2 Year Studies. Charles River Laboratories, Wilmington, MA. Available from: http://animalab.eu/sites/all/pliki/produkty-dopobrania/spontaneous-neoplastic-lesions-in-the-crlcd1icr-mouse-in-control-groups-from-18-month-to-2-year-studies-march-2010.pdf

While JMPR[59] stated that the tumor "incidences recorded in this study fell within the historical ranges for controls", OEHHA notes, "concurrent controls are considered the most relevant comparison group for evaluating potential exposure-related tumor effects"[60]. In discussing the use of historical control data, IARC states "less weight is given to historical controls when they show a high degree of variability, and greater weight when they show little variability. It is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls, particularly when historical controls show high between-study variability and are, thus, of little relevance to the current experiment"[61].

OEHHA agrees with IARC's determination that the increased incidence of hemangiosarcomas observed in this study of male CD-1 mice is treatment-related.

No changes were made based on this comment.

Comment 16: (Ramboll Environ, on behalf of The Scotts Company, LLC): The data used to derive the NSRL does not establish consistency across studies that is needed to provide a causal connection between exposure to glyphosate and cancer: there was no dose-related incidence of hemangiosarcoma reported in the female mouse study and no statistically significant increases in any tumors in another study with comparable concentrations.

Response 16: Section 25703(1) specifies that animal cancer bioassays must meet generally accepted scientific principles (e.g., the thoroughness of experimental protocol, the degree to which dosing resembles the expected manner of human exposure, the temporal exposure pattern, the duration of study, the purity of test material, the number and size of exposed groups, the route of exposure, and the extent of tumor occurrence) in order to be used in the development of NSRLs. In carcinogenicity testing there is no requirement or expectation that the same tumors will be seen in male and female animals of the same species and strain. It is also recognized that differences in study design (*e.g.*, doses tested; length of exposure; length of study) and implementation (*e.g.*, test substance purity/composition/lot; animal strain/substrain/colony/supplier of

[59] JMPR (2006). Glyphosate. In: Joint FAO/WHO Meeting on Pesticide Residues. Pesticide residues in food – 2004: toxicological evaluations. Report No. WHO/PCS/06.1. Geneva: World Health Organization; pp. 95 – 169

[60] National Toxicology Program (NTP, 2015). Handbook for Preparing Report on Carcinogens Monographs. Office of the Report on Carcinogens, Division of the NTP, National Institute of Environmental Health Sciences, US Department of Health and Human Services. Available online at https://ntp.niehs.nih.gov/pubhealth/roc/handbook/index.html

[61] IARC (2006). Preamble. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. IARC, World Health Organization, Lyon, France, p. 14. Available online at: http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf

origin; diet composition; laboratory site, other animal husbandry conditions) may result in differences in response across animal carcinogenicity studies. Thus, consistency across animal studies is not required to establish a causal connection.

IARC concluded "[t]here is *sufficient evidence* in experimental animals for the carcinogenicity of glyphosate" based on findings from two studies in male mice. Specifically, IARC found "a significant positive trend in the incidence of haemangiosarcoma in male CD-1 mice" in a two-year diet study[62], and "a positive trend in the incidence of renal tubule carcinoma and of renal tubule adenoma and carcinoma (combined)" in male CD-1 mice in a different two-year diet study[63], with IARC noting that these malignant kidney tumors are rare in this strain of mice. Thus, IARC found dose-related increases in tumor incidence in these studies and OEHHA agrees with this determination.

In developing the NSRL for glyphosate, OEHHA followed the guidance set forth in Section 25703 and based the NSRL on the results of the most sensitive scientific study deemed to be of sufficient quality. No changes were made to the regulation based on this comment.

Comment 17 (Ramboll Environ, on behalf of The Scotts Company, LLC): "Conducting dose-response modeling with a limited dataset – such as the dataset used in the derivation of the NSRL for glyphosate, which provides the observation of incidence above zero only at the highest concentration – creates significant model uncertainty." They also state that "this type of dataset lacks the necessary information to inform the shape of the dose-response curve in the low concentration region, which is needed for extrapolation to concentrations relevant to the human population and thus to estimate the NSRL."

Response 17: The proposed NSRL for glyphosate is based on the results of the most sensitive scientific study deemed to be of sufficient quality from which an NSRL can be derived, pursuant to Section 25703. Use of the multistage cancer model is generally

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[62] As noted in the Initial Statement of Reasons, this study of glyphosate (purity 98.6%) met the criterion in Section 25703 as the most sensitive study of sufficient quality, and was used to derive the NSRL. This study was performed by Inveresk Research International and summarized in the 2006 Joint FAO/WHO Meeting on Pesticide Residues report (JMPR, 2006. Glyphosate. In: Joint FAO/WHO Meeting on Pesticide Residues. Pesticide residues in food – 2004: toxicological evaluations. Report No. WHO/PCS/06.1. Geneva: World Health Organization; pp. 95 – 169.) and by IARC (IARC, 2015, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112. Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France).

[63] In summarizing this study of glyphosate (purity 99.7%), IARC cited four US EPA documents (US EPA 1985a, b, 1986, 1991a) (IARC, 2015, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112. Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France).

accepted as the default approach to modeling lifetime cancer data as it is considered sufficiently flexible to fit most cancer bioassay data[64]. As stated in the ISOR for glyphosate[65], OEHHA determined that the study it used to derive the NSRL demonstrated a treatment-related increase in hemangiosarcomas, with a statistically significant positive trend. OEHHA disagrees with the commenter that modeling this data using the multistage cancer model "creates significant model uncertainty"; in fact, examination of the goodness-of-fit criteria[66,67] subsequent to fitting the model supports the appropriateness of the default approach. In particular, the global goodness-of-fit p-value is 0.9365, which is well above the cutoff of 0.05, the scaled residuals are all less than two in absolute value, and the plot shows that the multistage cancer model fits the data very well. The relatively low incidence of hemangiosarcoma in the high dose group (8%) effectively limits the possibilities the shape of the curve fit to the data can take. In fitting the multistage cancer model to this data, OEHHA followed the guidance in Section 25703, which is consistent with scientific practices in other OEHHA programs[68] and other scientific guidance, including US EPA's 2005 cancer risk assessment guidelines[69]. No changes were made to the proposed regulation based on this comment.

Comment 18 (Baum, Hedlund, Aristei & Goldman, P.C.): 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." The dietary ingestion of glyphosate as evaluated in the animal cancer bioassay considered by OEHHA does not resemble the expected manner of human exposure through application.

Response 18: The commenter has quoted only a portion of Section 25703(a)(1); OEHHA provides the full statement from the regulations for context and clarity:

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[64] US EPA (2014). Module 5: Benchmark Dose Modeling - Cancer Models [Webinar]. In *Benchmark Dose Software (BMDS) Training Webinars.* Available from: https://clu-in.adobeconnect.com/_a1089459318/p3a32k3l8of/?launcher=false&fcsContent=true&pbMode=normal&archiveOffset=488800

[65] OEHHA (2017). Initial Statement of Reasons, Title 27, California Code of Regulations, Proposed Amendment to: Section 25705(b) Specific Regulatory Levels Posing No Significant Risk. Glyphosate. Available at https://oehha.ca.gov/media/downloads/crnr/glyphosate032917isor.pdf

[66] US EPA (2014). Module 5: Benchmark Dose Modeling - Cancer Models [Webinar]. In *Benchmark Dose Software (BMDS) Training Webinars.* Available from: https://clu-in.adobeconnect.com/_a1089459318/p3a32k3l8of/?launcher=false&fcsContent=true&pbMode=normal&archiveOffset=488800

[67] US EPA (2012). Benchmark Dose Technical Guidance. Washington, DC: US EPA. Available from: https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf

[68] OEHHA (2009). Technical Support Document for Cancer Potency Factors. https://oehha.ca.gov/media/downloads/crnr/tsdcancerpotency.pdf

[69] US EPA (2005). US Environmental Protection Agency. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum. Washington, DC. EPA/630/P-03/001B. March 2005.

> "Animal bioassay studies for quantitative risk assessment shall meet generally accepted scientific principles, including the thoroughness of experimental protocol, the degree to which dosing resembles the expected manner of human exposure, the temporal exposure pattern, the duration of study, the purity of test material, the number and size of exposed groups, the route of exposure, and the extent of tumor occurrence."

As can be seen in the full quotation of Section 25703(a)(1) above, "the degree to which dosing resembles the expected manner of human exposure" is one of *several* key considerations in determining whether or not an animal cancer bioassay is suitable for use in the development of an NSRL. OEHHA found the data used to derive the NSRL for glyphosate to be sufficient with respect to each of these considerations. With regard to the manner in which animals were dosed, diet is one of the expected routes of glyphosate exposure in humans and thus deriving the NSRL from study data in which test animals were administered glyphosate through the diet is consistent with the regulations. Animal bioassays employing dietary exposure are commonly used and routinely accepted for toxicity testing of pesticides.

Comment 19 (Dr. Thomas McDonald): OEHHA should make its own determination on the genotoxicity of glyphosate and not rely on IARC. He states that other authoritative bodies have concluded that glyphosate poses no genotoxicity risk in mammals, and that a Margin of Exposure (MOE) approach [to dose-response assessment] appears more appropriate.

Response 19: To the extent that the comment is directed toward the listing of glyphosate, it is not relevant to the determination of an NSRL for this chemical. OEHHA has reviewed the discussion of the mechanistic data for glyphosate provided in the IARC monograph and agrees with IARC's conclusion that "Overall, the mechanistic data provide strong evidence for genotoxicity and oxidative stress. There is evidence that these effects can operate in humans."[70]

OEHHA notes that IARC[71] further elaborated on this evidence, stating:

- "There is strong evidence that exposure to glyphosate or glyphosate-based formulations is genotoxic based on studies in humans in vitro and studies in experimental animals. One study in several communities in individuals exposed to glyphosate-based formulations also found chromosomal damage in blood cells; in this study, markers of chromosomal damage (micronucleus formation)

[70] IARC (2015) p. 78, full citation provided in footnote 3.
[71] IARC (2015) pp. 78-79, full citation provided in footnote 3.

were significantly greater after exposure than before exposure in the same individuals."

- "There is strong evidence that glyphosate, glyphosate-based formulations, and aminomethylphosphonic acid can act to induce oxidative stress based on studies in experimental animals, and in studies in humans in vitro. This mechanism has been challenged experimentally by administering antioxidants, which abrogated the effects of glyphosate on oxidative stress. Studies in aquatic species provide additional evidence for glyphosate-induced oxidative stress."

OEHHA disagrees that a Margin of Exposure approach is more scientifically appropriate for derivation of the NSRL for glyphosate than the procedure used by OEHHA. Section 25703 sets forth a default approach, using a multistage model for deriving a cancer potency estimate, which is used "in the absence of principles or assumptions scientifically more appropriate"[72]. No information has been provided in support of another mechanism of action that would suggest a different approach to dose-response analysis.

In deriving the NSRL, OEHHA used the Benchmark Dose (BMD) method, as described both in OEHHA's guidance[73] and in the US EPA guidelines[74], applying a multistage mathematical model to describe the relationship between the risk of cancer and the dose. As part of the procedure OEHHA used for determining the cancer potency using the BMD method, a determination is made as to the proper type of extrapolation from the point of departure (typically the 95% lower confidence limit of the ED_{05} or ED_{10} for tumor induction) to low doses. OEHHA considered whether there was a more scientifically appropriate method for the NSRL derivation than linear extrapolation, but did not identify one, stating in the Initial Statement of Reasons:

> "Based on consideration of the available mechanistic information on glyphosate and the above conclusions reached by IARC[75], a multistage model is applied to derive a cancer potency estimate, following the guidance in Section 25703. There are no principles or assumptions scientifically more appropriate, based on the available data, than this approach."[76]

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[72] Section 25703(a)
[73] OEHHA (2009). Technical Support Document for Cancer Potency Factors. Available from: https://oehha.ca.gov/media/downloads/crnr/tsdcancerpotency.pdf
[74] US EPA (2005). Guidelines for Carcinogen Risk Assessment, March 2005. Risk Assessment Forum, US Environmental Protection Agency, Washington, DC.
[75] IARC (2015). Full citation provided in footnote 3.
[76] OEHHA (2017). Initial Statement of Reasons, Title 27, California Code of Regulations, Proposed Amendment to: Section 25705(b) Specific Regulatory Levels Posing No Significant Risk. Glyphosate. Available at https://oehha.ca.gov/media/downloads/crnr/glyphosate032917isor.pdf

No changes were made to the regulatory proposal based on this comment.

Comment 20 (Food Democracy Now, The Agricultural Council of California, The California Farm Bureau Federation, Monsanto, Ramboll Environ on behalf of The Scotts Company LLC, Anthony Samsel, Jessica Denning, and PT Rothschild): Suggest alternative values for the NSRL for glyphosate:

Anthony Samsel, Frank Menhams and others commented that a value of 0 µg/day should be used because there is no safe level of glyphosate.

PT Rothschild recommended setting an NSRL based on a concentration of 0.01 parts per trillion.

Jessica Denning recommended setting an NSRL based on a concentration of a concentration of 0.01 parts per trillion because at a part per trillion, breast cell proliferation occurs.

Food Democracy Now suggested 0.1 µg/day.

The Agricultural Council of California and the California Farm Bureau Federation request that the proposed NSRL [1,100 µg/day] be considered a minimum value and that no consideration be given to anything lower.

Monsanto states that glyphosate does not cause cancer, therefore, exposure at any level poses no significant risk of cancer to humans, therefore the NSRL should be infinite.

Ramboll Environ on behalf of The Scotts Company LLC, states that if OEHHA insists on setting an NSRL for glyphosate, it should be infinite.

Response 20: Section 25703 of the regulations states that the assessment used to derive the NSRL "shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer"[77]. Section 25703 further states that "risk analysis shall be based on the most sensitive study deemed to be of sufficient quality." No data that met these criteria were provided to support setting the NSRL at 0 or 0.1 µg/day, or setting an NSLR based on a concentration of 0.01 parts per trillion or 10 parts per quadrillion, nor were such data provided to support setting an infinite NSRL.

[77] Section 25703(a)(4)

In developing the NSRL for glyphosate, OEHHA followed the guidance set forth in Section 25703 and based the NSRL on the results of the most sensitive scientific study deemed to be of sufficient quality. OEHHA determined that the two-year study conducted in male CD-1 mice fed glyphosate (purity 98.6%) in the diet met the criteria in 25703 precisely because this study led to the highest cancer potency and subsequently the lowest NSRL among studies deemed to be of comparable scientific validity as those which formed the scientific basis for the listing of glyphosate. As already noted, OEHHA agrees with IARC's determination that the increased incidence of hemangiosarcomas observed in this study of male CD-1 mice is treatment-related.

No changes were made to the regulatory proposal based on this comment.

Comment 21 (The Environmental Working Group): OEHHA should set the limit at 10 µg/day which factors in a tenfold safety factor to account for the increased vulnerability of children, a one-in-a-million cancer risk standard used for carcinogens in drinking water, and rounding.

The commenter states that including a tenfold safety factor in the development of the NSRL for glyphosate is supported by OEHHA's 2009 report "*In Utero* and Early Life Susceptibility to Carcinogens", NRC's 1993 report "Pesticides in the Diets of Infants and Children", NRC's 2009 report "Science and Decisions" which advises public health agencies to include a factor of up to 25 to account for individual variation in susceptibility, and the 1996 Food Quality Protection Act which specifically required pesticide risk assessors to consider children's susceptibility to pesticides using a tenfold safety factor.

The commenter also states that OEHHA should use the one-in-a-million standard applied for carcinogens in drinking water for setting the NSRL for all exposures.

Response 21: The Food Quality Protection Act (FQPA), a federal law, is separate and distinct from Proposition 65, a California state law. Moreover, these two laws were established for different purposes and have different regulations and requirements. In particular, the FQPA relates to the setting of safety standards for pesticide residues in food, while Proposition 65 requires businesses to provide a warning when they cause an exposure to a listed chemical unless they can show the exposure does not exceed the safe harbor level, and prohibits the discharge of listed chemicals to sources of drinking water. Proposition 65 warnings are not required and the discharge prohibition does not apply when exposures are at or below the safe harbor level.

The NSRL is defined as "[the level] which is calculated to result in one excess case of cancer in an exposed population of 100,000, assuming lifetime exposure at the level in

question"[78]. Thus, OEHHA cannot use a one-in-a-million level of risk in setting the NSRL. Similarly, OEHHA cannot apply a tenfold safety factor to the NSRL. The NSRL for glyphosate was derived according to the requirements set forth in Section 25703.

NSRLs do not conflict with permissible levels set by the federal government or with the one-in-a-million cancer risk standard for carcinogens in drinking water. These other laws have no bearing on Proposition 65, and it has no bearing on them. No changes to the regulatory proposal were made based on this comment.

Comment 22 (Food Democracy Now!, Joanie Blaxter): OEHHA should wait to consider a high NSRL for glyphosate until the studies showing carcinogenic effects in human populations can be replicated and extended. Joanie Blaxter commented that the testing model should be replaced with a more real life model of the effects of sub-acute low-level exposure over long periods of time in combination with exposure to other potentially activating chemicals and heavy metals.

Response 22: As stated in the response to Comment 1, glyphosate was listed pursuant to the Labor Code listing mechanism[79] as a result of IARC's classification of glyphosate in Group 2A ("probably carcinogenic to humans"), with a finding of "sufficient evidence of carcinogenicity in experimental animals" and "limited evidence" in humans[80,81]. Section 25703 of the regulations states that the assessment used to derive the NSRL "shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer"[82]. Given that the listing of glyphosate is based on sufficient evidence in animals, basing the potency estimate for the NSRL on animal studies is both appropriate and consistent with Section 25703. It is not appropriate for OEHHA to wait for additional studies to be conducted in humans, or otherwise delay the adoption of the NSRL for glyphosate, which is intended to aid businesses in complying with Proposition 65. Should additional scientific studies become available in the future that meet the criteria set out in Section 25703, OEHHA can consider revising the NSRL for glyphosate at that time. No changes were made to the regulatory proposal based on this comment.

Comment 23 (Comments from Food Democracy Now): "A two year study on rats published in 2015 found that just 0.05 ppb changed the function of more than 4000 genes. It would behoove the commission to pay attention to any and all studies which

[78] Section 24703.
[79] Section 25249.8(a) of the Act
[80] OEHHA (2015). Notice of Intent to List - Tetrachlorvinphos, Parathion, Malathion, Glyphosate. https://oehha.ca.gov/media/downloads/crnr/090415noillcset27.pdf
[81] IARC (2015). Full citation provided in footnote 3.
[82] Section 25703(a)(4)

suggest adverse human health effects at such miniscule levels. The study found steatohepatosis which predisposes to liver cancer at a glyphosate equivalent dose of only 4 nanograms per kg per day. The amount of glyphosate ingested by these rats is approximately 4000 times lower than what is typically ingested based on levels found in urine. This is the only study of its type providing a direct causative link between an environmentally relevant dose of Roundup and a serious disease."

Response 23: The commenter appears to be referring to a 2015 publication by Mesnage *et al.*[83], that analyzed differences in gene expression, not gene function, in the liver and kidney of female rats administered a glyphosate-based herbicide in drinking water for two years, as compared with controls receiving "plain water". Changes in gene expression levels were observed for more than 4000 genes in the liver and kidney of treated animals, as compared with controls. Treatment-related tumors were not reported in this study. This study does not provide data that would affect the cancer dose-response analysis that forms the basis for the NSRL. No changes were made to the regulatory proposal based on this comment.

Comment 24 (A number of commenters, including Meghan Lawler): Raised concerns about exposure to glyphosate, whether through food, consumer products, the environment, or during application as a pesticide. Some state that the proposed NSRL does not reflect real-world exposure scenarios or expected exposure concentrations. Some state that it is unclear how the increased exposure of agricultural workers will be factored in, when setting an NSRL. Some have reported various levels that a typical adult is exposed to on a daily basis. Some state that there is no way to establish or enforce a safe level because it is impossible to quantify cumulative exposure. Meghan Lawler commented that no comprehensive, long term, independent study has been done that shows real life exposure levels for glyphosate.

Response 24: Following the guidance set forth in Section 25703, NSRLs are based on cancer dose-response assessments, which are conducted using tumor incidence data from the most sensitive scientific studies deemed to be of sufficient quality. Cancer dose-response assessments are performed to estimate a carcinogen's cancer potency, and the NSRL is derived based on the cancer potency estimate. Specifically, the NSRL is defined as "[the level] which is calculated to result in one excess case of cancer in an exposed population of 100,000, assuming lifetime exposure at the level in question"[84]. Thus, the NSRL is a level of exposure or intake, expressed in units of µg/day that is associated with a risk of cancer of one-in-100,000.

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[83] Mesnage R, Arno M, Costanzo M, Malatesta M, Seralini G-E, Antoniou MN (2015). Transcriptome profile analysis reflects rat liver and kidney damage following chronic ultra-low dose Roundup exposure. *Environmental Health* 14:70 DOI 10.1186/s12940-015-0056-1.

[84] Section 24703.

Exposure information (*e.g.*, exposure routes, exposure levels) is not used in dose-response assessment. Rather, estimates of exposure may be used *together* with estimates of cancer potency to predict cancer risk within a population.

As noted in response to comment 1, the estimate of cancer potency for glyphosate is equally valid for estimating risks to agricultural workers and to other exposed individuals, and the NSRL for glyphosate is not limited to a specific route of exposure[85,86].

Many conventional regulatory standards are developed using the kind of real-world exposure information cited by the commenters. Those standards identify legally mandated, health-protective levels of exposures to chemicals that can be feasibly achieved by manufacturers and employers. The NSRL is not a conventional regulatory standard, as it is based strictly on the scientific criteria cited above. It is intended to guide businesses in determining whether a warning is necessary or whether discharges of a chemical into drinking water sources are prohibited. A Proposition 65 warning enables Californians to make informed choices about their exposures to listed chemicals.

Comment 25 (Several commenters): The proposed level is too high, and one commenter stated that, in comparison, the NSRL for TCDD is much lower.

Response 25: The comment compares the proposed NSRL for glyphosate, 1100 µg/day, to the NSRL for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), which is 0.000005 µg/day. It has long been recognized that carcinogens vary in strength, or potency, with some being extremely potent, and others much less potent[87]. Indeed, the cancer potencies of carcinogens vary by several orders of magnitude[88]. NSRLs, which are derived from cancer potency estimates, can similarly vary by orders of magnitude, as can be seen when comparing the NSRL for glyphosate to that for TCDD. Thus, the fact that the NSRL for glyphosate is much higher than the NSRL for TCDD is not an indication that the glyphosate NSRL is too high, or otherwise inappropriate.

In developing the NSRL for glyphosate, OEHHA followed the guidance set forth in Section 25703 and based the NSRL on the results of the most sensitive scientific study deemed to be of sufficient quality. OEHHA determined that the two-year study

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[85] OEHHA (2017). Initial Statement of Reasons, Title 27, California Code of Regulations, Proposed Amendment to: Section 25705(b) Specific Regulatory Levels Posing No Significant Risk. Glyphosate. Available at https://oehha.ca.gov/media/downloads/crnr/glyphosate032917isor.pdf

[86] Section 25703(a)(4)

[87] Gold, L. S., et al. (1984) A carcinogenic potency database of the standardized results of animal bioassays. *Environ Health Perspect* **58**: 9-319.

[88] *Ibid.*

conducted in male CD-1 mice fed glyphosate (purity 98.6%) in the diet met the criteria in 25703 precisely because this study led to the highest cancer potency and subsequently the lowest NSRL among studies deemed to be of comparable scientific validity as those which formed the scientific basis for the listing of glyphosate. As already noted, OEHHA agrees with IARC's determination that the increased incidence of hemangiosarcomas observed in this study of male CD-1 mice is treatment-related. No changes were made based on this comment.

Comment 26 (Laura Hayes, Pesticide Free Zone and Tamsin Lisa Kelly, JD, MD): The proposed level is a random rate that cannot be accurately monitored or enforced. Pesticide Free Zone asked how OEHHA would determine the amount that humans are exposed to on a daily basis. Tamsin Lisa Kelly, JD, MD, stated that if use is allowed, testing of food and water supplies must be required regularly to assure exposure is limited.

Response 26: OEHHA disagrees with the statement that the proposed NSRL for glyphosate is a random rate. As described in more detail in Response 19 OEHHA followed standard cancer dose-response assessment practice in deriving an NSRL of 1100 µg/day for glyphosate, which is based on the most sensitive study of sufficient quality. OEHHA's approach is consistent with Section 25703, scientific practices in other OEHHA programs[89] and other scientific guidance, including US EPA's 2005 cancer risk assessment guidelines[90].

OEHHA has no authority under Proposition 65 to monitor exposures to listed chemicals. Businesses are responsible for determining if they are causing exposures to listed chemicals at levels that require warnings. The purpose of the NSRL is to assist businesses in making these determinations. Similarly, OEHHA has no authority under Proposition 65 to require testing of food and water supplies. No changes were made to the regulatory proposal based on this comment.

Comment 27 (A Voice for Choice, Organic Sacramento, and several others): The NSRL does not account for differences in vulnerability due to size, age, stage of development, health status, or socioeconomic status.

Response 27: As specified in Section 25703, the "risk analysis shall be based on the most sensitive study deemed to be of sufficient quality", and "the risk level which represents no significant risk shall be one which is calculated to result in one excess

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[89] OEHHA (2009). Technical Support Document for Cancer Potency Factors. https://oehha.ca.gov/media/downloads/crnr/tsdcancerpotency.pdf

[90] US EPA (2005). US Environmental Protection Agency. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum. Washington, DC. EPA/630/P-03/001B. March 2005.

case of cancer in an exposed population of 100,000, **assuming lifetime exposure at the level in question**". (Emphasis added)

In developing the NSRL for glyphosate, OEHHA followed the guidance set forth in Section 25703 and based the NSRL on the results of the most sensitive scientific study deemed to be of sufficient quality. The calculation assumes lifetime exposure at the level in question to an average person in the general population. No changes were made to the regulation based on this comment.

Comment 28 (A number of commenters): Urge OEHHA to ban glyphosate, that it be declared a "restricted use" chemical, that it not be available to the public, or that OEHHA should ensure labeling of all products, businesses, and public spaces containing any amount of glyphosate. Bob Sanders commented that instead of considering an NSRL, OEHHA should be discussing glyphosate as "not safe for human consumption" (NSFHC) and including 10 mile safety zones to protect children and families.

Response 28: Proposition 65 does not give OEHHA authority to remove products or chemicals from the market or to restrict their use. While OEHHA has regulatory authority to broadly identify acceptable methods and content for Proposition 65 warnings, OEHHA does not have the authority to directly regulate product labeling as suggested by the commenters. Similarly, Proposition 65 does not give OEHHA the authority to categorize glyphosate as not safe for human consumption or to impose safety zones as suggested by the commenter. These comments are outside the scope of the current rulemaking and no changes were made based on this comment.

Comment 29 (Larry Wartels, Susan[91] and others): OEHHA should use the precautionary principle in developing the NSRL for glyphosate. OEHHA should only allow use of the lowest effective levels of glyphosate so that plants do not become glyphosate resistant.

Response 29: In developing the NSRL for glyphosate, OEHHA followed the guidance set forth in Section 25703 of the regulations, which states that the assessment used to derive the NSRL "shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer"[92]. Glyphosate was listed pursuant to the Labor Code listing mechanism[93] as a result of IARC's classification of glyphosate in Group 2A ("probably carcinogenic to humans"), with a finding of sufficient evidence of

[91] The commenter did not provide a last name.
[92] Section 25703(a)(4)
[93] Section 25249.8(a) of the Act

carcinogenicity in experimental animals[94,95]. OEHHA reviewed the available data from the rodent carcinogenicity studies of glyphosate discussed by IARC[96], 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. OEHHA agrees with IARC's determination that the increased incidence of hemangiosarcomas observed in this study of male CD-1 mice is treatment-related. OEHHA then performed a standard dose-response assessment using the data from this study to derive the NSRL for glyphosate. The resistance of plants to glyphosate is not relevant for purposes of deriving an NSRL. No changes were made based on this comment.

Comment 30 (One commenter (anonymous)): Extrapolating cancer risk to humans from hemangiosarcomas, which are very rare in humans, seems misleading and to use this to determine the NSRL seems unscientific.

Response 30: The premise underlying this comment is incorrect. It is a generally accepted principle that the ability of a chemical to cause cancer in animals is predictive that the chemical also poses a cancer hazard in humans[97]. However, it is not assumed that the same tumor type observed in animals will be observed in humans[98]. Similarly, the fact that cancer potency is estimated based on animal tumor data for a particular tumor type does not imply that the cancer potency applies specifically to that same tumor type in humans. The human cancer potency estimate is a measure of the carcinogenic hazard posed by a particular carcinogen, and can be used to estimate the risk of cancer (at all sites that may be affected by this carcinogen) associated with a specific level of exposure in humans. No changes were made in response to this comment.

Comment 31 (Baum, Hedlund, Aristei & Goldman, P.C., Meredith Newton, Timothy Litzenburg and others): Raised concerns over OEHHA meeting with representatives from Monsanto in October 2015. The commenters state that OEHHA should be presented with an impartial and comprehensive scope of data in determining the NSRL and that industry meetings with regulators should be open to public scrutiny. Timothy

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[94] OEHHA (2015). Notice of Intent to List - Tetrachlorvinphos, Parathion, Malathion, Glyphosate. Available from: https://oehha.ca.gov/media/downloads/crnr/090415noillcset27.pdf
[95] IARC (2015). Full citation provided in footnote 3.
[96] IARC (2015). Full citation provided in footnote 3.
[97] IARC (2006). Preamble. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. World Health Organization, International Agency for Research on Cancer, Lyon, France, 2006. Available from: http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf)
[98] US EPA (2005). Guidelines for Carcinogen Risk Assessment, March 2005. Risk Assessment Forum, US Environmental Protection Agency, Washington, DC.

Litzenburg] requested that OEHHA schedule a meeting with stakeholders before making a decision on the safe harbor threshold.

Response 31: This comment is not directed towards the rulemaking. In compliance with the Administrative Procedure Act (APA), OEHHA published a Notice of Proposed Rulemaking, thereby opening a 45-day public comment period, and held a public hearing where all interested parties were allowed to provide their input regarding the proposed rulemaking. OEHHA provided the public with the opportunity to provide written comments during the comment period. OEHHA is publicly responding to all the oral and written comments received during the rulemaking in this Final Statement of Reasons. Nothing in the APA prohibits OEHHA from meeting with stakeholders to hear all viewpoints on an issue. The October 2015 meeting occurred before glyphosate was added to the Proposition 65 list of chemicals and before the current rulemaking proposal. OEHHA also met with many of the commenters, including representatives of Baum, Hedlund, Aristei & Goldman, P.C. and Timothy Litzenburg and others in August 2017 to understand their position concerning the NSRL. No changes were made to the proposed regulation based of this comment.

Comment 32 (Zen Honeycutt): Section 25703 requires OEHHA to consider all available studies showing harm. Provided many references for OEHHA's consideration, many of which were not included in IARC's review (Table 2.)

Response 32: Section 25703 does not mandate a review of all available studies showing harm. Rather Section 25703 requires that the assessment "be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer", and the NSRL must be based on the results of the most sensitive scientific study deemed to be of sufficient quality.

Of the 72 published scientific articles listed in the comments from Zen Honeycutt, 54 were not cited in the IARC Monograph[99] that OEHHA relied on in developing the NSRL for glyphosate. These 54 publications are listed in Table 2. OEHHA reviewed each of these publications in the context of the guidance set forth in Section 25703, i.e., "the assessment shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer"[100] and determined that none of the studies provide data that would affect the cancer dose-response analysis (See Table 2). No changes were made to the regulatory proposal based on this comment.

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[99] IARC (2015). Full citation provided in footnote 3.
[100] Section 25703(a)(4)

Table 2. Studies related to glyphosate that were identified by Zen Honeycutt and not considered by IARC

Reference	Comments
Arbuckle TE, Lin Z, Mery LS (2001). An exploratory analysis of the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population. *Environ Health Perspect* **109**(8):851-7.	This human epidemiological study investigated the effects of glyphosate exposure on spontaneous abortion. This reproductive toxicity study is not relevant to cancer dose-response analysis.
Astiz M, Alaniz MJT de, Marra CA (2009). The impact of simultaneous intoxication with agrochemicals on the antioxidant defense system in rat. *Pesticide Biochemistry and Physiology* **94**:93-99.	This study in rats examined the effects of glyphosate on oxidative stress, and hormone levels. This mechanistic study does not provide data that would affect the cancer dose-response analysis that forms the basis for the NSRL.
Barbosa ER, Leiros da Costa MD, Bacheschi LA, Scaff M, Leite CC (2001). Parkinsonism after glycine-derivate exposure. *Mov Disord* **16**(3):565-8.	This is a case report of an incidence of Parkinson's disease following exposure to glyphosate, and is not relevant to cancer dose-response analysis.
Bellé R, Le Bouffant R, Morales J, Cosson B, Cormier P, Mulner-Lorillon O (2007). Sea urchin embryo, DNA-damaged cell cycle checkpoint and the mechanisms initiating cancer development. *J Soc Biol* **201**(3):317-27. [Article in French]	This study examined the effects of glyphosate on sea urchin development. This toxicity study may provide data on possible mechanisms of action, but it does not provide data that can be used in the cancer dose-response analysis.
Benedetti AL, Vituri Cde L, Trentin AG, Domingues MA, Alvarez-Silva M (2004). The effects of sub-chronic exposure of Wistar rats to the herbicide Glyphosate-Biocarb. *Toxicol Lett* **153**(2):227-32.	This study examined the effects of Glyphosate-Biocarb® on the livers of Wistar rats following 75 days of exposure. This subchronic toxicity study does not provide data that can be used in the cancer dose-response analysis.
Benedetti D, Nunes E, Sarmento M, Porto C, Dos Santos CE, Dias JF, da Silva J (2013). Genetic damage in soybean workers exposed to pesticides: evaluation with the comet	This study in farm workers assessed the effects of exposure to complex mixtures of pesticides, including glyphosate, on DNA. The authors reported that DNA damage and genomic hypermethylation of DNA were significantly increased in individuals exposed

and buccal micronucleus cytome assays. *Mutat Res* **752**(1-2):28-33.	to pesticide mixtures, but it does not provide data that can be used in the cancer dose-response analysis.
Beuret CJ, Zirulnik F, Giménez MS (2005). Effect of the herbicide glyphosate on liver lipoperoxidation in pregnant rats and their fetuses. *Reprod Toxicol* **19**(4):501-4.	This study investigated the effects of glyphosate on pregnant female Wistar rats and their fetuses. This reproductive toxicity study provides no data that can be used in the cancer dose-response analysis.
Cox C (2004). Herbicide factsheet: glyphosate. *Journal of Pesticide Reform* **24**(4):10-15.	This factsheet is a short review and does not provide data that would affect the cancer dose-response analysis that forms the basis for the NSRL.
da Costa Mdo D, Gonçalves LR, Barbosa ER, Bacheschi LA (2003). Neuroimaging abnormalities in parkinsonism: study of five cases. *Arq Neuropsiquiatr* **61**(2B):381-6. [Article in Portuguese]	This study reports neuroimaging results in five patients with Parkinson's disease, one of whom was exposed to glyphosate. This study is not relevant to cancer dose-response analysis.
Dallegrave E, Mantese FD, Coelho RS, Pereira JD, Dalsenter PR, Langeloh A (2003). The teratogenic potential of the herbicide glyphosate-Roundup in Wistar rats. *Toxicol Lett* **142**(1-2):45-52.	This study examined the teratogenicity of glyphosate-Roundup® to Wistar rats. This developmental toxicity study provides no data relevant to cancer dose-response analysis.
Dallegrave E, Mantese FD, Oliveira RT, Andrade AJ, Dalsenter PR, Langeloh A (2007). Pre- and postnatal toxicity of the commercial glyphosate formulation in Wistar rats. *Arch Toxicol* **81**(9):665-73.	This study investigated the reproductive effects of glyphosate-Roundup® on male and female offspring of Wistar rats exposed during pregnancy and lactation. This reproductive toxicity study provides no data relevant to cancer dose-response analysis.
Daruich J, Zirulnik F, Gimenez MS (2001). Effect of the herbicide glyphosate on enzymatic activity in pregnant rats and their fetuses. *Environ Res* **85**(3):226-31.	This study investigated the effects of glyphosate exposure to pregnant Wistar rats on enzymes in the dams and their fetuses. This reproductive toxicity study provides no data relevant to cancer dose-response analysis.
de Liz Oliveira Cavalli VL, Cattani D, Heinz Rieg CE, Pierozan P, Zanatta L, Benedetti Parisotto E, Wilhelm	This study investigated the effects of glyphosate on male rat Sertoli cells and testis

Filho D, Mena Barreto Silva FR, Pessoa-Pureur R, Zamoner A (2013). Roundup disrupts male reproductive functions by triggering calcium-mediated cell death in rat testis and Sertoli cells. *Free Radic Biol Med* **65**:335-46.	*in vitro*. This *in vitro* toxicity study provides no data to cancer dose-response analysis.
de Souza JS, Kizys MM, da Conceição RR, Glebocki G, Romano RM, Ortiga-Carvalho TM, Giannocco G, da Silva ID, Dias da Silva MR, Romano MA, Chiamolera MI (2017). Perinatal exposure to glyphosate-based herbicide alters the thyrotrophic axis and causes thyroid hormone homeostasis imbalance in male rats. *Toxicology* **377**:25-37.	This study investigated the effects of a glyphosate-based herbicide on the hypothalamic-pituitary-thyroid axis of male rats following *in utero* exposure. The authors reported that exposure affected thyroid hormone homeostasis. While this study contributes to the data on possible mechanisms of action, it does not provide data that can be used in the cancer dose-response analysis.
Geng D et al. (2000). Study of Herbicide Roundup impact on yellow eel mutagenic. *Journal of Xuzhou Normal University* (Natural Science Edition) **2**. [Article in Chinese] Available from http://www.cnki.com.cn/ Article/ CJFDTotal-XZSX200002018.htm	This study investigated the genotoxicity of glyphosate in the erythrocytes of *Monopterus albus* (Asian swamp eel) *in vivo*. It suggests that glyphosate induces chromosomal aberrations. While this study contributes to the data on possible mechanisms of action, it does not provide data that can be used in the cancer dose-response analysis.
Hokanson R, Fudge R, Chowdhary R, Busbee D (2007). Alteration of estrogen-regulated gene expression in human cells induced by the agricultural and horticultural herbicide glyphosate. *Hum Exp Toxicol* **26**:747-52.	This *in vitro* study investigated the effects of glyphosate on human MCF-7 cells and found altered gene expression. This mechanistic study does not provide data that can be used in the cancer dose-response analysis.
Huang C, Li B, Xu K, Liu D, Hu J, Yang Y, Nie H, Fan L, Zhu W (2017). Decline in semen quality among 30,636 young Chinese men from 2001 to 2015. Fertil Steril **107**(1):83-88.	This study provides no information or data that is specific to glyphosate.
Jayawardena UA, Rajakaruna RS, Navaratne AN, Amerasinghe PH	This toxicity study of glyphosate and other pesticides observed malformations in exposed

(2010). Toxicity of agrochemicals to common hourglass tree frog (*Polypedates cruciger*) in acute and chronic exposure. *International Journal of Agriculture and Biology*, 12, 641-648.	tree frogs. This study provides no data relevant to cancer dose-response analysis.
Kamel F, Tanner C, Umbach D, Hoppin J, Alavanja M, Blair A, Comyns K, Goldman S, Korell M, Langston J, Ross G, Sandler D (2007). Pesticide exposure and self-reported Parkinson's disease in the agricultural health study. *Am J Epidemiol* **165**(4):364-74.	This study on Parkinson's disease is not relevant to cancer dose response-analysis.
Kang J et al. (2008). Study of glyphosate effect causing mutagenic on rats. Carcinogenesis, Teratogenesis & Mutagenesis **3**. [Article in Chinese] Available from http://www.cnki.com.cn/ Article/ CJFDTotal-ABJB200803018.htm	The hyperlink provided by the commenter leads to an article by Kang et al. (2008), named "Study on mutagenesis induced by glyphosate in mice". The full text also indicates that this study was in mice, but not rats. Other than the title, the rest of the citation is correct. This study reports that glyphosate induced micronucleus formation in bone marrow polychromatic erythrocytes of Kunming mice, increased sperm aberrations, and decreased sperm count. While this study contributes to the data on possible mechanisms of action, it does not provide data that would affect the cancer dose-response analysis that forms the basis for the NSRL.
Kruger M, Schledorn P, Schrodl W, Hoppe HW, Lutz W, Shehata AA (2014). Detection of Glyphosate Residues in Animals and Humans. *J Environ Anal Toxicol* **4**(2):210.	This study measured glyphosate residues in animals and humans using ELISA and gas chromatography-mass spectroscopy. Glyphosate residues were detected in the kidney, liver, lung, spleen, muscles, and intestine in dairy cows (minimum = 1.36 µg/g; maximum of 108 µg/mg). Glyphosate residues were detected in the urine of dairy cows (minimum = 0 µg/ml; maximum = 164

	µg/ml), rabbits (minimum = 2.37 µg/ml; maximum = 70 µg/ml) and humans (minimum = 0.1 µg/ml; maximum = 71.3 µg/ml). Significantly higher urinary glyphosate residues were reported in chronically ill humans than in healthy individuals. This study provides no data relevant to cancer dose response analysis.
Lajmanovich RC, Sandoval MT, Peltzer PM (2003). Induction of mortality and malformation in Scinax nasicus tadpoles exposed to glyphosate formulations. *Bull Env Contam Toxicol* **70**:612–618.	This study investigated the effects of glyphosate on tadpoles exposed for 96 hours. This acute toxicity study in amphibians provides no data relevant to cancer dose-response analysis.
Li Q, et al. (2010). Acute toxicity of eight types of pesticides to sea urchin embryos during different phases of development. *Asian Journal of Ecotoxicology*. [Article in Chinese] Available from http://d.wanfangdata.com.cn/Periodical_cyyhj 201002014.aspx	This study investigated the acute toxicity of glyphosate on the development of sea urchin embryos. This study provides no data relevant to cancer dose-response analysis.
Lioi MB, Scarfi MR, Santoro A, Barbieri R, Zeni O, Salvemini F, Di Berardino D, Ursini MV (1998). Cytogenetic damage and induction of pro-oxidant state in human lymphocytes exposed in vitro to glyphosate, vinclozolin, atrazine, and DPXE9636. *Environ Mol Mutagen* **32**(1):39-46.	This *in vitro* study in human peripheral lymphocytes reported that glyphosate exposure increased chromosomal aberrations, sister chromatid exchanges, and a change in the redox state of the cell. This study contributes to the data on possible mechanisms of action, but it does not provide data that would affect the cancer dose-response analysis that forms the basis for the NSRL.
Marc J, Mulner-Lorillon O, Boulben S, Hureau D, Durand G, Bellé R (2002). Pesticide Roundup provokes cell division dysfunction at the level of CDK1/cyclin B activation. *Chem Res Toxicol* **15**(3):326-31.	This study investigated the effects of Roundup® and glyphosate on cell cycle regulation in sea urchin embryos. This mechanistic study does not provide data that can be used in the cancer dose-response analysis.

Marc J, Bellé R, Morales J, Cormier P, Mulner-Lorillon O (2004a). Formulated glyphosate activates the DNA-response checkpoint of the cell cycle leading to the prevention of G2/M transition. *Toxicol Sci* **82**(2):436-42.	This *in vitro* study investigated the effects of glyphosate on the cell cycle of sea urchins. This mechanistic study does not provide data that can be used in the cancer dose-response analysis.
Marc J, Mulner-Lorillon O, Bellé R (2004b). Glyphosate-based pesticides affect cell cycle regulation. *Biol Cell* **96**(3):245-9.	This paper investigated the effects of several glyphosate-based pesticides on cell cycle regulation in sea urchins. This mechanistic study does not provide data that can be used in the cancer dose-response analysis.
Marc J, Le Breton M, Cormier P, Morales J, Bellé R, Mulner-Lorillon O (2005). A glyphosate-based pesticide impinges on transcription. Toxicol Appl Pharmacol **203**(1):1-8.	This study investigated the effects of glyphosate on sea urchin development and found effects on transcription in early development. This study does not provide data that can be used in the cancer dose-response analysis.
McComb BC, Curtis L, Chambers CL, Newton M, Bentson K (2008). Acute toxic hazard evaluations of glyphosate herbicide on terrestrial vertebrates of the Oregon Coast Range. *Environ Sci Pollut Res Int* **15**(3):266-72.	This study evaluated the effects of acute exposure to glyphosate on white lab mice and 9 wild vertebrate species from the Oregon coast (deer mouse, chipmunk, shrew, vole, newt, frog, and three types of salamanders). This acute toxicity study does not provide data that can be used in the cancer dose-response analysis.
Mesnage R, Clair E, Spiroux de Vendômois J, Séralini GE (2010). Two cases of birth defects overlapping Stratton-Parker syndrome after multiple pesticide exposure. *Occup Environ Med* **67**(5):359.	This is a report of two instances of congenital malformations in children whose parents had been exposed to multiple pesticides, including glyphosate. These case reports are not relevant to cancer dose-response analysis.
Mesnage R, Renney G, Seralini GE, Ward M (2017) Multiomics reveal non-alcoholic fatty liver disease in rats following chronic exposure to an ultra-low dose of Roundup herbicide. *Sci Rep* **7**:39328.	This study used metabolome and proteome analyses of rat liver tissue to investigate the effects of low-dose exposure of rats to a glyphosate-based herbicide. The authors concluded that the metabolome and proteome changes observed were indicative of non-alcoholic fatty liver disease. This study does

	not provide data that can be used in the cancer dose-response analysis.
Nan X (2001). Impact of glyphosate herbicide on carp peripheral blood erythrocyte micronucleus and nuclear anomalies, *Journal of Anhui Normal University* (Natural Science Edition) **24**(4): 329-331. [Article in Chinese] Available from http://www.cqvip.com/qk/97138X/200006/ 4887295.html	The hyperlink provided by the commenter leads to a study by Nan et al. (2000), titled "Effects of Herbicide (Glyphosate) on Micronuclei and Nuclear Anomalies in Erythrocyte of Bufo bufo Gargarizans". It was conducted in Asiatic toads, not carp as the title provided by the commenter states. This study found that glyphosate increased the frequency of micronuclei and nuclear abnormalities in the erythrocytes of Asiatic toads after oral treatment. While this study contributes to the data on possible mechanisms of action, it does not provide data that can be used in the cancer dose-response analysis.
Nan X (2002). Study of impact of glyphosate herbicide on carp blood cells and hemoglobin. *Gansu Science* **2**. [Article in Chinese] Available from http://www.cnki.com.cn/Article/CJFDTotal-GSKX200204015.htm	This study investigated the toxicity of glyphosate on carp (*Carassius auratus*) by measuring hemoglobin levels and erythrocyte and leucocyte counts. This study provides no data relevant to cancer dose-response analysis.
Nan X et al. (2003). Impact of glyphosate herbicide on loach white blood cells. *Journal of Wenzhou Normal University* (Natural Science Edition) **24**(2): 72-74. [Article in Chinese] Available from http://www.cnki.com.cn/Article/CJFDTotal-WZSF200302019.htm	The hyperlink provided by the commenter leads to an article by Nan et al. (2003), titled "Effect of Mi[s]gurnus Anguillicaudatus induced by glyphosate". Other than the title, the rest of the citation is correct. This study investigated the effect of glyphosate on lymphocyte and granulocyte counts in the peripheral blood of *Misgurnus Anguillicaudatus* (pond loach, a fresh water fish). This study provides no data relevant to cancer dose-response analysis.

Negga R, Stuart JA, Machen ML, Salva J, Lizek AJ, Richardson SJ, Osborne AS, Mirallas O, McVey KA, Fitsanakis VA (2012). Exposure to glyphosate- and/or Mn/Zn-ethylene-bis-dithiocarbamate-containing pesticides leads to degeneration of γ-aminobutyric acid and dopamine neurons in *Caenorhabditis elegans*. *Neurotox Res* **21**(3):281-90.	This study on the effect of glyphosate on neurons in the roundworm *C. elegans* provides no data relevant to cancer dose response-analysis.
Oliveira AG, Telles LF, Hess RA, Mahecha GA, Oliveira CA (2007). Effects of the herbicide Roundup on the epididymal region of drakes Anas platyrhynchos. *Reprod Toxicol* **23**(2):182-91.	This study investigated the effects of Roundup® on the epididymis and testes of adult male ducks exposed for 15 days. This male reproductive toxicity study provides no data relevant to cancer dose-response analysis.
Perkins PJ, Boermans HJ, Stephenson GR (2000). Toxicity of glyphosate and triclopyr using the frog embryo teratogenesis assay—*Xenopus*. *Environmental Toxicology and Chemistry* **19**: 940–945.	The effects of glyphosate were studied on the embryonic development of *Xenopus laevis.* This developmental toxicity study is not relevant to cancer dose-response analysis.
Relyea RA (2012). New effects of Roundup on amphibians: predators reduce herbicide mortality; herbicides induce antipredator morphology. *Ecol Appl* **22**(2):634-47.	This study examined the effects of Roundup on the response of amphibians to predators. This behavioral study is not relevant to cancer dose-response analysis.
Romano RM, Romano MA, Bernardi MM, Furtado PV, Oliveira CA (2010). Prepubertal exposure to commercial formulation of the herbicide glyphosate alters testosterone levels and testicular morphology. *Arch Toxicol* **84**(4):309-17.	This paper reports the effects of glyphosate on testicular development in male rats exposed on postnatal days 23 to 53. This study does not provide data that can be used in the cancer dose-response analysis.
Roy NM, Ochs J, Zambrzycka E, Anderson A (2016). Glyphosate induces cardiovascular toxicity in *Danio rerio*. *Environmental Toxicology and Pharmacology*	This study investigated the effects of glyphosate on heart development in zerbrafish. This developmental toxicity study is not relevant to cancer dose-response analysis.

46:292–300.	
Savitz DA, Arbuckle T, Kaczor D, Curis KM (1997). Male pesticide exposure and pregnancy outcome. *Am J Epidemiol* **146**(12):1025-35.	This human epidemiology study assessed pesticide exposure, including exposure to glyphosate, on male reproductive outcomes. This male reproductive toxicity study is not relevant to cancer dose-response analysis.
Soso AB, Barcellos LJ, Ranzani-Paiva MJ, Kreutz LC, Quevedo RM, Anziliero D, Lima M, Silva LB, Ritter F, Bedin AC, Finco JA (2007). Chronic exposure to sub-lethal concentration of a glyphosate-based herbicide alters hormone profiles and affects reproduction of female Jundiá (Rhamdia quelen). *Environ Toxicol Pharmacol* **23**:308–313.	This study examined the effects of glyphosate on the Jundia fish and found effects on reproductive status. This fish reproductive toxicity study does not provide data that can be used in the cancer dose-response analysis.
Soto AM, Sonnenschein C (2010). Environmental causes of cancer: endocrine disruptors as carcinogens. *Nat Rev Endocrinol* **6**(7):363-70.	This study provides no data specific to glyphosate.
Sparling DW, Matson C, Bickham J, Doelling-Brown P (2006). Toxicity of glyphosate as Glypro and LI700 to red-eared slider (trachemys scripta elegans) embryos and early hatchlings. *Environ Toxicol Chem* **25**(10):2768-74.	This study examined the effects of glyphosate on the development of turtle eggs. This developmental toxicity study in turtles is not relevant to cancer dose-response analysis.
Swanson NL, Leu A, Abrahamson J, Wallet B (2014). Genetically engineered crops, glyphosate and the deterioration of health in the United States of America. *Journal of Organic Systems* **9**(2).	This descriptive study conducted correlation analyses based on time trends in genetically engineered crop data, glyphosate application data, and disease rates in the US. A significant correlation was reported between glyphosate application rates and incidence of thyroid, liver, bladder, pancreas, and kidney cancer, and myeloid leukemia. Incidences of these cancers were also correlated with percentages of genetically engineered corn and soy planted in the US.

	This descriptive study provides correlations between glyphosate usage and disease rates. However, a descriptive study does not provide evidence of causation. Additionally, there is a latency period between exposure to a carcinogen and development of cancer. In this study, however, there was often a temporal overlap between increases in glyphosate use and increases in cancer incidence (e.g., no evidence of latency between exposure and cancer). In some cases, cancer incidences increased before glyphosate use did. Descriptive studies such as this do not provide data that can be used in cancer dose-response analysis.
van der Mark M, Brouwer M, Kromhout H, Nijssen P, Huss A, Vermeulen R (2012). Is pesticide use related to Parkinson disease? Some clues to heterogeneity in study results. *Environ Health Perspect* **120**(3):340-7.	This paper conducted a systematic review and meta-analysis of pesticide use (including glyphosate) and Parkinson's disease. This study on Parkinson's disease is not relevant to cancer dose response-analysis.
Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR Jr, Lee DH, Shioda T, Soto AM, vom Saal FS, Welshons WV, Zoeller RT, Myers JP. Hormones and endocrine-disrupting chemicals: Low-dose effects and nonmonotonic dose responses. *Endocr Rev*. 2012;33(3):378-455.	This study provides no data specific to glyphosate.
Wang G, Fan XN, Tan YY, Cheng Q, Chen SD (2011). Parkinsonism after chronic occupational exposure to glyphosate. *Parkinsonism Relat Disord* **17**(6):486-7.	This study on Parkinson's disease is not relevant to cancer dose-response analysis.
Wu H (1996). Glyphosate impact on rat cytochrome P450 2 B1 and P450 2 c11 gene expression. *Health*	The hyperlink provided by the commenter leads to an article by Wu and Prough (1996), titled "CYP450 2B1 and 2C11 expression in

Toxicology Journal, **10**(4): 231-234 [Article in Chinese] Available from http://www.cnki.com.cn/Article/CJFDTotal-WSDL604.004.htm	rat by glyphosate". Other than the different title, the rest of the citation is correct. This study examined liver microsomal enzyme activity as well as expression levels of CYP450 2B1 and 2C11 mRNA in rats after glyphosate treatment by oral gavage. This study does not provide data that can be used in the cancer dose-response analysis.
Yousef MI, Salem MH, Ibrahim HZ, Helmi S, Seehy MA, Bertheussen K (1995). Toxic effects of carbofuran and glyphosate on semen characteristics in rabbits. *J Environ Sci Health B* **30**(4):513-34.	This study investigated the effects of glyphosate on body weight and semen in male New Zealand white rabbits exposed for six weeks. This male reproductive toxicity study is not relevant to cancer dose-response analysis.
Yu H et al. (2012). Progress in study of glyphosate toxicity **6**. [Article in Chinese] Available from http://www.cnki.com.cn/Article/CJFDTOTAL-BANG201206050.htm and http://www.doc88.com/p-666125982792.html	This is a review of literature on the toxicity of glyphosate. This review did not identify any studies that would affect the cancer dose-response analysis.
Zeng M, Huang T et al. (2014). Glyphosate toxicity to mice GC-1 sperm cells and the interference effect of N-acetyl cysteine, *Ecological Toxicology Bulletin* **1.** [Article in Chinese] Available from http://www.cnki.com.cn/Article/CJFDTotal-STDL201401031.htm	The hyperlink provided by the commenter leads to an article by Zeng et al. (2014), titled "Cytotoxicity of Glyphosate to GC-1 Mice Spermatogonium and Antagonistic Effects of N-acetylcysteine". Other than the title, the rest of the citation is correct. This study examined the cytotoxicity of glyphosate on GC-1 (mouse spermatogonia) cells. The study found that glyphosate induced DNA damage as shown by the Comet assay, and suggests that glyphosate may increase reactive oxygen species production in GC-1 cells. While this study contributes to the data on possible mechanisms of action, it does not provide data that would affect the cancer dose-response analysis that forms the basis for the NSRL.
Zhao W et al. (2011). Study of oxidative damage of the body	This study examined oxidative damage induced by glyphosate in Kunming mice.

caused by glyphosate. *Toxiology Journal* **25**(5):364-366 [Article in Chinese] Available from http://www.cnki.com.cn/Article/CJFDTotal-WSDL201105013.htm	Oxidative damage was measured as levels of total antioxidant capacity (TAC) and malondialdehyde (MDA) in serum and several tissues, and as serum levels of advanced oxidation products. While this study contributes to the data on possible mechanisms of action, it does not provide data that would affect the cancer dose-response analysis that forms the basis for the NSRL.
Zhao W, Yu H, Zhang J, Shu L (2013). Effects of glyphosate on apoptosis and expressions of androgen-binding protein and vimentin mRNA in mouse Sertoli cells. *Journal of Southern Medical University* **33**(11):1709-1713. [Article in Chinese]	This *in vitro* study investigated the effects of glyphosate on cultured mouse Sertoli cells. This male reproductive toxicity study does not provide data that can be used in the cancer dose-response analysis.

Comment 33: Teri Persico, Sandy DeSimone, William Brooks, Dr. Stephanie Seneff, and a number of other commenters provided lists of references for OEHHA's consideration.

Response 33: Of the published scientific articles listed in these comments, OEHHA carefully reviewed each of the cited documents in the context of the guidance set forth in Section 25703, in the same manner as was done in response to comment 32 above. Specifically the regulations states that "the assessment shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer".[101] OEHHA determined that none of the cited studies provide data that would affect the cancer dose-response analysis[102]. No changes were made to the regulatory proposal based on these comments.

Comment 34 (Baum, Hedlund, Aristei and Goldman, P.C.): "Additional documents pertinent to the Safe Harbor NSRL and Roundup/glyphosate carcinogenicity are presently still under seal and it is strongly recommended that OEHHA obtain access to

[101] Section 25703(a)(4)
[102] In fact, most of the articles were unrelated to carcinogenicity and instead focused on topics such as ecotoxicity, environmental fate and transport, analytical methods, mechanisms unrelated to carcinogenicity, and more.

such documents before OEHHA takes the potentially precarious step of issuing an NSRL of 1100 micrograms."

Response 34: OEHHA used publicly available scientific studies to calculate the NSRL. There is no legal basis for OEHHA to ask a court in a third party matter to provide it with sealed documents. In the event these materials become publicly available in the future and they are relevant to the calculation of the NSRL, OEHHA can reconsider the NSRL at that time. No changes were made to the regulatory proposal based on this comment.

Comment 35: Carcinogen Identification Committee members Dr. Jason Bush, Dr. Luoping Zhang, and Dr. Shanaz Dairkee had no objections to the proposed NSRL. Colton Bond commented that the NSRL is a reasonably conservative benchmark. Chris Portier supported use of the multistage model and the extrapolation plan for the evaluation of glyphosate carcinogenicity. Anne Surdzial recommended that OEHHA adopt the NSRL as is, which is supported by science.

Response 35: No response is required. No changes were made to the regulatory proposal based on this comment.

Comment 36 (Linda Causey): Request determination on the economic cost to finding glyphosate in California wines.

Response 36: This comment is not related to the rulemaking. An NSRL does not require a business to test for the presence of glyphosate in California wines or any other products. In the Economic Impact Analysis for this rulemaking, OEHHA noted:

"One year after the date of listing, businesses that manufacture, distribute or sell products with glyphosate in the state must provide a warning if their product or activity exposes the public or employees to significant amounts of this chemical. *The regulatory proposal does not create additional compliance requirements, but instead provides a "safe harbor" value that aids businesses in determining whether a warning is required for a given exposure*. (Emphasis added.)

Benefits of this regulation include sparing businesses the expense of calculating their own NSRL and possibly enabling them to reduce or avoid litigation costs..."

No changes were made based on this comment.

Comment #37 (Timothy Litzenburg): The single mouse study that OEHHA relied on was done by a glyphosate producer.

Response #37: Studies conducted or contracted by the chemical manufacturer often form part of the scientific data supporting carcinogenicity. As noted in the response to

comment #5, IARC found that two sets of studies in mice and six sets of studies in rats were adequate for the evaluation of glyphosate carcinogenicity. OEHHA reviewed the available data from the rodent carcinogenicity studies of glyphosate in light of the requirement of Section 25703 that the assessment "be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause 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. No changes were made based on this comment.

Local Mandate Determination

OEHHA has determined this regulatory action will not impose a mandate on local agencies or school districts nor does it require reimbursement by the State pursuant to Part 7 (commencing with Section 17500) of Division 4 of the Government Code. Local agencies and school districts are exempt from Proposition 65. OEHHA has also determined that no nondiscretionary costs or savings to local agencies or school districts will result from this regulatory action. The regulation does not create additional compliance requirements, but instead provides a "safe harbor" value that aids businesses in determining whether a warning is required for a given exposure.

Alternatives Determination

Pursuant to Government Code section 11346.5(a)(13), OEHHA initially determined that no reasonable alternative considered by OEHHA, or that has otherwise been identified and brought to the attention of OEHHA, would be more effective in carrying out the purpose for which the action is proposed, or would be as effective and less burdensome to affected private persons than the proposed action, or would be more cost-effective to affected private persons and equally effective in implementing the statutory policy or other provision of law.

In accordance with Government Code section 11346.9(a)(4), OEHHA has considered available alternatives to determine whether any alternative would be more effective in carrying out the purpose for which the regulations were proposed. OEHHA has also considered whether an alternative exists which would be as effective as and less burdensome to affected private persons than the proposed action. OEHHA has determined that no alternative considered would be more effective, or as effective as and less burdensome to affected private persons than the proposed regulation. No alternative that is less burdensome yet equally as effective in achieving the purposes of the regulation in a manner that achieves the purposes of the statute has been proposed. The NSRL provides a "safe harbor" value that aids businesses in determining if they are complying with the law. The regulation does not create additional compliance requirements, but instead provides a "safe harbor" value that aids

businesses in determining whether a warning is required for a given exposure. The alternative to the proposed amendment to Section 25705(b) would be to not adopt an NSRL for the chemical. Failure to adopt an NSRL would leave the business community without a “safe harbor” level to assist businesses in complying with Proposition 65. Some commenters proposed alternative NSRLs and approaches for deriving an NSRL. These comments were not reasonable alternatives and are fully discussed in responses to comments within this FSOR. There were no small-business specific alternatives submitted during the rulemaking process.

Exhibit 3

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

PURPOSE AND BACKGROUND OF PROPOSED AMENDMENTS OF REGULATION

This proposed regulatory amendment would adopt a No Significant Risk Level (NSRL) for glyphosate under Proposition 65[1] in Title 27, California Code of Regulations, section 25705(b)[2]. The proposed NSRL of 1100 micrograms per day (µg/day) is based on a carcinogenicity study in rodents and was derived using the methods described in Section 25703.

Proposition 65 was enacted as a ballot initiative on November 4, 1986. The Office of Environmental Health Hazard Assessment (OEHHA) within the California Environmental Protection Agency is the lead state entity responsible for the implementation of Proposition 65[3]. OEHHA has the authority to adopt and amend regulations to implement and further the purposes of the Act[4].

The Act requires businesses to provide a warning when they cause an exposure to a chemical listed as known to the state to cause cancer or reproductive toxicity. The Act also prohibits the discharge of listed chemicals to sources of drinking water. When exposures are insignificant, warnings are not required and the discharge prohibition does not apply. The NSRL provides guidance for determining when this is the case for exposures to chemicals listed as causing cancer.

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1 The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code section 25249.5 et. seq., commonly known as Proposition 65, hereafter referred to as "Proposition 65" or "The Act".
2 All further regulatory references are to sections of Title 27 of the Cal. Code of Regs., unless otherwise indicated.
3 Section 25102(o).
4 Health and Safety Code, section 25249.12(a).

A Notice of Listing for glyphosate as known to the state to cause cancer under Proposition 65 was published on our website on March 27, 2017. *Gyphosate (CAS No. 1071-83-6)* will be added to the list of chemicals known to the state to cause cancer for purposes of Proposition 65[5]. The effective date of this listing will be determined following a decision from the Court of Appeal regarding a request for a stay in the pending case *Monsanto v OEHHA*.[6] A separate Notice will be published, along with an updated Proposition 65 list, when the chemical is added to the list.

DEVELOPMENT OF PROPOSED NSRL

To develop the proposed NSRL for glyphosate, OEHHA relied on Volume 112 in the series of International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans entitled "Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos"[7], which summarizes the available data from rodent carcinogenicity studies of glyphosate, as well as other information relevant to the carcinogenic activity of the chemical. The NSRL is based on the results of the most sensitive scientific study deemed to be of sufficient quality[8].

Selection of Study Used to Determine Cancer Potency

OEHHA reviewed the available data from the rodent carcinogenicity studies of glyphosate discussed by IARC[9], 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.

The two-year diet study of glyphosate conducted in CD-1 male mice was performed by Inveresk Research International and summarized in the 2006 Joint FAO/WHO Meeting

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5 The Safe Drinking Water and Toxic Enforcement Act of 1986, Health and Safety Code, section 25249.5, et seq.

6 *Monsanto et al v OEHHA et al.*, Fresno County Superior Court case #16CECG00183, recently appealed to the California Court of Appeal (5th District). A case number has not yet been assigned.

7 International Agency for Research on Cancer (IARC, 2015). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112, Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France. Available at: http://monographs.iarc.fr/ENG/Monographs/vol112/index.php

8 Section 25703(a)(4)

9 International Agency for Research on Cancer (IARC, 2015). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112, Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France. Available at: http://monographs.iarc.fr/ENG/Monographs/vol112/index.php

on Pesticide Residues report[10] and by IARC[11]. In this study, groups of 50 male CD-1 mice were fed a diet containing glyphosate (purity, 98.6%) at concentrations intended to achieve dose rates of 0, 100, 300, or 1000 milligrams of glyphosate per kilogram of body weight per day (mg/kg-day) for two years[12]. Survival was not affected by treatment with glyphosate at any dose in the study[13]. A glyphosate treatment-related increase in hemangiosarcomas was observed, with a statistically significant positive trend[14]. The tumor incidence data used to estimate cancer potency from this study are presented in Table 1.

Table 1. Tumor incidences[a] of treatment-related lesions in male CD-1 mice administered glyphosate in the diet for two years (IARC, 2015; JMPR, 2006)

Tumor type	Dose group (mg/kg-day)				Trend test p-value[b]
	0	100	300	1000	
Hemangiosarcoma	0/50	0/50	0/50	4/50	p = 0.0036

[a] Data as reported by IARC (2015) and JMPR (2006).
[b] Exact test for linear trend.

Estimation of Cancer Potency in Mice Using the Multistage Model

In the 2015 review of the mechanistic data for glyphosate, IARC[15] concluded:

> "Overall, the mechanistic data provide strong evidence for genotoxicity and oxidative stress. There is evidence that these effects can operate in humans."

Based on consideration of the available mechanistic information on glyphosate and the above conclusions reached by IARC[16], a multistage model is applied to derive a cancer

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10 Joint FAO/WHO Meeting on Pesticide Residues (JMPR, 2006). Glyphosate. In: Joint FAO/WHO Meeting on Pesticide Residues. Pesticide residues in food – 2004: toxicological evaluations. Report No. WHO/PCS/06.1. Geneva: World Health Organization; pp. 95–169. Available from: http://apps.who.int/iris/bitstream/10665/43624/1/9241665203_eng.pdf , accessed January 19, 2016.
11 International Agency for Research on Cancer (IARC, 2015). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112, Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France. Available at: http://monographs.iarc.fr/ENG/Monographs/vol112/index.php
12 International Agency for Research on Cancer (IARC, 2015). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112, Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France. Available at: http://monographs.iarc.fr/ENG/Monographs/vol112/index.php
13 *Ibid.*
14 *Ibid.*
15 *Ibid.*
16 *Ibid.*

potency estimate, following the guidance in Section 25703. There are no principles or assumptions scientifically more appropriate, based on the available data, than this approach.

The lifetime probability of a tumor at a specific site given exposure to the chemical at dose d is modeled using the multistage polynomial model:

$$p(d) = \beta_0 + (1-\beta_0)(1-\exp[-(\beta_1 d + \beta_2 d^2 + \cdots + \beta_j d^j)])$$

where the background probability of tumor, β_0, is between 0 and 1 and the coefficients β_i, i = 1…j, are positive. The β_i are parameters of the model, which are taken to be constants and are estimated from the data. The parameter β_0 provides the basis for estimating the background lifetime probability of the tumor.

In order to derive a measure of the cancer response to glyphosate (per mg/kg-day) in the male mouse study described above, the dose associated with a 5% increased risk of developing a tumor was calculated and the lower bound for this dose was estimated using the multistage polynomial model for cancer in US EPA's Benchmark Dose Software (BMDS)[17]. The ratio of the 5% risk level to that lower bound on dose is known as the "animal cancer slope factor (CSF_{animal})", or the "animal cancer potency".

The animal cancer slope factor calculated from the male mouse study summarized in JMPR (2006) and IARC (2015) and described above is 0.00000897 $(mg/kg\text{-}day)^{-1}$.

Estimation of Human Cancer Potency

Human cancer potency is estimated by an interspecies scaling procedure. According to Section 25703(a)(6), dose in units of mg per kg bodyweight scaled to the three-quarters power is assumed to produce the same degree of effect in different species in the absence of information indicating otherwise. Thus, scaling to the estimated human potency (CSF_{human}) is achieved by multiplying the animal potency (CSF_{animal}) by the ratio of human to animal body weights (bw_{human}/bw_{animal}) raised to the one-fourth power when CSF_{animal} is expressed in units $(mg/kg\text{-}day)^{-1}$:

$$CSF_{human} = CSF_{animal} \times (bw_{human} / bw_{animal})^{1/4}$$

[17] US EPA Benchmark Dose Software (BMDS) Version 2.6.0.1 (Build 88, 6/25/2015). National Center for Environmental Assessment. Available from: http://bmds.epa.gov

The default human body weight is 70 kg. In the absence of animal body weight data from the male mouse study, the default[18] average body weight of 0.03 kg for male mice was used. The derivation of the human cancer slope factor using the default body weight values and the animal cancer slope factor of 0.0000897 $(mg/kg\text{-}day)^{-1}$ is shown below:

$$CSF_{human} = 0.0000897\ (mg/kg\text{-}day)^{-1} \times (70\ kg / 0.03\ kg)^{1/4} = 0.00062\ (mg/kg\text{-}day)^{-1}$$

Calculation of No Significant Risk Level

The NSRL can be calculated from the cancer slope factor as follows. The Proposition 65 no-significant-risk value is one excess case of cancer per 100,000 people exposed, expressed as 10^{-5}. This value is divided by the slope factor, expressed in units of one divided by milligram per kilogram bodyweight per day. The result of the calculation is a dose level associated with a 10^{-5} risk in units of mg/kg-day. This dose then can be converted to an intake amount in units of mg per day by multiplying by the bodyweight for humans. When the calculation is for the general population, the bodyweight is assumed to be 70 kg in NSRL calculations[19]. The intake can be converted to a µg per day amount by multiplying by 1000. This sequence of calculations can be expressed mathematically as:

$$NSRL = \frac{10^{-5} \times 70\ kg}{CSF_{human}} \times 1000\ \mu g/mg.$$

As indicated previously, the slope factor for glyphosate derived from the male mouse study data and exposure parameters presented in Table 1 is 0.00062 per mg/kg-day. Inserting this number into the equation above results in an NSRL of 1129 µg/day; rounding yields an NSRL of 1100 µg/day.

PROPOSED REGULATORY AMENDMENT

Section 25705(b)

The proposed change to Section 25705(b) is provided below, in underline and strikeout.

(1) The following levels based on risk assessments conducted or reviewed by the lead agency shall be deemed to pose no significant risk:

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[18]Gold LS, Zeiger E (1997). Handbook of Carcinogenic Potency and Genotoxicity Databases. CRC Press, Inc., Boca Raton.

[19] Section 25703(a)(8)

Chemical name	Level (micrograms per day)
Acrylonitrile	0.7
…	
Glyphosate	1100
…	

PROBLEM ADDRESSED BY THIS PROPOSED RULEMAKING

Proposition 65 does not provide guidance regarding how to determine whether a warning is required or a discharge is prohibited. OEHHA is the implementing agency for Proposition 65 and has the resources and expertise to examine the scientific literature and calculate a level of exposure, in this case an NSRL, that does not require a warning or for which a discharge is not prohibited.

ECONOMIC IMPACT ASSESSMENT (see below)

NECESSITY

This proposed regulatory amendment would adopt an NSRL that conforms with the Proposition 65 implementing regulations and reflects the currently available scientific knowledge about glyphosate. The NSRL provides assurance to the regulated community that exposures at or below this level are considered not to pose a significant risk of cancer. Exposures at or below the NSRL are exempt from the warning and discharge requirements of Proposition 65[20].

BENEFITS OF THE PROPOSED REGULATION

See "Benefits of the Proposed Regulation" under ECONOMIC IMPACT ANALYSIS below.

TECHNICAL, THEORETICAL, AND/OR EMPIRICAL STUDIES, REPORTS, OR DOCUMENTS

The 2015 IARC monograph entitled "Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos"[21], was relied on by OEHHA for calculating the NSRL for glyphosate. It includes data used in

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[20] Health and Safety Code sections 25249.9(b) and 25249.10(c)

[21] International Agency for Research on Cancer (IARC, 2015). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112, Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France. Available from: http://monographs.iarc.fr/ENG/Monographs/vol112/index.php

the potency calculation and on mechanisms of carcinogenesis that are relevant to evaluating the most appropriate method for deriving the NSRL in the context of Section 25703. OEHHA also relied on information on the animal carcinogenicity studies of glyphosate presented in the 2006 Joint FAO/WHO Meeting on Pesticide Residues report[22], and on the default male mouse body weight value of Gold and Zeiger[23]. Copies of these documents will be included in the regulatory record for this proposed action. These documents are available from OEHHA upon request.

OEHHA also relied on the attached Economic Impact Analysis in developing this proposed regulation.

REASONABLE ALTERNATIVES TO THE REGULATION AND THE AGENCY'S REASONS FOR REJECTING THOSE ALTERNATIVES

The NSRL provides a "safe harbor" value that aids businesses in determining if they are complying with the law. The alternative to the proposed amendment to Section 25705(b) would be to not adopt a NSRL for the chemical. Failure to adopt an NSRL would leave the business community without a "safe harbor" level to assist businesses in complying with Proposition 65. No alternative that is less burdensome yet equally as effective in achieving the purposes of the regulation in a manner that achieves the purposes of the statute has been proposed.

REASONABLE ALTERNATIVES TO THE PROPOSED REGULATORY ACTION THAT WOULD LESSEN ANY ADVERSE IMPACT ON SMALL BUSINESSES

OEHHA is not aware of significant cost impacts that small businesses would incur in reasonable compliance with the proposed action. Use of the proposed NSRL by businesses is voluntary and therefore does not impose any costs on small businesses. In addition, Proposition 65 is limited by its terms to businesses with 10 or more employees (Health and Safety Code, section 25249.11(b)) so it has no effect on very small businesses.

EVIDENCE SUPPORTING FINDING OF NO SIGNIFICANT ADVERSE ECONOMIC IMPACT ON BUSINESS

Because the proposed NSRL provides a "safe harbor" level for businesses to use when determining compliance with Proposition 65, OEHHA does not anticipate that the regulation will have a significant statewide adverse economic impact directly affecting

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[22] Joint FAO/WHO Meeting on Pesticide Residues (JMPR, 2006). Glyphosate. In: Joint FAO/WHO Meeting on Pesticide Residues. Pesticide residues in food – 2004: toxicological evaluations. Report No. WHO/PCS/06.1. Geneva: World Health Organization; pp. 95–169. Available from: http://apps.who.int/iris/bitstream/10665/43624/1/9241665203_eng.pdf , accessed January 19, 2016.

[23] Gold LS, Zeiger E (1997). Handbook of Carcinogenic Potency and Genotoxicity Databases. CRC Press, Inc., Boca Raton.

businesses, including the ability of California businesses to compete with businesses in other states.

EFFORTS TO AVOID UNNECESSARY DUPLICATION OR CONFLICTS WITH FEDERAL REGULATIONS CONTAINED IN THE CODE OF FEDERAL REGULATIONS

Proposition 65 is a California law that has no federal counterpart. There are no federal regulations addressing the same issues and, thus, there is no duplication or conflict with federal regulations.

ECONOMIC IMPACT ANALYSIS
Gov. Code section 11346.3(b)

It is not possible to quantify any monetary values for this proposed regulation given that its use is entirely voluntary and it only provides compliance assistance for businesses subject to the Act.

Impact on the Creation or Elimination of Jobs in California: This regulatory proposal will not affect the creation or elimination of jobs within the State of California. Proposition 65 requires businesses with ten or more employees to provide warnings when they knowingly and intentionally expose people to chemicals that are known to cause cancer or developmental or reproductive harm. The law also prohibits the discharge of listed chemicals into sources of drinking water. *Glyphosate (CAS No. 1071-83-6)* will be added to the list of chemicals known to the state to cause cancer for purposes of Proposition 65[24]. The effective date of this listing will be determined following a decision from the Court of Appeal regarding a request for a stay in the pending case *Monsanto v OEHHA*.[25] A separate Notice will be published, along with an updated Proposition 65 list, when the chemical is added to the list.

One year after the date of listing, businesses that manufacture, distribute or sell products with glyphosate in the state must provide a warning if their product or activity exposes the public or employees to significant amounts of this chemical. The regulatory proposal does not create additional compliance requirements, but instead provides a "safe harbor" value that aids businesses in determining whether a warning is required for a given exposure.

Impact on the Creation of New Businesses or Elimination of Existing Businesses within the State of California: This regulatory action will not impact the creation of new businesses or the elimination of existing businesses within the State of California. The regulatory proposal does not create additional compliance requirements, but instead provides a "safe harbor" value that aids businesses in determining if they are complying with the law.

Impact on Expansion of Businesses within the State of California: This regulatory action will not impact the expansion of businesses within the State of California. The

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[24] The Safe Drinking Water and Toxic Enforcement Act of 1986, Health and Safety Code, section 25249.5, et seq.

[25] *Monsanto et al v OEHHA et al.*, Fresno County Superior Court case #16CECG00183, recently appealed to the California Court of Appeal (5th District). A case number has not yet been assigned.

regulatory proposal does not create additional compliance requirements, but instead provides a “safe harbor” value that aids businesses in determining if they are complying with the law.

Benefits of the Proposed Regulation: The NSRL provides a “safe harbor” value that aids businesses in determining if they are complying with the law. Some businesses may not be able to afford the expense of establishing an NSRL and therefore may be exposed to litigation for a failure to warn of an exposure to or for a prohibited discharge of the listed chemical. Adopting this regulation will save these businesses those expenses and may reduce litigation costs. By providing a safe harbor level, this regulatory proposal does not require, but may encourage, businesses to lower the amount of the listed chemical in their product to a level that does not cause a significant exposure, thereby providing a public health benefit to Californians.

Exhibit 4

SUPERIOR COURT OF THE STATE OF CALIFORNIA
FOR THE COUNTY OF SAN FRANCISCO
CASE NO.: CGC-16-550128

DEWAYNE JOHNSON,

Plaintiff,

vs.

MONSANTO COMPANY,

Defendant.

_____/

* * * * CONFIDENTIAL * * * * *

VIDEOTAPED DEPOSITION OF WILLIAM SAWYER, PH.D.

Monday, February 26, 2018
8:12 a.m. - 5:04 p.m.

Sanibel, Florida

Stenographically Reported By:
Tracie Thompson, RMR, CRR, CLR
Registered Merit Reporter
Certified Realtime Reporter
Certified LiveNote Reporter

Pages 1-264

and the specifics in terms of whether or not a procedure meets compliance. I have training and experience, but I'm not an expert on that, per se.

Q And when you say specifics in whether procedures meet compliance, what procedures are you referring to?

A For example, whether the human factors handbook manual was followed correctly or whether the methodology for a cancer bioassay was followed correctly, all of the rules and regulations are printed in numerous volumes of EPA documents which in the past I have had to use as part of my work as a toxicologist.

Q You're not an expert on human factors, right?

A No.

Q You're not an expert on human factors?

A I am not.

Q You're not an expert on California's Proposition 65?

A No.

Q You're not testifying that anyone in this case violated any EPA regulations, are you?

A I don't believe so.

Q You've never interpreted Proposition 65 on

right, and the determination about glyphosate?

A Yes.

Q Do you have any opinions about Proposition 65 that are not stated in your report?

A Only that the more potent, more sensitive animal studies from Wood 2009 B would have been a more appropriate animal model to use in the cancer potency calculation.

Q Why do you say that?

A Because the Wood 2009 B animal studies for lymphoma provided a more sensitive analysis, the dose response period was monotonic and highly significant, as opposed to the hemangiosarcoma study used in the proposed NSRL.

Q Anything else?

A No.

Q You used the Wood 2009 B study on lymphomas, right?

A Yes.

Q Do you have any opinions regarding the hemangiosarcomas that are not in your expert report?

A No.

Q You testified earlier that you had used Roundup. Over what period of time have you used Roundup?

CERTIFICATE OF REPORTER

STATE OF FLORIDA

COUNTY OF LEE

I, TRACIE THOMPSON, Registered Merit Reporter, do hereby certify that I was authorized to and did stenographically report the foregoing videotape deposition of WILLIAM SAWYER, PH.D.; pages 1 through 265; that a review of the transcript was requested; and that the transcript is a true record of my stenographic notes.

I FURTHER CERTIFY that I am not a relative, employee, attorney, or counsel of any of the parties, nor am I a relative or employee of any of the parties' attorneys or counsel connected with the action, nor am I financially interested in the action.

Dated this 27th day of February, 2018.

Tracie Thompson
Notary Public
State of Florida
My Commission No. GG 175178
Expires: March 1, 2022

Exhibit 5

TCAS

Toxicology Consultants & Assessment Specialists, LLC
6450 Pine Avenue, Sanibel, FL 33957
29 Fennell Street, Skaneateles, NY 13152
(239) 472-2436 [FL] (315) 685-2345 [NY] (800) 308-0080
E-mail: drsawyer@experttoxicologist.com & Website: experttoxicologist.com

Toxic Exposures · Environmental Testing · Risk Assessment · Forensic Toxicology · Causation Evaluation

Toxicological Assessment of Dewayne Johnson and Toxicological Risk Assessment of Glyphosate and Roundup® and Ranger PRO® Formulations

William R. Sawyer, Ph.D., D-ABFM
Toxicologist

December 21, 2017

Prepared for

Michael J. Miller, Esq.
Jeffrey A. Travers, Esq.
Timothy Litzenburg, Esq.

The Miller Firm, LLC
108 Railroad Avenue
Orange, VA 22960

which purport to reduce the apparent percentage of glyphosate absorbed thus bringing the value below the minimum required for regulatory approval.

- **Absorption Factors:** Additives within Roundup® formulations increase glyphosate dermal absorption. These include (a) "co-formulants" (ingredients other than glyphosate) such as surfactants (compounds which lower surface tension) and humectants (to inhibit moisture loss) and (b) adjuvants (chemicals which modify the effect of other agents). Other factors affecting absorption include skin damage such as lesions, cracks and other irregularities, lack of personal protective gear, etc. Co-formulants are of particular concern as they can be more toxic than glyphosate itself.

- **Pharmacokinetics:** This refers to the amount and the rate at which a substance is directly absorbed, distributed and metabolized by the body and how much is excreted. While normally an objective measurement, there are examples cited herein showing that the percent absorbed versus excreted is higher than that purported by the manufacturer. Additionally, Monsanto (knowingly or unknowingly) has regularly misstated glyphosate dermal absorption recovery in its communications. These are regarded as pertinent issues with respect to credibility and weight of evidence.

- **Industrial Secrecy:** IARC relied solely on *independent research* to render its conclusion. Monsanto-sponsored studies played little or no part in the IARC classification ruling. Similarly, this toxicological assessment has primary relied upon independent studies though Monsanto-sponsored studies were also assessed, noting inconsistencies and consistencies where appropriate.

- **Regulatory Considerations:** Regulatory rulings play a role no more or less important in a toxicological assessment than any other objective evidence. It is noteworthy that there is presently disagreement within the U.S. EPA itself with respect to some of the issues raised in this assessment. Although the State of California listed glyphosate as a carcinogen on July 7, 2017, *this toxicological assessment does not assume any position of advocacy*. The opinions expressed herein are based on objective, reliable evidence without deviation from the assessment methodology.

- **Carcinogenic Studies:** This assessment takes into account numerous studies and cancer bioassays in animals as well as chronic dietary studies and carcinogenicity

Part C: Toxicological Assessment of Glyphosate Carcinogenicity

Methodology

For the purposes of toxicological assessment, regulatory rulings play a role no more or less important than any other objective evidence. The generally-accepted, peer-reviewed toxicological literature is not based on unsubstantiated, subjective opinions. A responsible scientific investigation applies a well-established and prescribed risk assessment methodology.

This assessment applies the generally accepted and U.S. EPA-prescribed investigative methodology in assessing the potential carcinogenicity of glyphosate. Expert opinions must always be based on objective, reliable evidence without deviation from the methodology. The strands of evidence are never assumed to stand by themselves in isolation but are viewed as pieces of a larger puzzle. Scientific interpretation of the puzzle forms the basis of the investigative process in which each piece is assessed on its merits. Only in this manner can a scientifically credible assessment be conducted.

Regulatory Considerations

On July 7, 2017, the State of California listed glyphosate as a carcinogen, a chemical "*known to cause cancer*" under the state's Proposition 65 law. The ruling followed a move by the World Health Organization's International Agency for Research on Cancer (IARC) classifying glyphosate as a "*probable human carcinogen*." Monsanto is fighting the state's action but the California Supreme Court denied the company's request to stop the listing from taking effect while litigation is underway. Monsanto's vice president of global strategy announced that *"We will continue to aggressively challenge this improper decision."* Monsanto further alleged that IARC *"ignored crucial scientific data that undermines its conclusion."* To date, Monsanto has produced no objective evidence to directly support its contention.

Glyphosate is currently undergoing registration review as mandated by the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) which requires all registered pesticides to be re-evaluated every 15 years. As part of the review, the U.S. EPA's Office of Pesticide Programs (OPP) released a report dated September 12, 2016, focusing on

Part D: Glyphosate Carcinogenicity Assessment

Introduction

A cancer slope factor (CSF) estimates the risk of cancer associated with exposure to a carcinogenic or potentially carcinogenic substance. Mathematically, a slope factor is an upper bound, approximating a 95% confidence limit. It is used to demonstrate cancer risk from a lifetime exposure to a substance by ingestion, dermal exposure or inhalation.

As previously noted, the generally-accepted, peer-reviewed toxicological literature is not based on unsubstantiated, subjective opinions. A responsible scientific investigation applies a generally accepted and well documented risk assessment methodology. Thus, calculating a reliable cancer slope factor is predicated upon applying the best available information "as per schedule" according to the prescribed methodology.

U.S. EPA guidelines[231] repeatedly stress the need for good information in its guidance, which is specific and demanding. U.S. EPA methodology recommends any study used for the purpose of calculating a cancer slope factor should meet the following criteria:

- Study should apply at least two dose groups plus a control group.
- Study should have sufficient sensitivity to provide data for multiple dose ranges
- Study should meet all statistical testing requirements.
- Study should characterize exposure at multiple exposure levels.
- Study should demonstrate statistically-significant results and show clear trends with respect to dose-response outcomes.

Following U.S. EPA methodology the Wood, et al., 2009b[232] study was chosen as the primary study to derive an exposure cancer slope factor for glyphosate since it is the most

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[231] U.S. EPA, "Guidelines for carcinogen risk assessment," EPA/630/P-03/001B, March, 2005

[232] (b) Wood, E., Dunster, J., Watson, P., and Brooks, P., "Glyphosate technical: Dietary carcinogenicity study in the mouse," 2009b, Harlan Laboratories Limited, Shardlow Business Park, Shardlow, Derbyshire DE72 2GD, UK. Study No. 2060-011. April, 22, 2009. MRID 49957402. From "Glyphosate issue paper: Evaluation of Carcinogenic Potentia," U.S. EPA's Office of Pesticide Programs, September 12, 2016.

sensitive study and meets and exceeds the statistical testing requirements. Wood, et al., 2009b, is the most recent chronic carcinogenicity study performed and used three large dose groups plus a control group. The study doses characterize exposure at low, mid and high exposure levels. Wood, et al., 2009b, also noted a significant trend in hepatocellular tumors and the observed trend was monotonic. As such, *the study exceeds the stated U.S. EPA assessment criteria.*

Dose-Response Data

Of the various studies noted herein, three chronic dietary bioassays provided incidence data for malignant lymphomas and occurred in mice only, these being: Sugimoto (1997), Kumar, (2001) and Wood, et al., (2009b). The dose-response data from each of these studies is summarized in Table 21. There were statistically significant increasing trends in tumor incidences in the males of the species.

Table 21

Incidence of Malignant Lymphomas in Male Mice Exposed to Glyphosate in Diet for two Years

Study	Strain/ Species	Animal dose (mg/kg/day)	Incidence of malignant lymphomas (percentage)	Numbers of animals examined
Sugimoto, 1997	CD-1 Mice	0	0 (0) [a]	26
		165	0 (0)	34
		838.1	1 (4)	27
		4,348	5 (17)	29
Kumar, 2001	Swiss Albino Mice	0	10 (20)	50
		14.7	15 (30)	50
		150.5	16 (32)	50
		1,460.3	19 (38)	50
Wood, et al., 2009b	CD-1 Mice	0	0 (0) [b] (monotonic)	51
		71.4	1 (2)	51
		234.2	2 (4)	51
		810	5 (10) [c]	51

[a] Cochran-Armitage Trend Test ($p \leq 0.01$)
[b] Cochran-Armitage Trend Test ($p = 0.007$)
[c] Fisher's Exact Test ($p=0.028$)

Dose Adjustments and Extrapolation Method(s)

Human equivalent doses (HEDs) were derived from the doses administered to the Wood, et al., 2009b study's male CD-1 mice using a body weight (BW) scaling factor of 0.75 as provided by the U.S. EPA.[233] HEDs were calculated using the following equation:

$$\text{HED} = \text{animal mg}\cdot\text{kg}^{-1}\text{ dose x (animal weight (kg)/human weight (kg))}^{1-b}$$

Where,

b = allometric exponent (0.75)

$$\text{HED} = 810\frac{\text{mg}}{\text{kg}}\text{bw x}\left(\frac{0.027\ kg}{70\ kg}\right)^{0.25} = 113.5\frac{\text{mg}}{\text{kg}}$$

For all HED calculations, a human body weight of 70 kg was used for the primary Wood, et al, study. The U.S. EPA "Exposure Factors Handbook" notes that 70 kg is commonly assumed in U.S. EPA risk assessments.[234] HEDs were also calculated for the other lymphoma studies as shown in Table 22.

The "Tier II summaries for glyphosate carcinogenicity studies from Greim, et al., 2015 paper" only provided the range of body weights of the mice used at the initiation of the experiment. Consequently, the lower animal doses provide a more conservative estimate of the human equivalent dose as the mice would have an increase in body weight over the 80 week feeding study period.

For Wood, et al., 2009b, the mice body weights ranged from 22 - 32 grams with the midpoint weight at 27 grams. The Sugimoto, 1997, study revealed mice body weights

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[233] U.S. EPA, "Recommended use of body weight 3/4 as the default method in derivation of the oral reference dose," 2011, (EPA/100/R11/0001), Office of the Science Advisor, Risk Assessment Forum, US Environmental Protection Agency, Washington, DC.

[234] U.S. EPA, "Exposures Factors Handbook: Chapter 8 – Body Weight Studies," 2011, U.S. Environmental Protection Agency.

that ranged from 15 - 25 grams with the midpoint at 20 grams. Kumar, 2001, cited mice weights ranging from 25 - 47 grams with the midpoint at 36 grams. The midpoint weights were used for HED determination.

Table 22

Calculated Human Equivalent Doses (HED) for the Lymphoma Incidence Data Used for Dose-Response Modeling

Study	Strain/ Species	Initial Midpoint Mice BW (kg)	Animal Dose (mg/kg/day)	HED (mg/kg/day)[a]
Sugimoto, 1997	CD-1 Mice	0.02	0	0
		0.02	165	21.5
		0.02	838.1	109
		0.02	4,348	565.3
Kumar, 2001	Swiss Albino Mice	0.036	0	0
		0.036	14.7	2.21
		0.036	150.5	22.7
		0.036	1,460.3	219.9
Wood, et al., 2009b	CD- 1 Mice	0.027	0	0
		0.027	71.4	10
		0.027	234.2	32.8
		0.027	810	113.5

[a] HEDs are calculated as HED = (animal dose) x (animal BW / Human BW)$^{0.25}$

Cancer Slope Factor

According to the U.S. EPA's "Guidelines for Carcinogen Risk Assessment,"[235] when quantifying the cancer risk of a chemical whose carcinogenic mode of action is not established, the linear approach is recommended as the default option. In the case of glyphosate, the genotoxic mode of carcinogenic action has been recently postulated[236] and there is limited human study evidence of genotoxicity. Thus, a linear low-dose extrapolation approach was used **as required by the methodology** to estimate human carcinogenic risk associated with glyphosate oral exposure.

Glyphosate Potential for Genotoxicity

There is evidence that that glyphosate is genotoxic and glyphosate-based formulations such as Roundup cause oxidative stress. The recent study of Suarez-Larios et al. (2017) reveals a genotoxic mode of action for glyphosate pesticides. An investigation was undertaken by Suarez-Larios, et al.,[237] to determine whether or not exposure to pesticides would induce double strand breaks (DSB) in cells (a lesion related to the formation of chromosomal rearrangements and increased leukemia risk). Of the eight pesticides tested (endosulfan, glyphosate, pentachlorophenol, permethrin, propoxur, AMPA, endosulfan lactone and paraoxon), four showed a significant effect on the number of cells with double strand breaks. However, glyphosate and paraoxon (both organo-phosphates) showed the greatest increase in the number of cells with DSB compared to the concentration. Further, it was determined that glyphosate and paraoxon reduced the number of viable cells in a dose-dependent manner; specifically, going from 100% cell viability to 70% with glyphosate.

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[235] U.S. EPA, "Guidelines for carcinogen risk assessment," 2005, EPA/630/P-03/001F, Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC.

[236] Suarez-Larios, K., et al., "Screening of pesticides with the potential of inducing DSB and successive recombinational repair," 2017, Journal of Toxicology. Volume 2017.

[237] Suarez-Larios, K., et al., "Screening of pesticides with the potential of inducing DSB and successive recombinational repair," 2017, Journal of Toxicology. Volume 2017.

Not only did these two pesticides induce greater breakage, they also induced the phosphorylation[238] of KU80, a protein that participates in the c NHEJ recombinational repair pathway which is responsible for repair of the cells when DSB occur.

It was further noted in the study that these effects occurred at low concentrations in an acute treatment to cells in the laboratory setting. "*Effects over longer exposure in actual environmental settings are expected to produce cumulative damage if repeated events of recombination take place over time.*" In other words, the more often a cell is damaged by glyphosate-induced breakage, the less likely the c NHEJ recombinational repair pathway will be able to repair it. Thus, the linear approach required by the U.S. EPA methodology is appropriate as the mode of action proposed by Suarez-Larios et al. is not a threshold-based genotoxic mechanism. Other studies indicate that glyphosate can act as an endocrine disruptor[239] and has tumor-promoting activity.[240]

In vivo observations of human populations exposed to spraying of Roundup have revealed statistically significant outcomes demonstrating genotoxicity at low exposure levels[241] as well as *in vivo* studies of laboratory animals fed Roundup.[242] These studies challenge both animal and human systems providing *in vivo* doses of Roundup® with resulting genotoxicity.

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[238] Phosphorylation plays a critical role in the regulation of cellular processes.

[239] Gasnier, C., et al., "Glyphosate-based herbicides are toxic and endocrine disruptors in human cell lines," 2009, Toxicology, Vol. 262, pg. 184 -191.

Thongprakaisang, S., et al., "Glyphosate induces human breast cancer cells growth via estrogen receptors," 2013, Food and Chemical Toxicology, doi: http://dx.doi.org/10.1016/j.fct.2013.05.057

[240] George, J., et al., "Studies on glyphosate-induced carcinogenicity in mouse skin: A proteomic approach," 2010, Journal of Proteomics, Vol. 73, pg. 951 – 964.

[241] Paz-y-Miño, C., et al., "Evaluation of DNA damage in an Ecuadorian population exposed to glyphosate," *2007,* Genetics and Molecular Biology, **30**(2).

Bolognesi, C., et al., "Biomonitoring of genotoxic risk in agricultural workers from five Colombian regions: Association to occupational exposure to glyphosate," 2009, Journal of Toxicology and Environmental Health, Part A, Vol. 72, pg. 986 -997.

[242] Peluso, M., et al, "32P-postlabeling detection of DNA adducts in mice treated with herbicide roundup," 1998, Environmental and Molecular Mutagenesis. Vol. 31(1), pp. 55 -59. DOI: 10.1002/(SICI)1098-2280(1998)31:1<55::AID-EM8>3.0.CO;2-A

Furthermore, the human studies present conditions with "real world" dosing and concentrations.

The U.S. EPA's "Guidelines for Carcinogens" states that "*In the absence of sufficiently scientifically justifiable mode of action information, U.S. EPA generally takes public health-protective, default positions regarding the interpretation of toxicological and epidemiologic data: animal tumor findings are judged to be relevant to humans, and cancer risks are assumed to conform with low dose linearity*."[243]

Modeling: Cancer Slope Factor

According to the U.S. EPA's "Guidelines for Carcinogenic Risk Assessment," "*For linear extrapolation, the POD* (point of departure) *is used to calculate a slope factor."* Furthermore, the guidelines state that *"in a risk characterization, the POD is part of the determination of a margin of exposure.*"

The cancer slope factor (CSF) for glyphosate was derived via a linear extrapolation from the POD which was calculated by fitting the studies in the experimental dose response data to a curve in the U.S. EPA's "*Benchmark Dose Software*" (BMDS). The POD is the 95% lower confidence limit of the dose indicated by the model as the benchmark dose (BMD).

The BMD addresses the many limitations of the "No Observed Adverse Effect Level" (NOAEL) method as it is less dependent on dose selection and spacing and takes into account the shape of the dose-response curve. Furthermore, the BMD 95% lower confidence limit (BMDL) results in a point of departure that accounts for study quality issues (such as adequate sample size).[244] The CSF can be calculated from information provided from the BMD, as shown below:

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[243] U.S. EPA, "Guidelines for carcinogen risk assessment," 2005, EPA/630/P-03/001F, Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC.

[244] "Dose-Response Assessment," n.d., Tox Tutor, U.S. National Library of Medicine, National Institute of Health, Retrieved from: https://toxtutor.nlm.nih.gov/06-003.html

$$CSF = BMR / BMDLHED$$

Where:

BMR: Benchmark Response Level

BMDLHED: Benchmark Dose Lower Bound Human Equivalent Dose

The dichotomous models in the Benchmark Dose Software (*BMDS version 2.6.0.1*) were fit to the lymphoma incidence data in mice. The mice doses were used for BMD modeling, and the BMDHED and BMDLHED values were calculated using the $BW^{3/4}$ scaling using the initial midpoint mice weights (final mice weights were not provided nor were individual mice weights) and a human body weight of 70 kg. For the models, a BMR of 10% extra risk was employed. BMDs and BMDLs from all models are shown in **Appendix A**.

The multi-stage model provided an adequate fit for the Sugimoto, 1997, CD-1 mice study as well as the Wood, et al., 2009b, CD-1 mice study. Other studies did not fit the multi-stage model adequately (see Table 23). The CD-1 mice were clearly the most sensitive species/strain, and the Wood, et al., 2009b, study is the most sensitive study as also shown in Table 23. Other models such as the probit model or log-logistic model could be used to provide adequate fit for the other cancer studies.

Table 23

BMD_{HED} and $BMDL_{HED}$ Values from Best-fit Models (using 10% BMR) to Lymphoma Incidence Data from Mice Exposed to Chronic Dietary Concentrations of Glyphosate Daily with Corresponding Cancer Slope Factors (CSFs)

Study	Gender/strain/ species	Carcinoma type	BMD_{HED} (mg/kg-day)	$BMDL_{HED}$ (mg/kg-day)	CSF $(mg/kg/day)^{-1}$
Sugimoto, 1997	Female CD-1 Mice	Hemangioma	1,239.7	822.4	1.21×10^{-4}
Sugimoto, 1997	Male CD-1 Mice	Malignant Lymphoma	1,832.16	1,000.15	1.0×10^{-4}
Wood, et al., 2009b	Male CD- 1 Mice	Malignant Lymphoma	100.76	59.28	1.7×10^{-3}

The multi-stage model using a 10% BMR is the standard method for establishing the cancer slope factor.[245] Consequently, the lymphoma cancer endpoint in CD-1 mice and the Wood, et al,, 2009b, study provided the best multi-stage model fit with p=0.91 (see Table 24).

Furthermore, a comparison of the BMD and BMDL estimates derived for mice from the Sugimoto, 1997, and Wood, et al., 2009b, studies indicate that male CD-1 mice are more sensitive to lymphoma induced by glyphosate compared to other species and tumor types.

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[245] Crump, K., "The linearized multi-stage model and the future of quantitative risk assessment," 1996, Hum Exp. Tox, Vol. 15(10), pg. 787 – 798.

"Dose-Response Assessment," n.d., Tox Tutor, U.S. National Library of Medicine, National Institute of Health, Retrieved from: https://toxtutor.nlm.nih.gov/06-003.html

Therefore, the $BMDL_{10HED}$ was chosen as the POD. The Cancer Slope Factor (CSF) of 0.0017 mg/kg/day was calculated as follows:

$$CSF = \frac{0.10}{59.28 \text{ mg/kg-day } (BMDL_{10HED} \text{ for male CD1 mice})} = 0.00169$$

The calculation of a CSF for glyphosate is based upon the dose-response data for the most sensitive species and gender as well as the study providing the best fit of the multi-stage cancer model.

Table 24 shows a summary of BMD modeling results for glyphosate in diet/chronic carcinogenicity studies with significant dietary doses causing neoplasms. The BMD modeling results are shown in detail in **Appendix A**.

Table 24

Summary of BMD Modeling Results for Glyphosate in Diet/Chronic Carcinogenicity Studies with Significant Dietary Doses Causing Neoplasms

Study	Model[a]	Goodness of Fit			BMD_{10Pct}	$BMDL_{10Pct}$	Basis for Selection
		p-value	Scaled Residual	AIC			
Lankas, 1981	Multi-stage cancer 1st degree	0.112	0.096	77.615	29.8	14.8	Not an ideal model as p-value is less than 0.5.
Stout and Ruecker, 1990	Multi-stage cancer 1st degree	0.134	-0.104	133.96	1415	474	Not an ideal model as p-value is less than 0.5.
Brammer, 2001	Multi-stage cancer 1st degree	0.110	0.242	59.257	1490	743	Not an ideal model as p-value is less than 0.5.
Wood, et al, 2009a	Multi-stage cancer 1st degree	0.348	0.415	100.45	1151	591	Not an ideal model as p-value is less than 0.5.
Sugimoto, 1997; hemangioma	Multi-stage cancer 1st degree	0.606	1.11	82.019	1729	1147	1st degree and 2nd degree provided the exact same BMD and BMDL
Sugimoto, 1997;- lymphoma	Multi-stage cancer 1st degree	0.88	0.069	37.699	2506	1368	Select the model with the lower BMDL (1st Model)
Sugimoto, 1997; lymphoma	Multi-stage cancer 2nd degree	0.881	-0.021	39.649	2669	1375	
Wood et al., 2009b lymphoma	Multi-stage cancer 1st degree	0.905	-0.316	61.916	719	423	1st degree and 2nd degree provided the exact same BMD and BMDL

Criteria for model selection:

- Beta coefficient 2 of the multi-stage cancer 2 model hit a boundary
- *p*-value has to be greater than 0.5
- Scaled residual must be less than absolute 2
- AIC – the lower the AIC, the better

Assessment of Dose-Dependent Linear Extrapolation and Saturation Potential

Despite the U.S. EPA's recommendation of linear low dose extrapolation for genotoxic chemicals and chemicals with unknown mode of action, there exists some dissension among certain scientific points-of-view which challenges the appropriateness of a linear non-threshold, dose-response model as biologically valid for cancer risk assessment. In the current assessment, the recent study of Suarez-Larios et al. (2017) reveals a genotoxic mode of action for glyphosate that is linear with respect to double strand breaks and cumulative. In this study, it was determined that glyphosate reduced the number of viable cells in a dose-dependent manner; specifically, going from 100% cell viability to 70% with glyphosate. Additionally, glyphosate induced the phosphorylation[246] of KU80, a protein that participates in the c NHEJ recombinational repair pathway which is responsible for repair of the cells when DSB occur. The Suarez-Larios et al. study stated "*Effects over longer exposure in actual environmental settings are expected to produce cumulative damage if repeated events of recombination take place over time.*" In other words, the more often a cell is damaged by Glyphosate-induced breakage, the less likely the c NHEJ recombinational repair pathway will be able to repair it. Thus, the linear approach required by the U.S. EPA methodology is appropriate as the mode of action proposed by Suarez-Larios et al. is not a threshold-based genotoxic mechanism.

For example, the opinion article by *Exponent* published by James Bus (July 2017) summarizes this position. He argues that biological homeostatic mechanisms protect against adverse effects from low dose exposure to chemicals determined to be carcinogenic using high dose studies. Which is to say, the opinion is that certain high dose exposures in scientific studies should not be used to extrapolate human health risk at low doses.

The Bus article points out that there are protective biological cellular mechanisms for alleviating toxic effects at low doses creating a dose threshold effect. It also proposes that studies showing elevated dose-specific toxicity are associated with adverse health effects

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[246] Phosphorylation plays a critical role in the regulation of cellular processes.

due to saturation of the biological mechanisms controlling the administration, distribution metabolism and excretion (ADME).[247] Based on these considerations, he opines:

- Against a linear, non-threshold hypothesis highlighting the development of Kinetically-derived Maximum Dose (KMD) that identifies the onset of non-linear ADME toxicity and proposed as an alternative or extension of the Maximum Tolerated Dose (MTD) currently accepted in toxicological health risk assessments.[248]
- Dosing in high throughput screening (HTS) *in vitro* testing (such as for determining genotoxicity), does not take into account chemical doses expected/attained *in vivo* (in real world situations in humans or model laboratory animals).

The determination of Roundup and other glyphosate-based formulations' genotoxicity as stated by IARC was not determined from *in vitro* testing in isolation. Rather *in vivo* observations of human populations exposed to spraying of Roundup revealed statistically significant outcomes demonstrating genotoxicity at low exposure levels[249] as well as *in vivo* studies of laboratory animals fed Roundup.[250] (This eliminates any confounding issues due to the controlled setting). These studies challenge both animal and human systems providing *in vivo* doses of Roundup® with resulting genotoxicity.

Furthermore, the human studies present conditions with "real world" dosing and concentrations. Perhaps the most compelling consideration comes from the objective

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[247] Bus, J., "The dose makes the poison: Key implications for mode of action (mechanistic) research in a 21st century toxicology paradigm," 2017, Current Opinion in Toxicology, DOI: 10.1016/j.cotox.2017.06.013

[248] OECD in Bus, J., "The dose makes the poison: Key implications for mode of action (mechanistic) research in a 21st century toxicology paradigm," 2017, Current Opinion in Toxicology, DOI: 10.1016/j.cotox.2017.06.013.

[249] Paz-y-Miño, C., et al., "Evaluation of DNA damage in an Ecuadorian population exposed to glyphosate," 2007, Genetics and Molecular Biology, 30(2).

Bolognesi, C., et al., "Biomonitoring of genotoxic risk in agricultural workers from five Colombian regions: Association to occupational exposure to glyphosate," 2009, Journal of Toxicology and Environmental Health, Part A, Vol. 72, pg. 986 -997.

[250] Peluso, M., et al, "32P-postlabeling detection of DNA adducts in mice treated with herbicide roundup," 1998, Environmental and Molecular Mutagenesis. Vol. 31(1), pp. 55 -59. DOI: 10.1002/(SICI)1098-2280(1998)31:1<55::AID-EM8>3.0.CO;2-A

evidence in published epidemiological studies which documents Roundup® in the development of lymphoma, a further connection to Roundup's genotoxicity at a 95% level of certainty.[251]

It is important to understand that toxicity assays have traditionally relied on Maximum Tolerated Dose (MTD) as a strategy to compensate for the limited statistical power that comes with the use of a small number of test experimental animals and other such surrogates. The MTD is used to determine efficacy by testing increasing doses of a chemical until a dose that produces "acceptable" side effects is found[252] thereby assuming a linear response to chemical exposure.

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[251] DeRoos, A., et al., "Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men," 2003, Occup Environ Medical, Vol. 60.

[252] Chevret, S., "Maximum Tolerable Dose," 2008, Wiley Stats Ref: Statistics Reference Online, DOI: 10.1002/9781118445112.stat07089

NCI, "Maximum Tolerated Dose," n.d., NCI Dictionary of Cancer Terms, National Cancer Institute, National Institute of Health. Retrieved July, 6, 2017 from: https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=546597

Low Dose Linear Extrapolation versus. Kinetically-Derived Maximum Dose

There are important fundamental toxicological issues to consider here. At doses above the MTD, toxicity has been proposed to be associated with saturation of the biological mechanisms that control the administration, distribution, metabolism and excretion (ADME) [253] and is, therefore, non-linear in producing toxic adverse health effects. *However, direct, objective evidence to support this contention in humans is absent as glyphosate/Roundup® genotoxicity and lymphoma has been demonstrated in low exposure level human epidemiological studies that are statistically significant.*

Further evidence can be seen in animals in the current evaluation. The Cancer Slope Factor (CSF) was determined from a glyphosate feeding study in CD-1 mice[254] with a high-dose, statistically-significant increased incidence of lymphoma and low-dose linear extrapolation to determine the CSF over a statistically significant monotonic trend ($p<0.007$). Health effects observed in this study were not due to saturation as glyphosate was administered orally in diet (not via acute IV or intraperitoneal administration) allowing for absorption through the digestive system to dictate the concentration in blood. If saturation had occurred, a near perfectly linear dose-response curve would not have appeared in the Wood 2009b study.

A pharmacokinetic study[255] of glyphosate in rats demonstrates that 35 to 40% of the administered dose was absorbed from the digestive tract. An intravenous dosing study is more likely to saturate the ADME mechanism due to the acute bolus load into systematic circulation with a significant (~80%) portion of the administered dose eliminated primarily as un-metabolized glyphosate in urine within 24 hours of

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[253] Bus, J., "The dose makes the poison: Key implications for mode of action (mechanistic) research in a 21st century toxicology paradigm," 2017, Current Opinion in Toxicology, DOI: 10.1016/j.cotox.2017.06.013

[254] Wood, et al., "Glyphosate technical: dietary carcinogenicity study in the mouse," 2009b, Harlan Laboratories Limited, Shardlow Business Park, Shardlow, Derbyshire DE72 2GD, UK, Study No. 2060-011.

[255] Brewster, D., Warren, J., Hopkins, W., "Metabolism of glyphosate in Sprague Dawley rats: Tissue distribution, identification and quantitation of glyphosate-derived materials following a single oral dose," 1991, Fundamental and Applied Toxicology, Vol. 17, pg. 43-51.

administering the dose.[256] The pharmacokinetics of oral or dermally absorbed glyphosate is limited in its absorption rate into the blood without extreme high peak blood levels (which occurs with IV administration) and does not reach saturation of the ADME mechanisms.

As noted by Bus (2017), a large proportion of toxicological hazards are identified at doses only in the range of an MTD and, thus, *kinetically-derived maximum dose* (KMD) modeling will fail to identify these toxicological hazards particularly when hazard responses are limited to doses above the KMD.

Bus notes that "*The pragmatic end-result of KMD-based toxicity testing considerations is that the need for high-dose specific MoA [*mode of action*] investigations is substantially reduced*." Meaning, that a KMD approach (which doesn't include high dosages) will essentially eliminate the need for further investigation of many chemicals.

Human health risk assessments are designed to estimate cancer risks at levels of $1x10^{-4}$ to $1x10^{-6}$. Without the use of linear extrapolation from higher dose levels, approximately 400 lab animals in each dose-level group (1,600 animals total) would be required (assuming a doubling of the cancer rate) per dose group to determine a $1x10^{-4}$ cancer risk and 40,000 animals per dose group (160,000 animals total) to determine a $1x10^{-6}$ cancer risk level. In order to achieve bioassay sample sizes and statistical power that would be directly comparable to expected human exposure, thousands of test animals would be required. Such expectations are, quite simply, unrealistic. Possibly this is why a preferred approach of proponents of this "novel theory" is to ignore its practical consequences.

Furthermore, although Bus stated that "*the dose makes the poison,*" low dose linear extrapolation from high dose (MTD bioassays) factors in differences between animals and humans. It is by design protective of sensitive groups accounting for differences amongst humans such as their life stages – children are more susceptible to genotoxic chemicals than adults as are fetuses in pregnant individuals.

The information obtained from low dose linear extrapolation is used not only to develop a cancer slope factor for increased cancer risk but also to develop regulatory toxicity values.

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[256] Wester, R., et al., "Glyphosate skin binding, absorption, residual tissue distribution and skin decontamination,"1991, Fundamental and Applied Toxicology, Vol. 16, pg. 725-732.

To dispense with such an important set of critical goals for the sake of embracing an unproven theory without overwhelming objective evidence to support it is more than merely dangerous. The consequences of such a decision would be far-reaching and highly unlikely to demonstrate positive outcomes for those most directly affected.

Consequently, it is both unrealistic and dangerous to human health to eliminate low dose linear extrapolation. To do so would mean the exposed human population would find itself serving as an experimental laboratory for evaluating chemical carcinogenicity. It is doubtful that many of our citizens would volunteer for such an experiment.

Glyphosate Biomonitoring and Dose Measurements

Exposure models have been used for about 20 years to estimate the exposure of professional operators during application of pesticides. How well these models predict actual exposure is primarily determined by the pharmacokinetic studies and assumptions upon which they are based (such as the dermal absorption rate). Biomonitoring and dosimetry data are combined with PK models to reconstruct or estimate the exposure dose. PK models simulate the ADME within a living system. It is, therefore, essential to have a good understanding of the pharmacokinetics to ensure a good estimate of the exposure dose.

As most Monsanto glyphosate formulations are "trade secrets" and unpublished, it is not a surprise that the pharmacokinetics (or ADME) of glyphosate are not well understood by the scientific community. However, it appears they are also not well understood by the herbicide manufacturers themselves. As Richard Garnett, the head of Monsanto's Regulatory Affairs Unit, wrote

> *"ADME has always been the weak link in our argument…we have not got rid of that problem."*[257]

When assumptions in a key Monsanto-contracted pharmacokinetics study were questioned by the Spanish regulators, Christophe Gustin wrote,

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[257] MONGLY02221147

Cancer Risk Assessment Results: Cancer Slope Factor (CSF) Basis

Cancer risk level is determined as a consequence of applying a standard set of equations as established by U.S. EPA to specific variables as shown in the equations below. This section presents cancer risk level calculations using the cancer slope factor (CSF) for glyphosate exposures to herbicide applicators and the general population as well as dietary exposure cancer risk to the U.S. general population

Cancer Risk for Herbicide Applicators and the General Population

The cancer risks introduced from dietary glyphosate within the general U.S. population as well as to exposed farmers and applicators is calculated based on determined glyphosate exposure doses and the frequency and duration of exposure to the carcinogen (glyphosate). This is then spread across the lifetime of the individual. The calculation uses the cancer slope factor and is determined by the following equation:

$$Cancer\ Risk = \frac{Exposure\ dose\ X\ risk\ factor\ (cancer(oral)\ slope\ factor) X\ years\ of\ exposure}{70\ years\ (lifetime)}$$

Cancer Risk to the U.S. General Population via Dietary Exposure

Glyphosate exposures occur through dietary consumption of glyphosate residue on food and in drinking water. As reported in Solomon, (2016),[266] the U.S. EPA Dietary Exposure Evaluation Model (DEEM) estimates the average exposure of the general population to glyphosate as 0.088 mg/kg bw/day from an estimate that ranged from 0.058 – 0.23 mg/kg bw/day.

Consequently, the upper range of the dietary exposure cancer risk level is determined as:

$$Cancer\ Risk = \frac{\left[0.23\frac{mg}{kg}per\ day\ X\ 0.00169\left(\frac{mg}{kg}per\ day\right)^{-1}\ X\ 70\ years\right]}{70\ years\ (lifetime)} = 3.9\ X\ 10^{-4}$$

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[266] Solomon, K., "Glyphosate in the general population and in applicators: a critical review of studies on exposures," 2016, Critical Reviews in Toxicology, Vol.46: sup 1, 21 -27, DOI: 10.1080/10408444.2016.1214678

Table 26 displays the range of cancer risk levels from typical dietary exposure.

Table 26

Cancer Risk Levels Based on the U.S. EPA DEEM Estimated Dietary and Drinking Water Exposure to Glyphosate

(US DEEM exposures from Solomon, 2016)

Exposure	Dietary Residue and Drinking Water Dose	Cancer Risk Level
Low	0.058 mg/kg bw/day	9.8×10^{-5}
Average	0.088 mg/kg bw/day	1.5×10^{-4}
High	0.23 mg/kg bw/day	3.9×10^{-4}

Acceptable risk levels have been generally recognized and applied in public health for decades. Levels exceeding the *de minimus* level are generally considered unsafe. In this context, the above levels of cancer risk to the general public are clearly unacceptable as the generally accepted *de minimus* benchmark level for cancer risk is 1×10^{-6} (one in one million). [267]

However, slightly higher levels of cancer risk are often used in public health and are based upon prudent regulatory judgement. Factors for consideration include the impacted population size, reasonable availability of technology to reduce risk, beneficial aspects of the ruling, etc. For example, chlorination of public water is extremely beneficial to reduce morbidity and mortality, but chlorination carries a low level risk of cancer due to the formation of trihalomethane contaminants in the water.

Thus, a *de minimus* benchmark increase to 1×10^{-5} (one in one hundred thousand) is occasionally applied in such a regulatory context, but the cancer risk levels shown in Table 26 far exceed this "enhanced" risk level as well.

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[267] Payne-Sturges, DC, "Personal exposure meets risk assessment: A comparison of measured and modeled exposures and risks in an urban community," 2004, Environmental Health Perspectives, Vol. 112(5), pg. 589-598.

Additionally, a study by Caldwell, et al., discusses the history and use of the *de minimus* benchmark $1x10^{-6}$ risk level for hazardous air pollutants (HAPs).[268] The Caldwell study, with two of the three authors affiliated with the U.S. EPA, states that "*much of the needed information and science policy judgments were previously compiled for U.S.EPA's proposed rulemaking under section 112(g) of the CAA and were supplemented by information from several other data sources…known, probable, or possible human carcinogens representing the upper-bound of a one in a million excess probability of contracting cancer over a lifetime of exposure. This benchmark was based on provisions of CAA sections 112(f) and 112 (c)(9) that allow source categories to be exempted from regulation and residual risk to be negligible when posing less than a one in a million ($1x10^{-6}$ risk level) lifetime risk to the most exposed individual.*"

Cancer Risk to Glyphosate Applicators

Also at risk are farmers and commercial applicators of glyphosate who are part of the agricultural industry and use glyphosate for weed management and in seeding and/or harvesting crops.

"The Agricultural Health Study" (AHS) is an ongoing cohort study which includes 89,000 farmers and their spouses from Iowa and North Carolina. The study is funded by the National Cancer Institute and the National Institute of Environmental Health Sciences and is partnered with the U.S. EPA and NIOSH.[269] In 1993, the AHS initial study[270] had a cohort of 20,235 private farmer and commercial applicators with 70.6 and 47.5 percent respectively reported to have applied herbicides. Their reported frequency of pesticide application is shown in Table 27.

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[268] Caldwell, JC, "Application of health information to hazardous air pollutants modeled in EPA's cumulative exposure project," 1998, Toxicology and Industrial Health, Vol. 14(3), pg. 429-454.

[269] Alavanja, M., et al., "The Agricultural Health Study," 1996, Environmental Health Perspectives, Vol. 104 (4), pg. 362 – 369. Retrieved from: https://aghealth.nih.gov/

[270] Id.

Table 27

Demographic Characteristics of "The Agricultural Health Study"[271] Cohort
(Total applicators n = 20,235)

Days per year personally mixed or applied pesticide	Percentage of applicators in each category of days per year	Years personally mixed/applied pesticide	Percentage of applicators in each year of application category
<5	13.5	<1	3.3
5 – 9	17.2	2 – 5	12.8
10 – 19	22.7	6 – 10	14.9
20 – 39	17.7	11 – 20	27.9
40 – 59	5.8	21 – 30	17.0
60 – 150	5.5	>30	9.1
>150	1.3	Unknown	15.0
Unknown	16.4		
Median days	**23.3**	**Median Years**	**15.4**

The days of pesticide application as well as the years of use can be used to determine the lifetime years of exposure as:

$$\left(\frac{\text{23.3 application days}}{\text{365 days}}\right) x\ 15.4\ \text{years} = 0.983\ years$$

Consequently, the risk of cancer, given the exposure levels to glyphosate amongst applicators, is calculated using the equation:

$$\text{Cancer Risk for Applicators} = [\text{applicator risk}] + [\text{dietary risk}]$$

---

[271] Id.

Derivation of Dermal Toxicity Values

The oral cancer slope factor of 0.00169 mg/kg/day was determined from dietary doses of glyphosate and requires an adjustment for absorption through the gastrointestinal tract. The oral slope factor can be converted to an absorbed slope factor, which can be applied to the dermal absorbed dose to calculate a cancer risk. The absorbed slope factor can be derived using methods provided in the Risk Assessment for Superfund: Volume 1, Human Health Evaluation Manual, Part A (EPA/540/1-89/002). The absorbed slope factor can be calculated as:

$$\frac{\text{Oral Slope Factor}}{\text{GI Absorption Factor}} = \text{Slope Factor}_{\text{absorbed}}$$

The default Gastro Intestinal (GI) absorption factor, which is being applied in the absence of a determined GI absorption factor for glyphosate in humans is 50%[272] - the default for semi-volatile organic compounds per EPA Region 4's Supplemental Guidance to RAGS:

$$\frac{0.00169}{0.5} = 0.00338 \; i.e., 3.38 \; X \; 10^{-3} \; \text{Slope Factor}_{\text{absorbed}}$$

Region 4 Bulletins Human Health Risk Assessment from November 1995.

For the highest exposure level reported among hand-held outdoor hydraulic nozzle applicators (see Tables 29 and 31), the cancer risk equation is:

---

[272] RAIS, "Toxicity Values" The Risk Assessment Information System. Retrieved from: https://rais.ornl.gov/tutorials/toxvals.html

Cancer Risk for Applicators = [applicator risk] + [dietary risk]

$$Cancer\ Risk = \frac{\left[4.635\frac{mg}{kg}per\ day\ X\ 0.00338\left(\frac{mg}{kg}per\ day\right)^{-1}\ X\ 0.983 years\right]+[0.23\ \frac{mg}{kg}per\ day\ X\ 0.00169\left(\frac{mg}{kg}per\ day\right)^{-1}\ X\ 70\ years]}{70\ years\ (lifetime)}$$

$$\frac{0.0154+0.0272}{70} = \frac{0.0426}{70} = 6.1\ X\ 10^{-4}$$

The resulting cancer risk level of **6.1 x 10^{-4}** is based on a mid-point dermal absorption rate of 10%[273] as shown in Tables 28 and 29.

The glyphosate exposure levels for applicators under various conditions were provided from Monsanto-derived exposure models and a realistic adjustment for glyphosate dermal absorption of 3%, 5% or 10% as shown in Tables 30 and 31.

It is important to note that exposure calculations should normally include the amount inhaled during herbicide spraying activity; however, the inhalation dose of 3.24 mg/day was excluded as the Inhalation Unit Risk (IUR) has not been established via inhalation chamber studies. *As a consequence, the risk values shown have been underestimated.*

---

[273] 10% Absorption was demonstrated in an unpublished Monsanto TNO study which is consistent with Wester et al. 1991, which revealed absorption range in primates of 4.4% - 22.6% with a midpoint value of 13.5%.

NO Study: Johan van Burgsteden, "In vitro percutaneous absorption study with [14C]-glyphosphate using viable rat skin membranes," June 14, 2002, Unaudited draft report V4478 (Tab 24).

Wester, R. et al. 1991. "Glyphosate skin binding, absorption, residual tissue distribution and skin decontamination". *Fundamental and Applied Toxicology* 16,725-732.

Tables 28 and 29 list the dose levels associated with each exposure scenario:

Table 28
Estimation of Spray Operator Exposure (Rotary Disc Atomizers)

Hand-held Outdoor Rotary Disc Atomizers	Dermal Exposure (Dose, mg/day)	Percentage Dermal Absorption (%)	Dermal Absorption (mg/day)	Exposure Level for a 60 Kg Operator, (mg/kg/day)
No gloves	1782	3	53.460	0.891
No gloves	1782	5	89.100	1.485
No gloves	1782	10	178.200	2.97
Gloves during mixing/loading	1766.1	3	52.983	0.883
Gloves during mixing/loading	1766.1	5	88.305	1.472
Gloves during mixing/loading	1766.1	10	176.610	2.944
Gloves at all times	1183.41	3	35.502	0.592
Gloves at all times	1183.41	5	59.171	0.986
Gloves at all times	1183.41	10	118.341	1.972
Boots, gloves, coveralls	357.21	3	10.716	0.179
Boots, gloves, coveralls	357.21	5	17.861	0.298
Boots, gloves, coveralls	357.21	10	35.721	0.595

Table 29
Estimation of Spray Operator Exposure (Hydraulic Nozzles)

Hand-held Outdoor Hydraulic Nozzles	Dermal Exposure (Dose, mg/day)	Percent Dermal Absorption (%)	Dermal Absorption (mg/day)	Exposure Level for a 60 Kg Operator, (mg/kg/day)
No gloves	2781	3	83.430	1.391
No gloves	2781	5	139.050	2.318
No gloves	2781	10	278.100	4.635
Gloves during mixing/loading	2755	3	82.650	1.378
Gloves during mixing/loading	2755	5	137.750	2.296
Gloves during mixing/loading	2755	10	275.500	4.592
Gloves at all times	1337.85	3	40.136	0.669
Gloves at all times	1337.85	5	66.893	1.115
Gloves at all times	1337.85	10	133.785	2.23
Boots, gloves, coveralls	507.6	3	15.228	0.254
Boots, gloves, coveralls	507.6	5	25.380	0.423
Boots, gloves, coveralls	507.6	10	50.760	0.846

Tables 30 and 31 list the calculated cancer risks associated with each exposure scenario:

Table 30
Cancer Risk Levels for Spray Operator Exposures (Rotary Disc Atomizers)

Hand-held Outdoor Rotary Disc Atomizers	Percentage Dermal Absorption (mg/day)	Exposure Level for a 60 kg Operator (mg/kg/day)	Cancer Risk Level	Including a Typical Average Dietary Risk Level of 1.5×10^{-4}
No gloves	3	0.891	4.2×10^{-5}	1.9×10^{-4}
No gloves	5	1.485	7.0×10^{-5}	2.2×10^{-4}
No gloves	10	2.97	1.4×10^{-4}	2.9×10^{-4}
Gloves during mixing/loading	3	0.883	4.2×10^{-5}	1.9×10^{-4}
Gloves during mixing/loading	5	1.472	7.0×10^{-5}	2.2×10^{-4}
Gloves during mixing/loading	10	2.944	1.4×10^{-4}	2.9×10^{-4}
Gloves at all times	3	0.592	2.8×10^{-5}	1.8×10^{-4}
Gloves at all times	5	0.986	4.7×10^{-5}	2.0×10^{-4}
Gloves at all times	10	1.972	9.3×10^{-5}	2.4×10^{-4}
Boots, gloves, coveralls	3	0.179	8.5×10^{-6}	1.6×10^{-4}
Boots, gloves, coveralls	5	0.298	1.4×10^{-5}	1.6×10^{-4}
Boots, gloves, coveralls	10	0.595	2.8×10^{-5}	1.8×10^{-4}

Table 31

Cancer Risk Levels for Spray Operator Exposures (Hydraulic Nozzles)

Hand-held Outdoor Hydraulic Nozzles	Percentage Dermal Absorption (mg/day)	Exposure Level for a 60 kg Operator, (mg/kg/day)	Cancer Risk Level	Including a Dietary Risk Level of 1.5×10^{-4}
No gloves	3	1.391	6.6×10^{-5}	2.1×10^{-4}
No gloves	5	2.318	1.1×10^{-4}	2.6×10^{-4}
No gloves	10	4.635	2.1×10^{-4}	3.7×10^{-4}
Gloves during mixing/loading	3	1.378	6.5×10^{-5}	2.1×10^{-4}
Gloves during mixing/loading	5	2.296	1.1×10^{-4}	2.6×10^{-4}
Gloves during mixing/loading	10	4.592	2.3×10^{-4}	3.7×10^{-4}
Gloves at all times	3	0.669	3.2×10^{-5}	1.8×10^{-4}
Gloves at all times	5	1.115	5.3×10^{-5}	2.0×10^{-4}
Gloves at all times	10	2.23	1.1×10^{-4}	2.5×10^{-4}
Boots, gloves, coveralls	3	0.254	1.2×10^{-5}	1.6×10^{-4}
Boots, gloves, coveralls	5	0.423	2.0×10^{-5}	1.7×10^{-4}
Boots, gloves, coveralls	10	0.846	4.0×10^{-5}	1.9×10^{-4}

Toxicological Conclusions

Toxicologists cannot assume a position of advocacy. A scientifically credible expert opinion is based solely on objective, reliable evidence. Additionally, analysis must be performed without deviation from the prescribed methodology. Weight of evidence must take all possible factors into account before reaching any conclusions. A strong attempt has been made to apply those principles throughout this assessment.

Based on the totality of evidence available at this time, it is my opinion to reasonable toxicological certainty that the recent IARC classification of glyphosate as a Level 2A carcinogen is appropriate. Additionally, it is my opinion to reasonable toxicological certainty that some formulations of glyphosate have greater potential for carcinogenic health risks then calculated above based on enhanced absorption by adjuvants used in the products. Glyphosate has been demonstrated to induce (but may not be limited to) lymphopoietic malignancies as supported by multiple, independent chronic dietary animal studies as well as the body of human epidemiological literature as assessed by IARC.

Mr. Dewayne Johnson was diagnosed with mycosis fungoides, an infrequently encountered, rare T-cell lymphoma, approximately 2.25 years following his frequent mixing and application of glyphosate/co-formulants for the Benicia Unified School District. His absorbed dose of glyphosate was within the range of that encountered within the generally accepted toxicological and epidemiological literature among hydraulic applicators. Mr. Johnson's medical history, family history, genetic predisposition, prior occupational chemical exposures or lifestyle risk factors do not reveal any known risk factors for lymphoma. Based on the documented and inherent properties of glyphosate to produce lymphoma in animal studies as well as the results of statistically significant human epidemiological studies, I am certain to reasonable toxicological certainty that Mr. Johnson's glyphosate exposures induced or significantly contributed to the onset of his T-cell lymphoma (mycosis fungoides).

William R. Sawyer, Ph.D., D-ABFM

Chief Toxicologist

Exhibit 6

reflect a self-serving attempt to characterize my findings as biased and/or unreliable.

b) **Methodological Relevancy of Human Exposure in Applicators:** Defendant has expressed multiple allegations that the methodology I applied to perform my assessment was flawed or inappropriate. In undertaking a risk assessment to determine if the lymphomas shown in animal studies were relevant to human exposure in applicators,[52] I applied the very methodologies used by the US EPA and California and scrupulously documented each step taken. For example, under Prop 65, a company is required to warn that its product causes cancer if the level of exposure in users exceeds the no-significant-risk-level ("NSRL") which is defined as *"one excess case of cancer per 100,000 people exposed."* To calculate the NSRL for glyphosate, California uses animal carcinogenicity data to extrapolate to humans and applies the US EPA's Benchmark Dose Software (BMDS).[53] This is the exact same software I utilized in my assessment and all steps were meticulously documented in my report. Additionally, US EPA applies a standard of one excess case in one million (not 100,000) to determine whether a product is safe. In the current matter, my cancer risk calculations of workers in the Agricultural Health Study ranged from 4.0 to 230 times above the California NSRL for spray operator exposures (using hydraulic nozzles similar to those used by Mr. Johnson) at 10% dermal absorption.[54] Defendant's assertions that this assessment methodology is "somehow" incorrect or inappropriate is highly erroneous and not supported by the objective evidence.

To further clarify this matter, I fully explained why I used the lymphoma findings in Wood (2009) to calculate this risk by stating, among other things, *"Following US EPA methodology, the Wood, et al., 2009b study was chosen as the primary study to derive an exposure cancer slope factor for glyphosate since it is the most sensitive study and meets and exceeds the statistical testing requirements."* I also noted in deposition that *"the trend test showed a highly significant relationship"*

---

[52] Sawyer Dep. at 430:5-12 *("This numerical dose calculation that I made was not for Mr. Johnson, but for applicators in general to determine their cancer risk. I cannot calculate a dose for a single individual and apply it to a slope factor for cancer risk. That's not how it's designed. It's for -- the cancer slope factors are used in the community or population, not for a single individual.")*

[53] California, however, was limited to animal studies considered by IARC whereas my assessment included a broader database of animal studies to consider.

[54] William Sawyer, "Toxicological Assessment of Dewayne Johnson and Toxicological Risk Assessment of Glyphosate and Roundup and Ranger PRO Formulations," December 21, 2017, page 154, Table 31.

with lymphomas and glyphosate. It should be further noted that the US EPA methodology requires these two primary factors in selection of animal studies.

c) **Animal Models vs. Human Models:** Defendant has expressed contentions that because animal models are not "exact" representations of human models, they are somehow inappropriate or inapplicable in the current matter. It is a ridiculous question to ask whether a mouse model is an "exact" model for humans. As I noted in deposition, "*That was my issue with your question, where I said do you mean modeling or exact modeling. Because we're never going to have exact modeling with an animal, but certainly modeling is done all the time.*" In the current matter, one major difference is that the mice were exposed to pure glyphosate whereas humans are exposed to "*formulations of glyphosate [that] have greater potential for carcinogenic health risks then calculated above based on enhanced absorption by adjuvants used in the products.*" In view of the biological differences, the formulaic variations, the ethical considerations of using human subjects in such tests and many other practical issues, presuming that animal models must be "exact" models as applicable to humans in the current matter is mere wishful thinking by defendant and will never be satisfied.

d) **Defendant's Rejection of Cancer Risk Calculations:** The cancer risk calculation pointed to by Defendant is not directly applicable to Mr. Johnson nor have I said that it was. The risk calculations I performed in my report demonstrate that the exposure of glyphosate applicators greatly exceeds any *de minimus* risk level based on animal models. My calculation showed a high end exposure cancer risk of 6.1×10^{-4} (61 cancers per 100,000). This is a considerable risk level by any standard.

To be clear on this point: I explicitly stated *"...the glyphosate exposure levels for applicators under various conditions were provided from Monsanto-derived exposure models and a realistic adjustment for glyphosate dermal absorption of 3%, 5% or 10% as shown in Tables 30 and 31."* I then further noted that these calculations underestimate exposure because they do not factor in inhalation. In fact, the conservative risk levels I presented also underestimate the risk by a factor of **4.5** because they are based on the assumption, promoted by Monsanto, that glyphosate is primarily excreted through the urine (used as a basis of the dose level). If we adjust the risk level accordingly, we find that the actual risk level is

William R. Sawyer, Ph.D.

SWORN TO and subscribed before me this

30 day of ~~January~~ March, 2018.

NOTARY PUBLIC

My commission expires Feb. 23, 2020

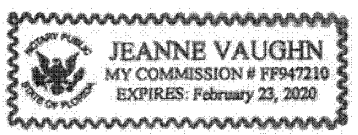

Exhibit 7

From:	Hilmert, James M.
To:	Krajewski, Sarah A.
Subject:	FW: Sawyer Nabhan Reliance Lists
Date:	Sunday, July 22, 2018 3:12:00 PM
Attachments:	Third Supplemental Reliance List of Dr Nabhan.pdf Supplemental Reliance list of sawyer.pdf Nabhan sup reliance.pdf Nabhan report FINAL signed.pdf Nabhan Supplemental Report.pdf Johnson Dewayne - Toxicological Assessment 12-22-2017 Sawyer.pdf

---

From: Jeffrey Travers [mailto:JTravers@millerfirmllc.com]
Sent: Friday, May 25, 2018 3:14 PM
To: 'JMalone@fbm.com' <JMalone@fbm.com>; 'Chris.Miller@huschblackwell.com' <Chris.Miller@huschblackwell.com>; 'Greg.Minana@huschblackwell.com' <Greg.Minana@huschblackwell.com>; 'Erik.Hansell@huschblackwell.com' <Erik.Hansell@huschblackwell.com>; 'Savinelli,' <Dominique.Savinelli@huschblackwell.com>; 'Jordan.Ault@huschblackwell.com' <Jordan.Ault@huschblackwell.com>; 'dfowler@hollingsworthllp.com' <dfowler@hollingsworthllp.com>; 'GChernack@Hollingsworthllp.com' <GChernack@Hollingsworthllp.com>; 'bcovington@Hollingsworthllp.com' <bcovington@Hollingsworthllp.com>; 'hjohnson@Hollingsworthllp.com' <hjohnson@Hollingsworthllp.com>; 'edowd@dowdbennett.com' <edowd@dowdbennett.com>; 'edowd@dowdbennett.com' <edowd@dowdbennett.com>; Hilmert, James M. <JHilmert@winston.com>; 'Sandra Edwards' <sedwards@fbm.com>; 'Griffis, Kirby T.' <KGriffis@Hollingsworthllp.com>; 'Cople, William J.' <WCople@Hollingsworthllp.com>; 'Hollingsworth, Grant' <ghollingsworth@Hollingsworthllp.com>; 'Salek, Stephanie' <SSalek@Hollingsworthllp.com>; 'Kalas, John' <JKalas@Hollingsworthllp.com>
Cc: Michael Miller <MMiller@millerfirmllc.com>; Timothy Litzenburg <TLitzenburg@MillerFirmLLC.com>; 'James Corrigan' <Corrigan@osclaw.com>; Jeff Seldomridge <jseldomridge@MillerFirmLLC.com>; Tayjes Shah <TShah@MillerFirmLLC.com>; Curtis Hoke <choke@MillerFirmLLC.com>
Subject: Sawyer Nabhan Reliance Lists

Counsel Please find the reliance lists for Dr. Nabhan and Dr. Sawyer. They are relying on all documents previously identified at deposition and in reports as well as the supplemental reliance lists attached.

From: Jeffrey Travers
Sent: Tuesday, May 15, 2018 5:34 PM
To: 'JMalone@fbm.com' <JMalone@fbm.com>; 'Chris.Miller@huschblackwell.com' <Chris.Miller@huschblackwell.com>; 'Greg.Minana@huschblackwell.com' <Greg.Minana@huschblackwell.com>; 'Erik.Hansell@huschblackwell.com' <Erik.Hansell@huschblackwell.com>; 'Savinelli,' <Dominique.Savinelli@huschblackwell.com>; 'Jordan.Ault@huschblackwell.com' <Jordan.Ault@huschblackwell.com>; 'dfowler@hollingsworthllp.com' <dfowler@hollingsworthllp.com>; 'GChernack@Hollingsworthllp.com' <GChernack@Hollingsworthllp.com>;

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Cc: Michael Miller <MMiller@millerfirmllc.com>; Timothy Litzenburg <TLitzenburg@MillerFirmLLC.com>; 'James Corrigan' <Corrigan@osclaw.com>; Jeff Seldomridge <jseldomridge@MillerFirmLLC.com>; Tayjes Shah <TShah@MillerFirmLLC.com>; Curtis Hoke <choke@MillerFirmLLC.com>
Subject: Benbrook Reliance List

Counsel,

Attached please find a supplemental reliance list for Dr. Benbrook. I've also attached the 2.2.18 supplemental reliance list previously served on the Monsanto defendants. His initial reliance list was appended to his report.

Jeffrey A. Travers, Esq.
The Miller Firm, LLC
108 Railroad Avenue
Orange, VA 22960
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From: Jeffrey Travers
Sent: Friday, February 02, 2018 6:13 PM
To: 'JMalone@fbm.com' <JMalone@fbm.com>; Timothy Litzenburg <TLitzenburg@MillerFirmLLC.com>; Curtis Hoke <choke@MillerFirmLLC.com>; Michael Miller <MMiller@millerfirmllc.com>
Cc: 'Sandra Edwards' <sedwards@fbm.com>; 'Griffis, Kirby T.' <KGriffis@Hollingsworthllp.com>; 'Cople, William J.' <WCople@Hollingsworthllp.com>; 'Hollingsworth, Grant' <ghollingsworth@Hollingsworthllp.com>; 'Salek, Stephanie' <SSalek@Hollingsworthllp.com>; 'Kalas, John' <JKalas@Hollingsworthllp.com>
Subject: Benbrook Reliance List

Counsel,

Attached please find a supplemental reliance list for Dr. Benbrook.

Jeffrey A. Travers, Esq.

The Miller Firm, LLC
108 Railroad Avenue
Orange, VA 22960
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Exhibit 8

SUPERIOR COURT OF THE STATE OF CALIFORNIA

COUNTY OF SAN FRANCISCO

DEWAYNE JOHNSON,

Plaintiff,

vs. Case No. CGC-16-550128

MONSANTO COMPANY, et al.,

Defendants.

_____/

Proceedings held on Thursday, June 28, 2018, Volume 4, Afternoon Session, before the Honorable Suzanne R. Bolanos, at 1:43 p.m.

REPORTED BY:

LESLIE ROCKWOOD ROSAS, RPR, CSR 3462

JOB No. 2950272B

PAGES 1181 - 1275

litigated, and it was lost. 14:04

In fact, the only reason why it wasn't listed in 14:04
2015 was because Monsanto filed a lawsuit in seeking to stop 14:04
it, which was ultimately dismissed on the pleadings, and then 14:04
affirmed by the California Court of Appeals. 14:04

So while there were these machinations to prevent 14:04
the listing, it was all meritless, and it lost. And the 14:05
Court's rulings on the -- I mean, they weren't mean, but they 14:05
said this, as a matter of law, is incorrect. 14:05

So while you can file a lawsuit to delay a listing, 14:05
it was first put on Monsanto's radar in 2015, when Mr. Johnson 14:05
had reached out to them about whether or not this stuff causes 14:05
cancer. 14:05

And it goes directly to punitive damages. Because 14:05
if they did know this information, which we know they did, and 14:05
we can prove that, and they didn't disclose that to him, that 14:05
is reckless disregard to human life. 14:05

Again, your Honor, we stand by our argument. I 14:05
think this was an important issue, one of which -- that's it,
your Honor. 14:05

THE COURT: Okay. So I do find the listing of 14:05
Proposition 65 -- the glyphosate listing under Prop 65 is more 14:05
prejudicial than probative and not relevant to the issues in 14:05
this case that the jury is going to have to decide. 14:06

So for all of those reasons, I'm going to grant 14:06

Defendants' Motion Number 27 to exclude any evidence relating to Prop 65.

MR. WISNER: Your Honor, the ruling is accepted. I just want to clarify, if they open the door by saying no regulatory agency has embraced IARC, I have every right to re-raise this issue -- I have every intent to re-raise this issue, because that would be a falsehood to the jury. And this would be clearly rebuttal evidence.

So I just want to leave that flag up that I think they're going to open this door. So we might be back at this issue later.

THE COURT: Defendants, do you wish to respond?

MR. GRIFFIS: We hear his admonition, your Honor.

THE COURT: Okay. All right. Now, Mr. Wisner you said there were two documents in the deposition designation exhibits that you wanted to discuss.

MR. WISNER: Do you have this binder, your Honor?

THE COURT: I do.

MR. WISNER: Okay. Great.

I first one, your Honor, is Goldstein 10. Exhibit 10.

THE COURT: Goldstein Exhibit 10. Uh-huh.

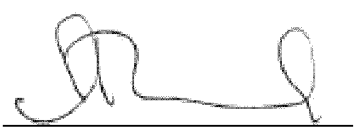
MR. WISNER: And this is an email exchange between a man by the name of Bruce Chassy and Daniel Goldstein. Again, Daniel Goldstein is a medical and product safety director at

REPORTER'S CERTIFICATE

I certify that the proceedings in the within-titled cause were taken at the time and place herein named; that the proceedings were reported by me, a duly Certified Shorthand Reporter of the State of California authorized to administer oaths and affirmations, and said proceedings were thereafter transcribed into typewriting.

I further certify that I am not of counsel or Attorney for either or any of the parties to said Proceedings, not in any way interested in the outcome of the cause named in said proceedings.

IN WITNESS WHEREOF, I have hereunto set my hand: June 28th, 2015.



Leslie Rockwood Rosas
Certified Shorthand Reporter
State of California
Certificate No. 3462

Exhibit 9

SUPERIOR COURT OF THE STATE OF CALIFORNIA

COUNTY OF SAN FRANCISCO

DEWAYNE JOHNSON,

Plaintiff,

vs. Case No. CGC-16-550128

MONSANTO COMPANY, et al.,

Defendants.

_____/

Proceedings held on Tuesday, July 10, 2018, Volume 6, before the Honorable Suzanne R. Bolanos, at 9:24 a.m.

REPORTED BY:

LESLIE ROCKWOOD ROSAS, RPR, CSR 3462

Job No. 2958708

PAGES 1534 - 1597

Honor.

THE COURT: Except for the speculation, right. The speculation's out. Everything else --

MR. GRIFFIS: I'm sorry, which page and line is that? 09:44:17

THE COURT: That is page 59, 17 through 22.

The rest may come in. And with regard to Prop 65, again, because the process was ministerial that led to the listing of glyphosate on the Proposition 65 list, for all the reasons I stated earlier, that's still out. 09:44:41

With regard to the no significant risk level, I'll hear your argument on that later, when we discuss -- when we have a, sort of, broader discussion about all of the foreign regulatory agencies. 09:44:56

But the no significant risk level process in labeling is very -- how shall we say? Is very unique. And I'm not convinced that that process is going to be helpful or probative in this situation, but I'll hear your argument on it. 09:45:20

But I'm somewhat familiar with that process from other litigation, and there -- it's problematic. But we'll discuss it when we talk about the other foreign regulatory agencies.

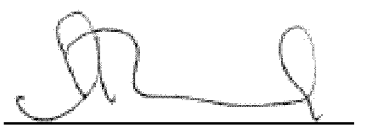
(Interruption in proceedings.) 09:45:37

REPORTER'S CERTIFICATE

I certify that the proceedings in the within-titled cause were taken at the time and place herein named; that the proceedings were reported by me, a duly Certified Shorthand Reporter of the State of California authorized to administer oaths and affirmations, and said proceedings were thereafter transcribed into typewriting.

I further certify that I am not of counsel or Attorney for either or any of the parties to said Proceedings, not in any way interested in the outcome of the cause named in said proceedings.

IN WITNESS WHEREOF, I have hereunto set my hand: July 10th, 2018.



Leslie Rockwood Rosas
Certified Shorthand Reporter
State of California
Certificate No. 3462

Exhibit 10

SUPERIOR COURT OF THE STATE OF CALIFORNIA

COUNTY OF SAN FRANCISCO

DEWAYNE JOHNSON,

Plaintiff,

vs. Case No. CGC-16-550128

MONSANTO COMPANY,

Defendant.

_____/

Reporter's Transcript of Proceedings

San Francisco, California

Wednesday, July 11, 2018

Volume 7

Reported by:

SHEILA PHAM

CSR NO. 13293

Pages 1598 - 1648

probative.

Here, IARC has reached an opinion. The State of California has said, you know, essentially, "If IARC acts, we're also going to call it a carcinogen." And it's directly relevant. The question of whether it's more prejudicial than probative is something that, you know, why Prop 65 may come out.

But with respect to the actual judicial notice statute, I mean, it says it shall be taken if it's a statutory law. And, you know, certainly, we can look into, and we'll file something more formally and maybe we can bring it up at that time with respect to relevance versus -- prejudicial versus probative.

But the fact that IARC has acted, California had implemented a statute that says, "If IARC acts, the State of California will find something as a carcinogen" is clearly relevant to this case. The only question is whether or not it's more prejudicial than probative.

THE COURT: Well, I'll look at your briefing if you wish to file something on that. At this time, I'm not going to take judicial notice on that Labor Code section because I don't think it's relevant. And with regard to the ministerial Prop 65 listing, it is more prejudicial than probative and it will result in an undue consumption of time. But I'll look at your

briefing if you wish to elaborate further on that.

And, you know, with regard to Dr. Portier, I think the way that this usually works with the experts is: The expert will write a report and/or give an opinion, and then we'll discuss what it is he's relied on in reaching that opinion. And then the opposing side cross-examines him and probes and makes sure that they are aware of everything that the expert has reviewed or relied on. Usually, that's the way it works.

So I would expect that if, in fact, Dr. Portier examined, relied on, reviewed the NSRL listings in reaching his opinion that that would have come out in his report or at deposition. So...

MR. DICKENS: Understood, Your Honor. And for the record, we'll also say -- you know, you cited to the evidence section with respect to cross-examination of witnesses. We're also going to raise the issue that foreign regulatory agencies, you know, their decisions are more prejudicial than probative as well and would be an undue waste of the jury and the Court's time.

Because, once again, you know, with respect to -- there's evidence in this case with respect to those foreign agencies that have banned foreign regulatory decisions, and, you know, once again, some other aspects with respect to cities and whatnot. That if their

I, the undersigned, a Certified Shorthand Reporter of the State of California, do hereby certify:

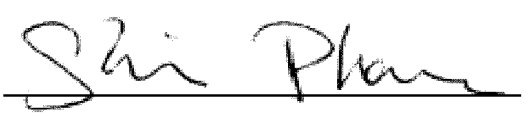
That the foregoing proceedings were taken before me at the time and place herein set forth; that any witnesses in the foregoing proceedings, prior to testifying, were duly sworn; that a record of the proceedings was made by me using machine shorthand which was thereafter transcribed under my direction; that the foregoing transcript is a true record of the testimony given.

Further, that if the foregoing pertains to the original transcript of a deposition in a Federal Case, before completion of the proceedings, review of the transcript [ ] was [ ] was not requested.

I further certify that I am neither financially interested in the action nor a relative or employee of any attorney or party to this action.

IN WITNESS WHEREOF, I have this date subscribed my name.

Dated: 07/12/2018



Sheila Pham

CSR No. 13293

Exhibit 11

SUPERIOR COURT OF THE STATE OF CALIFORNIA

COUNTY OF SAN FRANCISCO

DEWAYNE JOHNSON,

Plaintiff,

vs. Case No. CGC-16-550128

MONSANTO COMPANY, et al.,

Defendants.

_____/

Proceedings held on Tuesday, July 17, 2018, Volume 11, Afternoon Session, before the Honorable Suzanne R. Bolanos, at 1:23 p.m.

REPORTED BY:

LESLIE ROCKWOOD ROSAS, RPR, CSR 3462

Job No. 2965314B

Pages 2465 - 2511

talking about Prop 65, this is as close as we can get, but it's pretty relevant.

THE COURT: Well, Mr. Griffis.

MR. GRIFFIS: Yes, your Honor.

THE COURT: You know, Mr. Wisner makes a point. They're trying to show that Monsanto was concerned about the negative effect on sales of the evaluation by IARC that their product was carcinogenic. So we've already discussed why Prop 65 is misleading and confusing. But what would your proposal be with regard to this issue and this witness' testimony on the negative impact on sales? 13:36:42 13:37:19

MR. GRIFFIS: I mean, the think the fact is that the exclusion of this piece of evidence about scienter that they would like to put in is a Prop 65-piece. It's all about Prop 65. I don't think there's a way to extricate it, and Mr. Wisner's desire to have it and the relevance of such things, you know, in a world in which that wasn't Prop 65 isn't the issue here. 13:37:43

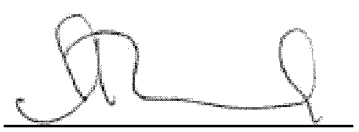
It's the -- it's that this is squarely in the middle of the lane of this motion in limine. It's all about Proposition 65. It's what prompted all of the things that he's talking about here. It's the -- it's what they were talking about when they said, "the European insanity has made it to California." And these edits substitute IARC for that, which is not what really 13:38:02 13:38:21

REPORTER'S CERTIFICATE

I certify that the proceedings in the within-titled cause were taken at the time and place herein named; that the proceedings were reported by me, a duly Certified Shorthand Reporter of the State of California authorized to administer oaths and affirmations, and said proceedings were thereafter transcribed into typewriting.

I further certify that I am not of counsel or Attorney for either or any of the parties to said Proceedings, not in any way interested in the outcome of the cause named in said proceedings.

IN WITNESS WHEREOF, I have hereunto set my hand: July 17th, 2018.



Leslie Rockwood Rosas
Certified Shorthand Reporter
State of California
Certificate No. 3462

Exhibit 12

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On September 4, 2015, the Office of Environmental Health Hazard Assessment (OEHHA) issued a Notice of Intent to List[1] tetrachlorvinphos, parathion, malathion, and glyphosate under Proposition 65[2] as chemicals known to the state to cause cancer. The September 4 notice initiated a 30-day public comment period that was scheduled to close on October 5, 2015. OEHHA extended the public comment period for parathion, malathion, and glyphosate to October 20, 2015 after receiving requests for an extension. The Monsanto Company, the Joint Glyphosate Task Force, and the Agricultural Council of California requested an extension of the comment period for glyphosate, and the Agricultural Council of California requested an extension of the comment period for parathion and malathion.

Effective October 1, 2015, the process by which OEHHA lists chemicals and substances via the Labor Code listing mechanism was adopted in regulation at Title 27, California Code of Regulations, section 25904[3]. Section 25904 outlines OEHHA's existing procedures for Labor Code listings and incorporates relevant court decisions interpreting the Proposition 65 statute as it applies to Labor Code listings[4]. In accordance with OEHHA's longstanding practice and now required by that regulation, OEHHA provided an opportunity for the public to comment on whether the chemicals identified in the Notice of Intent to List (NOIL) meet the requirements for listing as

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[1] Notice of Intent to List Chemicals by the Labor Code mechanism: Tetrachlorvinphos, Parathion, Malathion, Glyphosate, available at http://www.oehha.ca.gov/prop65/CRNR_notices/admin_listing/intent_to_list/090415LCset27.html.

[2] The Safe Drinking Water and Toxic Enforcement Act of 1986 (codified at Health and Safety Code section 25249.5 et seq.), hereinafter referred to as "Proposition 65" or "the Act."

[3] All further references are to sections of Title 27 of the California Code of Regulations unless otherwise indicated.

[4] Specifically, as required by *Styrene Information and Research Center v Office of Environmental Health Hazard Assessment* (2012) 210 Cal.App.4th 1082, Section 25904 excludes from listing any chemicals or substances classified by the International Agency for Research on Cancer (IARC) as Group 2B based on limited evidence of carcinogenicity in experimental animals. Additionally, in the Second Interim Order of the *Sierra Club v Schwarzenegger (Brown)* case (Alameda County Superior Court Case No. RG07356881), the court ordered OEHHA to list chemicals when IARC concludes there is sufficient evidence of carcinogenicity in humans or animals for that chemical or substance, regardless of whether the final IARC Monograph on the substance or chemical has been published. (See also *California Chamber of Commerce v Brown* (2011) 196 Cal.App.4th 233 [clarifying that Labor Code listings are ministerial acts required by statute].)

the pending litigation with Monsanto Company. OEHHA provides the following brief response without waiving any further responses that it may raise in the litigation.

As OEHHA noted in its Memorandum of Points and Authorities . . . "the Labor Code listing mechanism does not empower IARC to do anything, much less legislate: it merely provides a mechanism by which OEHHA can make the most of its scarce resources by relying on specific scientific determinations made by an expert agency, in a process that the voters explicitly considered and approved and that contains a number of effective safeguards. . . . As the California Supreme Court noted in *Kugler v Yocum* (1968) 69 Cal.2d 371, there is simply no delegation of legislative power when a statute merely relies on an existing authoritative source to exercise its independent authority to determine a technical factual issue. (Id. at p. 379, fn.6.) 'Nor does the fact that a third party, whether private or governmental, performs some role in the application and implementation of an established legislative scheme render the legislation invalid as an unlawful delegation.'" (Id. at pp. 379-380.) (Brief at p. 2)

î ò Ý±³ ³ »² ¬æBecause there are no safeguards on IARC's processes, OEHHA's unwillingness even to review IARC's scientific determinations and consider comments on them only furthers the injury to the democratic process and to the use of sound science in regulatory decision-making. OEHHA's unwillingness to consider scientific comments overlooks the significant limitations and errors in IARC's process in the misclassification of glyphosate. (ï ï , ï í ôï è)

Î »- ° ±² - »: Pursuant to the Labor Code mechanism, OEHHA is required by statute and case law to list the chemical based on IARC's identification[12] as long as IARC has classified the chemical as having sufficient animal or human evidence.[13] OEHHA cannot decline to list a chemical that meets the criteria for listing, simply based on comments that disagree with IARC's scientific evaluation.

OEHHA disagrees that there are no safeguards on IARC's processes. IARC is an internationally known, expert body dedicated to the identification of cancer hazards that is part of the United Nations World Health Organization. The United States was a founding member and remains a participating member of IARC. The process by which IARC makes its scientific determinations is well-documented and publicly available [14]. A summary of IARC's scientific review process as it was applied to the

[12] *California Chamber of Commerce v Brown* (2011) Cal.App. 4th 233
[13] *SIRC v OEHHA* (2012) 210 Cal.App.4th 1082
[14] See description of IARC's process here: http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf

OEHHA intends to propose a safe harbor level for glyphosate concurrent with the listing of the chemical.

IARC MONOGRAPH

çò Ý±³ ³ »² ¬æThere are errors in IARC's process that resulted in the misclassification of glyphosate. (ï ôî ôí ôéôï ëôï êôï èôï çôî î ôí í) During the IARC review, relevant scientific data were excluded and/or dismissed as not contributing to reach the conclusion, such as the recently completed review conducted on behalf of the European Union, as well as many animal studies. (î ôêôéôï ï ôï î ôï í ôï ëôï êôï éôî î ô í í ôí ì) IARC used studies that do not meet standards set by the Organization for Economic Co-operation and Development (OECD) guidelines. IARC's monograph does not present new research or data. IARC's classification does not establish a link between glyphosate and an increase in cancer. (í í)

Another commenter (ç) supports the listing of glyphosate and states that glyphosate is genotoxic and an inducer of oxidative stress – mechanisms that can lead to carcinogenesis.

Î »- ° ±² - »æThese comments are related to the underlying scientific basis for the classification of a chemical by IARC as causing cancer. As explained in response to previous comments, Labor Code listings are required where IARC has determined that there is sufficient evidence of carcinogenicity in experimental animals or humans. OEHHA does not review the scientific basis for IARC's decision, other than to determine that IARC concluded that there was "sufficient" evidence in animals or humans.[22] OEHHA will therefore not comment on the issues raised here.

ï ðòÝ±³ ³ »² ¬æThe IARC classification is based on a limited hazard identification approach and does not consider real-world use and exposure, which is a key element of the thorough risk assessments conducted by regulators. (ï ôí ôéôï êôî î)

Î »- ° ±² - »æConsiderations of the levels of actual human exposure to a chemical listed under Proposition 65 from a particular product, including determinations of whether a warning is required under Proposition 65, are dealt with in a later stage of

[22] Health & Safety Code, section 25249.8 (a); Title 27, Cal. Code Regs. section 25904. In *AFL-CIO v Deukmejian* (1989) 212 Cal.App. 3d 425, the court stated that OEHHA has a mandatory duty to list any chemical for which IARC has concluded there is sufficient evidence of cancer in humans or animals. Also, in *California Chamber of Commerce v Brown (2011)* Cal.App. 4th 233 at 260, the court concluded that "the absence of independent evaluation by OEHHA or the state's experts does not render the Labor Code reference method set forth in subdivision(a) an anomaly within the statutory scheme".

Assessment] is reviewing the IARC report, to seek a second opinion on its claims. (ï çôí é)

Î »- ° ±² - »: The underlying scientific evidence on which IARC relied for its identification is set out in the IARC Monograph. OEHHA does not have the discretion to disregard the IARC findings in favor of the conclusions of other regulatory institutions. The other programs and groups referenced by the commenters are not identified by Proposition 65 under the Labor Code mechanism as sources for identification of chemicals that must be listed as known to cause cancer. As discussed in earlier responses to comments, Proposition 65, through its incorporation of the relevant subsection of the Labor Code, has designated IARC as a scientific authority for the identification of carcinogenic chemicals for purposes of Proposition 65.

Health and Safety Code section 25249.8 expressly states that the Proposition 65 list must contain "at a minimum" those substances identified by reference in Labor Code sections 6382(b)(1) and (d). Health and Safety Code section 25249.8(a), provides that a chemical or substance shall be included on the list of chemicals known to the state to cause cancer if it is a chemical or substance identified by reference in Labor Code section 6382(b)(1), as causing cancer. This provision has been part of Proposition 65 since it was approved by California voters in 1986. The Labor Code section cited in the statute specifically identifies IARC by name.

While OEHHA is aware that there are differences in how other regulatory agencies and experts have evaluated the scientific evidence of carcinogenicity for glyphosate, OEHHA does not have the discretion to disregard the IARC findings in favor of the conclusions of other regulatory authorities or independent experts. See also response to comment 1.

SAFETY OF CHEMICAL

ï î ðÝ±³ ³ »² ¬¨A number of commenters either raised general concerns (including î éô ì ï ôì í ôì ì ôì ëôì ê) about the safety of glyphosate or stated that there were no safety concerns (including î é and î ç).

Scientific data on glyphosate consistently demonstrates no evidence of developmental and reproductive toxicity, genotoxicity, endocrine disruption potential, neurotoxicity and immunotoxicity. (î í) When used as labeled, glyphosate is not potentially hazardous to human health and there is no credible evidence that any adverse or chronic risk to human health may occur from exposure at occupational levels. (î ôëôêôéôî î ôí ì)

Exhibit 13

SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF SAN FRANCISCO

CASE NO.: CGC-16-550128

DEWAYNE JOHNSON,

Plaintiff,

vs.

MONSANTO COMPANY,

Defendant.

_____/

CONFIDENTIAL

Continued Videotaped Deposition of WILLIAM SAWYER, PH.D., taken at 1451 Middle Gulf Drive, Sanibel, Florida, commencing at 8:09 a.m. - 5:57 p.m., Tuesday, February 27, 2018, before Tracie Thompson, RMR, CRR, CLR, Registered Merit Reporter, Certified Realtime Reporter, Certified LiveNote Reporter.

JOB No. 2820385

PAGES 265 - 557

was in the -- a little less than the average of exposure of the like 26,000 applicators. And therefore, he qualified as an exposed applicator in the human epidemiologic studies that were conducted.

Now, this numerical dose calculation that I made was not for Mr. Johnson, but for applicators in general to determine their cancer risk. I cannot calculate a dose for a single individual and apply it to a slope factor for cancer risk. That's not how it's designed. It's for -- the cancer slope factors are used in the community or population, not for a single individual. And you know that.

Q You understand the Acquavella 2004 study was a urinary biomonitoring study in applicators, right?

A Yes.

Q It's your opinion that fecal excretion of the glyphosate is four times that of the urinary excretion of glyphosate, right?

A Yes. So the doses of those individuals are actually higher than reported, much higher than reported.

Q So you could have multiplied the urinary excretion by five to get the dose, right, in Acquavella?

A Yes.

Q Dr. Sawyer, you agree that you used the cancer slope factor from your Woodland study to calculate your applicator risk, right?

A For applicators, plural. For a group of them, not just one.

Q Understood. And you've been very candid that the cancer slope factors are not to be used for any individual's causations, right?

A Correct.

Q Likewise, you would agree that the lifetime risk you derived for applicators should not be used to determine any individuals's causation, right?

A Correct.

Q And that's because the lifetime cancer risk you estimated is not based on any individual cancer, right?

A It is by virtue of the fact that we have a body of human epidemiologic studies that point to one thing, lymphoma.

Q But you acknowledge that the mouse model from which you derived your cancer slope factor was not an exact model for human lymphoma, right?

A However, it is in agreement with the body of human data that I've deferred to Dr. Portier, et

Q And that number, .0009436 -- sorry.

That number, that .0009436 would more closely represent Mr. Johnson's applicator risk, right?

A I'm not going to calculate an individual risk level using the equation. As I stated yesterday, that would be using a regulatory risk assessment method for a single individual.

Q You're not going to tell the jury that this risk applies to Mr. Johnson?

A Correct.

Q It still wouldn't tell us whether glyphosate caused Mr. Johnson's mycosis fungoides in any event, right, because that's not what this is designed for?

MR. TRAVERS: Objection to the form.

THE WITNESS: No, I would use the human epidemiologic data and -- as I did and determine whether his exposure scenario was in compliance with those who were studied in the various epidemiological studies.

BY MR. DHINDSA:

Q Okay. Now, turning to the dietary exposure, in your report, that is not a figure that is particular to an applicator, right?

CERTIFICATE OF REPORTER

STATE OF FLORIDA

COUNTY OF LEE

I, TRACIE THOMPSON, Registered Merit Reporter, do hereby certify that I was authorized to and did stenographically report the foregoing videotape deposition of WILLIAM SAWYER, PH.D.; pages 269 through 558; that a review of the transcript was requested; and that the transcript is a true record of my stenographic notes.

I FURTHER CERTIFY that I am not a relative, employee, attorney, or counsel of any of the parties, nor am I a relative or employee of any of the parties' attorneys or counsel connected with the action, nor am I financially interested in the action.

Dated this 28th day of February, 2018.

Tracie Thompson

Notary Public

State of Florida

My Commission No. GG 175178

Expires: March 1, 2022