Office of Environmental Health Hazard Assessment 04-May-2022
California Environmental Protection Agency
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Sacramento, California 95814

Electronically Submitted through the OEHHA website at: https://oehha.ca.gov/comments

To those it may concern,

I appreciate the opportunity to provide comments to the Office of Environmental Health Hazard Assessment (OEHHA) in response to proposed rulemaking and warnings from exposures to glyphosate. I am a long-term resident of the State of California, holding degrees in Biochemistry and Molecular Biology (UCSB) and a doctorate in Environmental Toxicology (UCI) with some experience in toxicology & safety assessments and continuing interests in cancer research. I will assume opinions of OEHHA continue to be expressed as in proposed rulemaking titled "Initial Statement of Reasons, Clear and Reasonable Warnings, New Section 25607.48 and 25607.49 'Warning for Exposures to Glyphosate from Consumer Products' dated 23-July-2021.[1]

Transparency and Reproducibility

In the interests of transparency and reproducibility, OEHHA should: (1) provide any significant correspondence and consultations with the Carcinogen Identification Committee that contributed to records and rulemaking, and (2) add information on benchmark dose models and model selected for safe harbor calculations in determining the no significant risk level (NSRL) of 1,100 µg/day.[2]

Clear and Reasonable

Recent OEHHA correspondence with US EPA[3] suggests the proposed label may no longer be FALSE but continues to be MISLEADING and is neither CLEAR nor REASONABLE as required by California law.[4] While OEHHA openly acknowledges that "known to cause cancer" is "not the best fit" for glyphosate, the proposed label continues to fail in providing a balanced description of the likelihood that glyphosate can cause human cancer.

Regulatory Consensus

Glyphosate is not likely to be carcinogenic by overwhelming evidence and worldwide regulatory consensus.[5] Disturbing is that with hundreds of publications and regulatory documents available to

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[1] Office of Environmental Health Hazard Assessment (OEHHA), 'Initial Statement of Reasons Title 27, California Code of Regulations' <https://oehha.ca.gov/media/downloads/crnr/glyphosateisor071921.pdf> accessed 21 April 2022.

[2] Health & Safety Code § 25249.10. - <<https://oehha.ca.gov/media/downloads/proposition-65/chemicals/glyphosate032917isor.pdf>>

[3] Lauren Zeise, 'OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION' <https://www.regulations.gov/document/EPA-HQ-OPP-2009-0361-0073> accessed 27 April 2022.

[4] 'Notice of Amendments – Article 6 Clear and Reasonable Warnings, Section 25600.2, Responsibility to Provide Consumer Product Exposure Warnings - OEHHA' <https://oehha.ca.gov/proposition-65/crnr/notice-amendments-article-6-clear-and-reasonable-warnings-section-256002> accessed 21 April 2022.

[5] 'Procedure and Outcome of the Draft Renewal Assessment Report on Glyphosate, June 2021' <https://ec.europa.eu/food/plant/pesticides/glyphosate/assessment-group_en> accessed 21 April 2022; 'All News

OEHHA regarding assessments of the carcinogenicity of glyphosate, the agency has selected publications by Christopher Portier[6] and Dennis Weisenburger[7] to support its position. More concerning is that OEHHA points to multi-million-dollar verdicts as validation.[8] Perhaps OEHHA is unaware that Drs. Portier and Weisenburger have and continue to have clear conflicts of interest as receiving significant compensation from plaintiffs' lawyers in the multi-district ligation (MDL) of glyphosate. Additionally, OEHHA may not be aware that verdicts within the State of California brought by individuals claiming cancers caused by glyphosate are now mixed.[9]

Non-Significant Risk Levels Requirements in Labeling

Based on calculations of the current NSRL, OEHHA should further clarify WHEN the proposed labels will be appropriate and enforceable for glyphosate considering Health and Safety Code as effective 1-July-2018. Quoting the 23-July-2021 OEHHA document:[10]

> *"For example, exposure to a user that spills the product on the palmer surface of one hand could be estimated to be approximately 110 µg glyphosate via the dermal route, every time the product is used, and the product is not used every day by a typical home user."*

This suggests a consumer using residential grade glyphosate formulations could spill the product on their palm 9 times each day, every day for a lifetime, and not reach the NSRL or be concerned regarding cancer. To be CLEAR, "Exposures below the safe harbor NSRL do not require a Proposition 65 warning" (Title 27, Cal. Code of Regulations, Sections 25705, 25709 and 25805). NSRLs are defined as exposure that would result in not more than one excess case of cancer in 100,000 individuals (0.001%) over a 70-year lifetime.[11] OEHHA should share methods used and provide additional estimates of farmer & landscaper internal exposures and effects of adding personally protection equipment (PPE) to determine when required labeling would be enforceable as it appears the proposed warning may **or may not** be legally applicable to those handling more concentrated glyphosate formulations.

Glyphosate Deal

It may be important to document that the 'glyphosate deal' agreed to by both plaintiffs and defendants

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- ECHA' <https://echa.europa.eu/-/glyphosate-not-classified-as-a-carcinogen-by-echa> accessed 21 April 2022; 'Glyphosate | EFSA' <https://www.efsa.europa.eu/en/topics/topic/glyphosate> accessed 21 April 2022; Geneva, 'JOINT FAO/WHO MEETING ON PESTICIDE RESIDUES' <http://www.who.int/foodsafety/areas_work/chemical-risks/jmpr/en/> accessed 27 April 2022; 'Glyphosate - BfR' <https://www.bfr.bund.de/en/a-z_index/glyphosate-193962.html> accessed 21 April 2022; 'Glyphosate | Australian Pesticides and Veterinary Medicines Authority' <https://apvma.gov.au/node/13891> accessed 21 April 2022.

[6] Christopher J Portier, 'A Comprehensive Analysis of the Animal Carcinogenicity Data for Glyphosate from Chronic Exposure Rodent Carcinogenicity Studies' (2020) 19 Environmental Health </pmc/articles/PMC7014589/> accessed 21 April 2022.

[7] Dennis D Weisenburger, 'A Review and Update with Perspective of Evidence That the Herbicide Glyphosate (Roundup) Is a Cause of Non-Hodgkin Lymphoma' (2021) 21 Clinical Lymphoma, Myeloma and Leukemia 621 <https://doi.org/10.1016/j.clml.2021.04.009> accessed 21 April 2022.

[8] (OEHHA) (n 1).

[9] *Clark v Monsanto Company 20STCV46616*; *Stephens v Monsanto CGC-20-58576411 // CIVSB2104801*.

[10] (OEHHA) (n 1) Page 7, Footnote 14.

[11] 'Current Proposition 65 No Significant Risk Levels (NSRLs) Maximum Allowable Dose Levels (MADLs) - OEHHA' <https://oehha.ca.gov/proposition-65/general-info/current-proposition-65-no-significant-risk-levels-nsrls-maximum> accessed 21 April 2022.

in MDL mediation with Ken Fienberg / Judge Chhabria cite the NSRL.[12]

> *"…the Science Panel shall presume that such threshold internal dose level is 1100 microgram per day over a lifetime of 70 years, the NSRL adopted by the State of California, unless the Science Panel determines otherwise by calculating a threshold internal dose for added risk using the methodology used by California OEHHA in the Initial Statement of Reasons regarding setting a Benchmark Dose, Cancer Slope Factor, and NSRL for glyphosate (as described in Title 27, Article 7, Section 25721 of the California Code of Regulations…"*

As closely following trials, I am unaware of any instance where this value has been used to support or refute cancer claims or likelihood thereof. Regardless, current, and potential future litigation involving OEHHA should be enough to justify methods and data used for NSRL determination to be carefully documented and openly shared.

Current ECHA Re-Assessment

The most recent re-assessment of all animal studies and the publication of Portier is available in stakeholder presentations to Committee for Risk Assessment (RAC) meeting, 16-Mar-2022[13]. Assessment Group on Glyphosate (AGG) [consisting of authorities in France, Hungary, The Netherlands, and Sweden] indicates both one- or two-sided significance for animal bioassay data will be reported, however this may not cause a change in classification using weight of evidence approaches and biological plausibility. NO HAZARD CLASSIFICATION FOR CARCINOGENICITY for carcinogenicity is currently warranted for glyphosate according to the CLP criteria. OEHHA could offer an explanation as to how the AGG (ECHA/EFSA) have made mistakes in this hazard determination.

Portier and Séralini

A separate explanation as to why the study of Portier[14] has been cited seems necessary as including data from the retracted and republished work of Gilles-Éric Séralini that IARC deemed inadequate for evaluation. The same can be said for the Tarazona study as also including data and reference to the Séralini study data albeit noting IARC and EFSA considered this data inadequate for carcinogenicity assessment. IARC reasoning included: (1) the number of animals per group was small, (2) histopathological description of tumours was poor, and (3) incidences of tumours for individual animals were not provided.[15] While Portier previously defended the Séralini work without reference to egregious animal husbandry issues,[16] OEHHA should provide some statement regarding confidence in Séralini's work that has been fully refuted by European initiatives (GRACE, GMO90+, and G-TwYST).[17] Images of rats with tumors far larger than necessary[18] continue to circulate on the Internet even today

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[12] 'UNITED STATES DISTRICT COURT NORTHERN DISTRICT OF CALIFORNIA CLASS ACTION SETTLEMENT AGREEMENT' <http://www.glyphosatelitigationfacts.com/main/wp-content/uploads/2021/02/Settlement-Agreement-2.3.21.pdf> accessed 21 April 2022.[Section 12.2(c)]

[13] 'Glyphosate - ECHA' <https://echa.europa.eu/hot-topics/glyphosate> accessed 25 April 2022.

[14] Portier (n 6).

[15] Kathryn Z Guyton and others, 'Carcinogenicity of Tetrachlorvinphos, Parathion, Malathion, Diazinon, and Glyphosate' (2015) 16 The Lancet Oncology 490 <https://pubmed.ncbi.nlm.nih.gov/25801782/> accessed 16 March 2021.

[16] Christopher J Portier, Lynn R Goldman and Bernard D Goldstein, 'Inconclusive Findings: Now You See Them, Now You Don't!' A36 </pmc/articles/PMC3915254/> accessed 16 March 2021.

[17] 'Home | GRACE FP7' <https://www.grace-fp7.eu/> accessed 21 April 2022.

[18] P Workman and others, 'Guidelines for the Welfare and Use of Animals in Cancer Research' 1555 </pmc/articles/PMC2883160/> accessed 16 March 2021; P Workman and others, 'United Kingdom Co-Ordinating Committee on Cancer Research (UKCCCR) Guidelines for the Welfare of Animals in Experimental Neoplasia (Second Edition)' 1 <https://pubmed.ncbi.nlm.nih.gov/9459138/> accessed 16 March 2021.

promoting fear, uncertainly, and doubt. This publication as retracted and republished should serve as an example of lapses in publication ethics, need for more AAALAC accreditation, and increased adherence to principles of good laboratory practice. Note that Séralini's work was best criticized not by industry, but from the European Society of Toxicologic Pathology, ESTP[19] & Société Française de Pathologie Toxicologique (SFPT, French Society of Toxicologic Pathology).[20] Future reasoning should offer explanations to the people of California as to why this publication by Portier referencing the Séralini study reflects the best available science supporting OEHHA position.

Legal Reconsideration and State Qualified Experts

Regarding legal statutes, the State of California under Proposition 65 lists carcinogens under Health and Safety Code through several methods:[21] (1) Labor Code, (2) State Qualified Experts, (3) Authoritative Bodies, and (4) when a state or federal government requires. Glyphosate appears to be a candidate for reconsideration under the State Qualified Experts (SQE) mechanism pursuant to Health and Safety Code section 25249.8(b) and Title 27, CCR section 25305. OEHHA should clarify if state qualified experts without conflicts of interests have been engaged to contribute towards rulemaking as recent opinions appear to lack important recent references and scientific data. It seems reasonable to suspend efforts regarding rulemaking to seek additional consultations with state qualified experts with pending legal challenges.

Legal Jeopardy

Reviewing the first round of comments and previous tailored warning, the opinions of Judge William Shubb appear CLEAR and REASONABLE. Labels proposed will continue to face unnecessary jeopardy and legal challenge as the modified language continues: (1) to violate the First Amendment as lacking balance in the weight of scientific data and decision of the U.S. District Count (National Association of Wheat Growers v. Becerra (and notably OEHHA director Zeise) 468 F. Supp. 3d (E.D. Cal. 2020)[22], (2) may be subject to preemption under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) as adding information "in addition to or different from" those imposed by EPA (7 U.S.C. § 136v(b) [see *amicus briefs* and what may be pending arguments to the Supreme Court of the United States][23], also (3) directly clashes with the California Code of Regulations (CCR), Title 3, Food and Agriculture, Division 6 - Pesticides and Pest Control Operations, Chapter 2- Pesticides, Subchapter 1 - Pesticide Registration, Article 10 – Labeling, § 6242 - Warning or Caution Statement, and more importantly § 6243 - Scope of Labeling Requirements. "The labeling requirements in this article shall provide that pesticide products registered by the director meet, but not exceed, current U.S. EPA labeling requirements. The labeling requirements in this article shall apply equally to pesticide products currently registered by U.S. EPA and submitted to the director for registration, and those requiring registration only pursuant to section

[19] Frederic Schorsch, 'Serious Inadequacies Regarding the Pathology Data Presented in the Paper by Séralini et Al. (2012)' 450.
[20] Erio Barale-Thomas, 'Letter to the Editor' 458.
[21] 'How Chemicals Are Added to the Proposition 65 List - OEHHA' <https://oehha.ca.gov/proposition-65/how-chemicals-are-added-proposition-65-list> accessed 21 April 2022.
[22] Hato Rey and others, 'Plaintiffs-Appellees, v. XAVIER BECERRA, IN HIS OFFICIAL CAPACITY AS ATTORNEY GENERAL OF THE STATE OF CALIFORNIA, Defendant-Appellant, AMICUS CURIAE BRIEF OF THE NATIONAL BLACK FARMERS ASSOCIATION IN SUPPORT OF APPELLANT AND REVERSAL'.
[23] '21-241 Supreme Court of the United States (Hardeman)' <https://www.supremecourt.gov/search.aspx?filename=/docket/docketfiles/html/public/21-241.html> accessed 21 April 2022; '21-1272 Supreme Court of the United States (Pilliod)' <https://www.supremecourt.gov/search.aspx?filename=/docket/docketfiles/html/public/21-1272.html> accessed 21 April 2022.

12811 of the Food and Agricultural Code," and (4) Section 25249.6(a) An exposure for which federal law governs warning in a manner that preempts state authority. (Underlines added for emphasis)

Misbranding and Pending Legal Challenge

The label may continue to represent 'misbranding' where the extent to which this language is judged equivalent to and fully consistent with FIFRA's misbranding provisions may determine future legal outcomes. These types of challenges are not new and continue to face legal scrutiny. FIFRA may not preempt common-law claims for defective design, manufacture, negligent testing, and or breach of express warranty.[24] While the legal arguments may be a complex as those involving glyphosate science, it remains in the best interests of the State of California and the United States to await the pending brief of Solicitor General Prelogar and potential decisions by the Supreme Court. Perhaps more important is to recognize that members of legal community (i.e., lawyers & judges) up to and including Supreme Court justices are ONLY qualified to judge aspects of the LAW, NOT scientific evidence, wherein the later responsibility rests with those possessing the appropriate education, experience, and expertise to assess risk(s) and where acceptable risk(s) are clear, reasonable, and weighed with consideration of potential benefits. That OEHHA has suggested any reliance on jury verdicts may seriously undermine public confidence in the agency and science. Please explain OEHHA policy regarding current and future reliance on trial verdicts as evidence of false and misleading testimony, inflammatory rhetoric from plaintiffs' counsel at trial, poor judicial decisions (e.g., excluding EPA correspondence and interim decisions), and failures in the interpretation of Rule 702 from the glyphosate trials can be provided.

For example, William Sawyer who has now invoiced more than $2M as an expert witness in these matters in answering 'what is glyphosate?' (Pilliod vs Monsanto) answered by drawing comparisons to chemical warfare agent sarin and concluded with glyphosate's ability to DNA damage by phosphorylation. **Demonstrably false and misleading testimony, combined with an inept defense, flowing from an erroneously admitted non-expert, should not form a basis of legal or regulatory decisions and labeling.** Although perhaps too late for glyphosate, the United States Supreme Court may have an opportunity to impact future admissibility of expert testimony.[25]

Label Specific Issues and Weights of Authority

Given the weight of scientific evidence, preemption under FIFRA, and reference to CCR above, questions should arise regarding the proposed labeling as first listing the IARC determination BEFORE that of the US EPA and other authorities (note: this also suggested as an appeasement by Judge Chhabria, 21-Mar-2021). Additionally, the fragment 'other authorities have made similar determinations' is misleading as it creates as a 'near-equal split of authority regarding glyphosate's purported carcinogenicity'. Implying an equivalency of (1) 17 scientists, guests, and additional observers temporarily in residence at IARC and tasked with hazard determination as reviewing only published data for a few months and meeting for a few weeks, with (2) the work of 100s of scientists employed with worldwide regulatory authorities that are tasked full-time with hazard assessment, risk assessment, and risk management responsibilities in reviewing ALL available data for more than 30 years is most certainly MISLEADING.

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[24] 'FIFRA v. the Courts: Redefining Federal Pesticide Policy, One Case at a Time on JSTOR' <https://www.jstor.org/stable/23054895?refreqid=excelsior%3Aa1b62fab9885a8afb36b97b0cf6d2d24> accessed 18 April 2022.

[25] 'ANALYSIS: Say Goodbye to "Daubert Motion", Hello to New Rule 702 (1)' <https://news.bloomberglaw.com/bloomberg-law-analysis/analysis-say-goodbye-to-daubert-motion-hello-to-new-rule-702> accessed 22 April 2022.

Despite this contrast, an acknowledgment that most the above scientists possess more competency and knowledge of glyphosate hazards and risk is warranted. Especially in comparison to those that may "feel uncomfortable" with current regulatory opinions and consensus. I would agree and cite former EFSA chief Dr. Bernhard Url.[26]

> *"The letter of ninety-six persons was mentioned very often. To me this is a very good example on how different the two organizations work. We worked on glyphosate with 100 scientists from the member states. They see the evidence; they contribute, they challenge, they are in teleconferences. It is the peer review process and with a hundred scientists together we were able to produce this. We did not ask the scientists to sign a letter whether they like or not the outcome; and one members of Parliament has put it very rightly. She has said, 96 scientists feel uncomfortable with EFSA's opinion. And it's about that. People that have not contributed to the work, that have not seen the evidence most likely, that have not had the time to go into the detail, that are not in the process have signed a letter of support. Sorry to say that for me, with this, you leave the domain of science and enter into the domain of lobbying and campaigning, and this is not the way EFSA goes. For me this is the first sign of the Facebook age of science. You have a scientific assessment, you put it on Facebook, on you count how many how many people like it. For us, this is no way forward. We produce a scientific opinion, we stand for it, but we cannot take into account whether it will be liked or not."*
> ***EFSA chief accuses world-class cancer experts of 'Facebook science' https://youtu.be/ivQ0Ph9OWZU (2015)***

Accuracy in Labeling

As glyphosate toxicology and carcinogenesis continues to be a highly contentious issue worthy of significant scientific inquiry that considers all available data regardless of source, the following statements seem germane and important for disclosure in labeling: (1) IARC does not review all available data; (2) 'Key characteristics' described in most recent IARC preamble may be unreliable and no better than chance in predicting carcinogenic potential;[27] (3) IARC lacks competency in performing quantitative risk characterizations as acknowledged its own Advisory Group chaired by Christopher Portier and including the current OEHHA director Lauren Ziese;[28] and therefore, (4) has little or no regulatory authority with the possible exception of power over the OEHHA and the State of California to compel listing under Proposition 65.

Revised language for NOTICE is therefore proposed (Figure 1):

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[26] 'Open Letter: Review of the Carcinogenicity of Glyphosate by EFSA and BfR' <https://www.efsa.europa.eu/sites/default/files/Prof_Portier_letter.pdf> accessed 22 April 2022; 'The Man Who Haunts Europe's Food Safety Watchdog – POLITICO' <https://www.politico.eu/article/glyphosate-carcinogenic-debate-christoper-portier-the-man-europes-food-watchdog-fears-the-most/> accessed 22 April 2022. (https://www.politico.eu/wp-content/uploads/2018/07/SPOLITICO20-18070510570.pdf noting additional individuals)

[27] Richard A Becker and others, 'How Well Can Carcinogenicity Be Predicted by High Throughput "Characteristics of Carcinogens" Mechanistic Data?' (2017) 90 Regulatory Toxicology and Pharmacology 185 <https://pubmed.ncbi.nlm.nih.gov/28866267/> accessed 16 March 2021; James S Bus, 'IARC Use of Oxidative Stress as Key Mode of Action Characteristic for Facilitating Cancer Classification: Glyphosate Case Example Illustrating a Lack of Robustness in Interpretative Implementation' (2017) 86 Regulatory Toxicology and Pharmacology 157 <https://pubmed.ncbi.nlm.nih.gov/28274811/> accessed 17 March 2021.

[28] 'IARC Monographs on the Evaluation of Carcinogenic Risks to Humans'; Lyon and France, 'IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Report of the IARC Advisory Group To Recommend On Quantitative Risk Characterization IARC Monographs on the Evaluation of Carcinogenic Risks to Humans'.

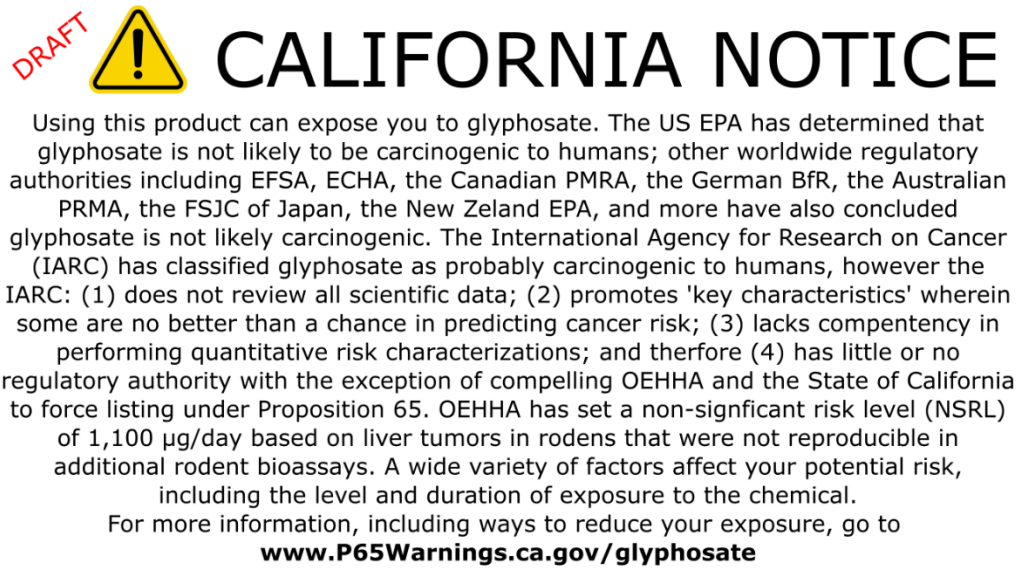

Figure 1

Arbitrary and Capricious

The tailored warning may fail arbitrary and capricious testing; one legal standard of review to be used by judges in assessing actions of administrative agencies defined under provisions of the 1946 Administrative Procedure Act (APA)[29] Courts must review agency actions and INVALIDATE any that they find to be "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." This is most frequently employed to assess the FACTUAL BASIS of an agency's rulemaking especially in instances regarding informal rulemaking.[30]

In previous suggested language, OEHHA appears to adopt suggested warning language of Judge Vincent Chhabria and offers partial justification of that language through citation of multi-million-dollar verdicts overseen by the same (Judge Vincent Chhabria). This may violate APA provisions regarding separation of powers outlined in the U.S. Constitution. Although perhaps a harmless error, this does represent evidence that OEHHA lacks autonomy and or an ability to independently review and assess glyphosate carcinogenic potential. This is where access to comprehensive reviews of scientific literature regarding glyphosate and any history of previous evaluations over the last 30+ years by OEHHA should be made available. Links to literature used and the studied reasoning of OEHHA should be provided.

Evidence of 'arbitrary and capricious' on a FACTUAL BASIS might be better perceived by comparisons to recent OEHHA rulemaking through examples linked to IARC determinations. Consider there is overwhelming evidence and consensus that acrylamide is genotoxic, mutagenic, and carcinogenic based on known biotransformation to DNA reactive intermediates that damage DNA and increase mutations

[29] '5 USC PART I, CHAPTER 5, SUBCHAPTER II: ADMINISTRATIVE PROCEDURE' <https://uscode.house.gov/view.xhtml?path=/prelim@title5/part1/chapter5/subchapter2&edition=prelim> accessed 27 April 2022.
[30] Todd Garvey, 'A Brief Overview of Rulemaking and Judicial Review' <www.crs.gov> accessed 27 April 2022.

that can potentially lead to cancer.[31] A comparison to acrylamide and glyphosate rulemaking provides additional support for this argument.

Table 1 – An effective yet overly simplified comparison of glyphosate and acrylamide*

	Glyphosate	Acrylamide
IARC	⚠ Probable Human Carcinogen (Group 2A)	⚠ Probable Human Carcinogen (Group 2A)
US EPA	☑ NOT likely to be carcinogenic[32]	⚠ Likely to be carcinogenic/probable carcinogen
EFSA	☑ NOT likely to be carcinogenic[33]	⚠ Acrylamide/Glycidamide genotoxic & carcinogenic[34]
NTP	☑ Non-genotoxic by Multiflow™ [35]	⚠ Reasonably anticipated to be a human carcinogen
JECFA/JMPR	☑ Unlikely to pose a carcinogenic risk** diet[36]	⚠ Margin of Exposure (MOE) <300 (<10,000 concerning)[37]
OEHHA	<< some actions pending judicial action >>	⚠ Listed - known to be a carcinogen
	⚠ << listed – additional actions[38] >>	(EXCEPT in COFFEE – rulemaking exemption ☑)
NSRL* **	**1,100 µg/day**	**0.2 µg/day**
	**exception, mice at high levels	

*Understood as a crude comparison of full agency opinions of glyphosate and acrylamide (**[Glyphosate** (CAS 1071-83-6, PCID: 3496] is listed as a **Group 2A probable carcinogen**. **Acrylamide** (CAS 79-06-1 PCID: 6579) is listed as a **Group 2A probable; carcinogen**. **Very hot beverages**, including coffee, mate and tea, are **Group 2A probably carcinogenic** (hot being above 149°F | 65°C)**] – (*see OEHHA citations to other agencies within acrylamide rulemakings for additional references)**

Acrylamide and other carcinogens are present in coffee. Rulemaking published 3-June-2019 as effective 1-Oct-2019 by OEHHA **exempts** cancer warnings for "Exposures to chemicals in coffee, listed on or before March 15, 2019, as known to the state to cause cancer, that are created by and inherent in the processes of roasting coffee beans or brewing coffee that do not pose a significant risk of cancer" under Section 25704.

While rulemaking in regards to coffee: (1) is popular amongst populists, (2) thwarts frivolous litigation by law firms seeking to extract millions of dollars from corporations serving coffee to consumers, (3) represents a successful outcome of campaigning and advocacy by the National Coffee Association, and (4) may reflect the truth that coffee does not deserve a warning (to which I might agree), it remains FACTUAL and indisputable that coffee contains chemicals known to the State of California to cause cancer. Not just acrylamide, but many more that are known and listed before 15-Mar-2019; most

[31] Maria Zhivagui and others, 'Experimental and Pan-Cancer Genome Analyses Reveal Widespread Contribution of Acrylamide Exposure to Carcinogenesis in Humans' (2019) 29 Genome Research 521 <https://pubmed.ncbi.nlm.nih.gov/30846532/> accessed 18 November 2020.
[32] 'Glyphosate | US EPA' <https://www.epa.gov/ingredients-used-pesticide-products/glyphosate> accessed 27 April 2022.
[33] 'Glyphosate | EFSA' (n 5).
[34] Diane Benford and others, 'Scientific Opinion on Acrylamide in Food' (2015) 13 EFSA Journal 4104.
[35] 'Glyphosate & Glyphosate Formulations' <https://ntp.niehs.nih.gov/whatwestudy/topics/glyphosate/index.html> accessed 29 April 2022.
[36] Geneva (n 5).
[37] 'Safety Evaluation of Certain Contaminants in Food: Prepared by the Seventy-Second Meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)' <https://apps.who.int/iris/handle/10665/44520> accessed 27 April 2022.
[38] 'Proposition 65 Initial Statement of Reasons Title 27, California Code of Regulations Proposed Amendments to Article 6: Safe Harbor Clear and Reasonable Warnings for Acrylamide Exposures from Food New Subsection 25607.2(B)'.

notably furan[39], 2-phenylphenol[40], additional natural products resulting from Maillard reactions, and that occurring by ubiquitous contamination with Aspergillus *sp*. adding ochratoxin A.[41] If the original intent of Proposition 65 is a 'right to know' or 'duty to warn' of the presence of carcinogens as stated by Director Ziese in her correspondence with EPA, then this rulemaking epitomizes failure on multiple counts.

The rulemaking for coffee also 'fails to warn' in a second aspect. Hot beverages, including coffee, mate, and tea, have been judged 'probably carcinogenic' by IARC where hot may be defined as above 149°F (65°C). Starbucks suggests the ideal temperature for brewing with a coffee press should be between 195–205°F and beverage resource manuals suggest standard temperatures for serving hot Starbucks drinks is to be between 150-170°F (65-77°C). Coffee served at these temperatures is 'probably carcinogenic' by IARC opinion yet hot coffee continues to be served without cancer warnings. It is also factual that 'hot water' is probably carcinogenic by IARC opinion. Lessons from 'tort history' and the non-cancer risks of hot coffee could also deserve as discussion regarding failures to warn. [Liebeck v. McDonald's Restaurants (P.T.S., Inc., No. D-202 CV-93-02419, 1995 WL 360309 (Bernalillo County, N.M. Dist. Ct. August 18, 1994))]. Additional further complexities is the rulemaking of 24-Sep-2021 where OEHHA also makes use NSRL for acrylamide and foods at 0.2 µg/day while adding new tailored language within rulemaking and reference to known litigation (e.g., acrylamide is not intentionally added by manufacturers).[42]

Conclude Arbitrary and Capricious

The above supports **warnings and rulemaking have become capricious, arbitrary, and unpredictable that is neither logical nor follows any scientific procedure**. A tailored warning was: (1) NOT sought for coffee and exemption made; (2) a different warning is sought for foods containing acrylamide; and now (3) a tailored warning label for glyphosate is sought without comprehensive review and in part is justified by reference to verdicts and publications by individuals directly involved with litigation. Furthermore, this proposed glyphosate label appears sought by OEHHA **with determination,** ignoring world-wide regulatory consensus and adds correspondence "disrespectful of the scientific process."[43]

Perhaps the increasingly arbitrary or capricious nature of OEHHA warnings is not the strongest of arguments, however naturalist fallacies, and bias (e.g., "we like coffee, we don't like pesticides") appears to represent one explanation for these disparities. An irony is that caffeine in coffee is a natural pesticide is more potent in most toxicological and ecotoxicological non-cancer endpoints in comparison

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[39] 'Furan - OEHHA' <https://oehha.ca.gov/chemicals/furan> accessed 27 April 2022; Zahra Batool and others, 'A Review on Furan: Formation, Analysis, Occurrence, Carcinogenicity, Genotoxicity and Reduction Methods' <https://pubmed.ncbi.nlm.nih.gov/32146825/> accessed 18 November 2020.

[40] 'O-Phenylphenol - OEHHA' <https://oehha.ca.gov/proposition-65/chemicals/o-phenylphenol> accessed 27 April 2022.

[41] 'Ochratoxin A - OEHHA' <https://oehha.ca.gov/proposition-65/chemicals/ochratoxin> accessed 27 April 2022.

[42] 'Proposition 65 Initial Statement of Reasons Title 27, California Code of Regulations Proposed Amendments to Article 6: Safe Harbor Clear and Reasonable Warnings for Acrylamide Exposures from Food New Subsection 25607.2(B)' (n 38).

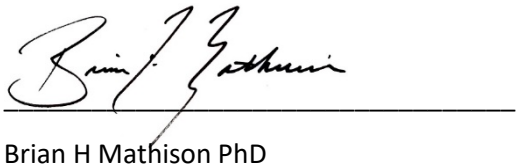
[43] 'OEHHA Statement Regarding US EPA's Press Release and Registrant Letter on Glyphosate - OEHHA' <https://oehha.ca.gov/proposition-65/general-info/oehha-statement-regarding-us-epas-press-release-and-registrant-letter> accessed 27 April 2022.

to glyphosate. There is one notable difference. Caffeine failed a recent registration attempt as a plant protection product in Europe.[44]

Conclude – "what we have here is a failure to communicate"

Failures in CLEAR and RESONABLE communication ultimately aid and promote litigation. Litigation settlements for glyphosate suggests that there are more than 10 billion reasons for lawyers to appreciate hazard assessments and glyphosate warning labels over risk assessments. At least one participating law firm will use new financial resources to litigate Gardasil-9 (a multivalent HPV vaccine) that has been estimated could prevent 50 million cancers this century.[45] The data on glyphosate appear to be remarkably consistent and in part based on the OEHHA NSRL calculations suggests it does not appreciably contribute to human cancer burden in agreement with worldwide regulatory assessment.

Thank you again for the opportunity to comment on this important issue,



Brian H Mathison PhD

Disclosures / Conflicts of Interest: I have not received any compensation from any individual or group involved with the production, sale, marketing, regulation, or litigation of glyphosate, glyphosate formulations, or coffee. I like coffee. It is not my intent to disparage coffee as a complex hot brew of chemicals containing multiple known and suspected carcinogens,[46] endocrine disruptors,[47] and one or more DNA methyltransferase and or DNA repair inhibitors.[48] My doctorate many years ago was supported by a training grant from NIEHS ~30 years ago in part concurrent with a toxicologist that served on the IARC monograph. I hold patent and patent applications related to therapeutic polynucleic acids with potential future claims regarding inflammation and neoplastic disease.

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[44] European Food Safety Authority (EFSA), 'Outcome of the Consultation with Member States and EFSA on the Basic Substance Application for Approval of Caffeine to Be Used in Plant Protection as Insecticide in Cabbage, Potatoes and Buxus and as Molluscicide in All Edible and Non-Edible Crops' (2021) <https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/sp.efsa.2021.EN-6423>.

[45] 'Gardasil Lawsuit | Deaths and Serious Injuries Linked to HPV Vaccine' <https://www.baumhedlundlaw.com/prescription-drugs/gardasil-lawsuit/> accessed 27 April 2022.

[46] 'Acrylamide | C3H5NO - PubChem' <https://pubchem.ncbi.nlm.nih.gov/compound/Acrylamide> accessed 2 May 2022; '2-Phenylphenol | C6H5C6H4OH - PubChem' <https://pubchem.ncbi.nlm.nih.gov/compound/7017> accessed 2 May 2022; 'Furan | C4H4O - PubChem' <https://pubchem.ncbi.nlm.nih.gov/compound/Furan> accessed 2 May 2022.

[47] Gerhard J Nohynek and others, 'Endocrine Disruption: Fact or Urban Legend?' (2013) 223 Toxicology letters 295 <http://www.ncbi.nlm.nih.gov/pubmed/24177261> accessed 28 August 2019; Ryoiti Kiyama, 'Estrogenic Activity of Coffee Constituents' (2019) 11 Nutrients <https://pubmed.ncbi.nlm.nih.gov/31234352/> accessed 2 May 2022.

[48] Michal Sabisz and Andrzej Skladanowski, 'Modulation of Cellular Response to Anticancer Treatment by Caffeine: Inhibition of Cell Cycle Checkpoints, DNA Repair and More' (2008) 9 Current pharmaceutical biotechnology 325 <https://pubmed.ncbi.nlm.nih.gov/18691092/> accessed 2 May 2022; Christopher P Selby and Aziz Sancar, 'Molecular Mechanisms of DNA Repair Inhibition by Caffeine' (1990) 87 Proceedings of the National Academy of Sciences of the United States of America 3522 <https://pubmed.ncbi.nlm.nih.gov/2185474/> accessed 2 May 2022; Won Jun Lee and Bao Ting Zhu, 'Inhibition of DNA Methylation by Caffeic Acid and Chlorogenic Acid, Two Common Catechol-Containing Coffee Polyphenols' (2006) 27 Carcinogenesis 269 <https://pubmed.ncbi.nlm.nih.gov/16081510/> accessed 2 May 2022; Pan Wang and others, 'Caffeic Acid Phenethyl Ester, a Coffee Polyphenol, Inhibits DNA Methylation in Vitro and in Vivo' (2020) 887 European Journal of Pharmacology <https://pubmed.ncbi.nlm.nih.gov/32781171/> accessed 18 November 2020.

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APPENDIX A – INITIAL REASONING

Rodent Bioassay Data

Selection of male mouse data from a single study and modeling continues to be problematic. Use of hemangiosarcomas as observed in male CD-1 mice (e.g., 0/50, 0/50, 0/50, 4/50 at 0, 100, 300, 1000 mg/kg-day) lends little confidence in establishing dose-response, points of departure, and slope factors. Hemangiosarcomas are commonly observed in mice and more common in males for the CD-1 strain [e.g., range 1.11-8.57%, from 2005 Charles River, ~2% may represent a better average].[49] Citing Portier, "The nature of science is such that individual studies are rarely, if ever, conclusive."[50] When examining all of the CD-1 mouse data, the 4/50 result at 1000 mg/kg-day does appear unique as rising to statistical significance. However, when a weight of evidence approach is used in conjunction with knowledge this mouse strain, tumor type, and historical data, glyphosate treatment appears insignificant and unremarkable.

Table 1 - Summary of selected tumour incidences in male CD-1 mice from Table 5 Tarazona[51]

Dose	0	0	0	0	71	100	157	165	234	300	810	814	838	1000	4348	4841
#**	0/48	0/50	0/50	2/51	1/51	0/50	0/49	0/50	2/51	0/50	1/51	1/50	0/50	4/50	2/50	0/49

Dose (mg/kg/bw per day) over **tumour incidence/number of animals examined (note: EPA shows 4/45 at 1000 mg/kg in the Glyphosate Issue Paper [Atkinson, 1993 (MRID 49631702)], Access original study to check incidence against that reported by EPA opinions on page 87 of 227.[52]

It is extremely rare to have such extensive animal data. Reviewing summarized histopathology, neoplastic changes across these studies less than 1,000 mg/kg/day appear non-significant for liver including the single study selected by OEHHA for modeling. Histopathology and incidence of tumors in additional studies at and above this level also appear non-reproducible. The lack of concordance between mouse and rat pathology further supports lack of carcinogenicity. Yet it is understandable that with a pathologically precautionary mindset, affixing the label 'carcinogen' to glyphosate can be made using one study. I would just add that key characteristics and terminology used within lexicons of toxicology in absence of quantitative dose-response analysis can be false and misleading where historical perspectives and previously regarded gold standards may not reflect true risk.[53]

As explained by Crump (also a member of the EPA SAP), statistically significant results for glyphosate from bioassays may be the result of false-positives where there was more evidence for negative dose-response trends; reasoning that "IARC did not account for the large number of tumor response analyzed and the increased likelihood that several of these would show statistically significant by

[49] Mary LA Giknis and Charles B Clifford, 'Spontaneous Neoplastic Lesions in the CrI:CD-1(ICR) Mouse in Control Groups from 18 Month to 2 Year Studies'.
[50] Portier, Goldman and Goldstein (n 16).
[51] Jose V. Tarazona and others, 'Glyphosate Toxicity and Carcinogenicity: A Review of the Scientific Basis of the European Union Assessment and Its Differences with IARC' 2723.
[52] US EPA, 'Glyphosate Issue Paper: Evaluation of Carcinogenic Potential EPA's Office of Pesticide Programs'.
[53] David W Gaylor, 'Are Tumor Incidence Rates from Chronic Bioassays Telling Us What We Need to Know about Carcinogens?' (2005) 41 Regulatory toxicology and pharmacology : RTP 128 <http://www.ncbi.nlm.nih.gov/pubmed/15698536> accessed 15 April 2020; Jay I Goodman, 'Goodbye to the Bioassay.' (2018) 7 Toxicology research 558 <http://www.ncbi.nlm.nih.gov/pubmed/30090606> accessed 5 April 2020.

chance."[54] These thoughts were also expressed by Tarazona in response to Portier and Clausing as carefully explaining dose-response, lack of progression, chance effects, and biological relevance of haemangiomas.[55] Ultimately, the work by Tarazona *et al.*, continues to reflect the best scientific interpretation and analysis of animal bioassay data using weight of evidence elements.[56]

OEHHA states agreement with IARC regarding liver observations without robust explanation. The current multi-district litigation (MDL) primarily concerns hematologic cancers (e.g., Non-Hodgkin's Lymphoma, (NHL)). OEHHA could share additional thoughts on data that supports the liver as a target organ for carcinogenesis as little to none appear elsewhere in the literature or supported by epidemiology.

Mechanism – Genotoxicity of Glyphosate

DNA damage due to oxidative stress in the absence of cytotoxicity is not currently supported by unpublished data generated by NIEHS/NTP for glyphosate and its formulations.[57] DNA damage by reactive oxygen species represents one biologically plausible mechanism potentially leading to cancer as noted by IARC. The lack of oxidative DNA by damage using Multiflow™ in residential formulations does not appear to have an explanation. Recent work by Mesnage also shows lack of DNA damage using ToxTracker™ despite the overall tone the publication's narrative.[58] The negative glyphosate response appears duplicative from a previous publication.[59] Clearly, none of the GFP-reporters from the ToxTracker™ assay system scored positive for activation of a DNA damage response or p53-mediated cellular stress that is remarkable as the assay was performed in regions of significant cytotoxicity with glyphosate and its formulations. ToxTracker™ and Multiflow™ are regarded by some as 'state-of-the-art' genetic toxicology platforms whose performance is claimed to exceed older genetic toxicology studies required for product registration. In other recent work, glyphosate did NOT induce changes to the normal level of 8-OHdG in human lymphocytes up to 200 μM but did show evidence of sister-chromatid exchanges at the highest concentration.[60] This being somewhat consistent with the work of Nagy where glyphosate caused statistically significant increase of MN frequency Human Peripheral White Blood Cells at 100 μM after 20-h exposure (also notably in the absence of significant cytotoxicity).[61] More recent

[54] Kenny Crump and others, 'Accounting for Multiple Comparisons in Statistical Analysis of the Extensive Bioassay Data on Glyphosate' (2020) 175 Toxicological Sciences 156 <https://academic.oup.com/toxsci/article/175/2/156/5810105> accessed 21 April 2022.
[55] Tarazona and others (n 51).
[56] ibid.
[57] 'Glyphosate & Glyphosate Formulations' (n 35).
[58] Robin Mesnage and others, 'Comparative Toxicogenomics of Glyphosate and Roundup Herbicides by Mammalian Stem Cell-Based Genotoxicity Assays and Molecular Profiling in Sprague-Dawley Rats' (2022) 186 Toxicological sciences : an official journal of the Society of Toxicology 83 <https://pubmed.ncbi.nlm.nih.gov/34850229/> accessed 29 April 2022.
[59] Robin Mesnage and others, 'Genotoxicity Evaluation of 2,4-D, Dicamba and Glyphosate Alone or in Combination with Cell Reporter Assays for DNA Damage, Oxidative Stress and Unfolded Protein Response' (2021) 157 Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association <https://pubmed.ncbi.nlm.nih.gov/34626751/> accessed 29 April 2022.
[60] Nafez Abu Tarboush and others, 'Genotoxicity of Glyphosate on Cultured Human Lymphocytes' (2022) 41 International journal of toxicology 126 <https://pubmed.ncbi.nlm.nih.gov/35240877/> accessed 29 April 2022.
[61] Károly Nagy and others, 'Micronucleus Formation Induced by Glyphosate and Glyphosate-Based Herbicides in Human Peripheral White Blood Cells' (2021) 9 Frontiers in public health <https://pubmed.ncbi.nlm.nih.gov/34109144/> accessed 29 April 2022.

data examining γH2AX and pATM foci support the DNA damage potential of glyphosate at lower concentrations (although it is curious that all pesticides tracked together);[62] these observations are somewhat consistent the earlier work Woźniak[63] and Kwiatkowska.[64] Ultimately, there is some irony in that modern platforms have failed to be consistent and detect similar endpoints when other techniques appear more sensitive. Despite conflicting information, the *in vitro* genotoxicity of glyphosate appears to be increasingly supported at concentrations at and above 100 µM, notably in the absence of cytotoxicity, and when extended times of incubation are used *in vitro*.

The question should then arise as to results of *in vivo* studies that better reflect real world exposures. The work of Zoller[65] and Anadón[66] require careful consideration regarding glyphosate pharmacokinetics, intake, and urinary biomonitoring. Anadón reports that following a single oral dose of 400 mg/kg body weight to rats, glyphosate C_{max} appears 4.62 µg/mL (~27 µM, using 169 µg/µmole F.W.). Given peak concentrations and the pharmacokinetics of glyphosate, it could be understood that glyphosate would be negative for micronuclei *in vivo* at these levels. Blood levels following doses approaching limits under OECD guideline 474 for 1000 or 2000 mg/kg body weights could be estimated and reach those eliciting responses as observed *in vitro* and are reproducible and consistently negative. The work of Zoller suggests human bioavailability and excretion are significantly different from rats (e.g., intakes 20x higher, systemic availability 20x lower, excretion complete <24h, half-life estimates of ~9h, and a median excretions rate 94.85 ng h^{-1}). Glyphosate does not bioaccumulate (ASTDR)[67] and "Dietary glyphosate is likely to be very poorly absorbed in humans and lower than in rats exposed by gavage".[68] Using estimated daily glyphosate exposure by OEHHA estimation and instantaneous absorption to approximately 6 L of total blood volume and assuming zero distribution into tissues might yield 100 nanomolar concentrations of glyphosate in peripheral blood as theoretical limit. True values would be lower, and how nanomolar concentrations of glyphosate could be associated with carcinogenic processes at this low level is ill defined. There does NOT appear to be evidence that glyphosate can cause direct DNA damage. Site(s) of potential reactive oxygen species generation, if any, has yet to be determined unequivocally. Dose-response and the biological relevance for this type phenomena (ROS

[62] Laurène Sonzogni and others, 'DNA Double-Strand Breaks Induced in Human Cells by 6 Current Pesticides: Intercomparisons and Influence of the ATM Protein' (2022) 12 Biomolecules <https://pubmed.ncbi.nlm.nih.gov/35204751/> accessed 29 April 2022.

[63] Ewelina Woźniak and others, 'The Mechanism of DNA Damage Induced by Roundup 360 PLUS, Glyphosate and AMPA in Human Peripheral Blood Mononuclear Cells - Genotoxic Risk Assessement' (2018) 120 Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association 510 <https://pubmed.ncbi.nlm.nih.gov/30055318/> accessed 29 April 2022.

[64] Marta Kwiatkowska and others, 'DNA Damage and Methylation Induced by Glyphosate in Human Peripheral Blood Mononuclear Cells (in Vitro Study)' (2017) 105 Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association 93 <https://pubmed.ncbi.nlm.nih.gov/28351773/> accessed 29 April 2022.

[65] Otmar Zoller and others, 'Urine Glyphosate Level as a Quantitative Biomarker of Oral Exposure' (2020) 228 International journal of hygiene and environmental health <https://pubmed.ncbi.nlm.nih.gov/32305862/> accessed 29 April 2022.

[66] A Anadón and others, 'Toxicokinetics of Glyphosate and Its Metabolite Aminomethyl Phosphonic Acid in Rats' (2009) 190 Toxicology Letters 91.

[67] Atsdr, 'Toxicological Profile for Glyphosate - Draft for Public Comment' (page 144).

[68] Zoller and others (n 65).

generation, and DNA Damage) will need careful characterization as reactive oxygen species are critical for life processes.[69]

Again, the complexities of dermal absorption and flux without the full disclosure of the work of OEHHA and value of 110 µg glyphosate within rulemaking suggest peak peripheral blood levels may at best reach low nanomolar concentrations. Zoller's work on human pharmacokinetics demonstrate oral "human systemic availability is most likely 20 times lower than in rats." This is where physiologically based pharmacokinetic (PBPK) models and *in vitro* to *in vivo* extrapolation (IVIVE) would be welcome yet appears not contemplated by those active in this research community despite litigation settlements measured in billions of USD ($).

With a big picture overview and considering the most recent data, glyphosate appears 'equivocally genotoxic' *in vitro*, but is NOT genotoxic *in vivo*. A weight of evidence approach lends to an overall characterization of glyphosate as non-genotoxic that is reflected by current regulatory consensus. Mechanisms of action and adverse pathways regarding oxidative stress leading to DNA damage continue to be suggested in some assays, but there also continues to be marked inconsistencies using sophisticated techniques (e.g., ToxTracker™ and Multiflow™) in the hands of what are presumably skilled scientists. Ultimately, *in vitro* observations do not easily translate into cancer risk where extensive bioassay data continues to support lack of carcinogenic potential. Given that listing and labeling must occur without rulemaking exception, the bioassay data continue to be most appropriate for BMD modeling and determination of NSRL. It is doubtful that IARC will reconsider an evaluation of glyphosate any time soon.

IARC and Expert Panel Review of Human Data

IARC placed great emphasis on evidence of human DNA damage following exposures to glyphosate.[70] A closer examination shows the studies and use by IARC to be of questionable quality and escaped critical analysis by both the IARC working group and expert panel review. An expert panel review (Brusick, Aardema, Kier, Kirkland, and Williams) reviewed evidence of the genotoxicity of glyphosate, glyphosate-based formulations, and aminomethyphosphonic acid (AMPA) that was later clouded by expressions of

[69] Helmut Sies and Dean P Jones, Reactive oxygen species (ROS) as pleiotropic physiological signalling agents 2020 363; Willem H Koppenol and Helmut Sies, 'Two Centuries since Discovery of Dawn-of-Life Molecule.' (2018) 559 Nature 181 <http://www.ncbi.nlm.nih.gov/pubmed/29991793> accessed 16 April 2020; Helmut Sies, 'Hydrogen Peroxide as a Central Redox Signaling Molecule in Physiological Oxidative Stress: Oxidative Eustress.' (2017) 11 Redox biology 613 <http://www.ncbi.nlm.nih.gov/pubmed/28110218> accessed 7 April 2020; Helmut Sies and Ludwig E Feinendegen, 'Radiation Hormesis: The Link to Nanomolar Hydrogen Peroxide.' (2017) 27 Antioxidants & redox signaling 596 <http://www.ncbi.nlm.nih.gov/pubmed/28699353> accessed 7 April 2020; Helmut Sies, Carsten Berndt and Dean P Jones, 'Oxidative Stress: Annual Review of Biochemistry' (2017) 86 Annual Review of Biochemistry 715 <http://www.annualreviews.org/doi/10.1146/annurev-biochem-061516-045037> accessed 16 April 2020.

[70] C Bolognesi and others, 'Biomonitoring of Genotoxic Risk in Agricultural Workers from Five Colombian Regions: Association to Occupational Exposure to Glyphosate' (2009) 72 Journal of toxicology and environmental health. Part A 986 <https://pubmed.ncbi.nlm.nih.gov/19672767/> accessed 3 May 2022; César Paz-Y-Miño and others, 'Evaluation of DNA Damage in an Ecuadorian Population Exposed to Glyphosate' <www.sbg.org.br> accessed 3 May 2022; César Paz-y-Miño and others, 'Baseline Determination in Social, Health, and Genetic Areas in Communities Affected by Glyphosate Aerial Spraying on the Northeastern Ecuadorian Border' (2011) 26 Reviews on environmental health 45 <https://pubmed.ncbi.nlm.nih.gov/21714381/> accessed 3 May 2022.

concern.[71] Despite what appeared to be clear disclosure of conflicts of interest upon original publication, subsequent addendums effectively precluded use at trials.

Regarding the study by Paz-y- Miño (2007), the Intertek expert panel under section 'Human genotoxicity biomonitoring studies' focused on signs of clinical toxicity reported in the population associated with acute intoxication. Eventually the panel concluded the study provided '…inconclusive evidence for *in vivo* human genotoxic effects.' Several years later, an examination of data in Table 1 regarding DNA migration (μm) suggested irregularities (testimony Stephens -v- Monsanto) noting the median for unexposed controls was 25.0 for all but one data point that was statistically unlikely (astronomically so).

In Bolognesi (2009) the expert panel was needlessly verbose "…although results were temporally consistent with glyphosate formulation spraying, the lack of significant correlation between increased post-spraying micronuclei (BNMN) required and self-report spray exposure, and inconsistency with application rates, indicate the MN effects cannot be associated with GBF exposure (Figure 2)." Bolognesi acknowledged in discussion that 'micronuclei induction was not correlated geographically with glyphosate exposure,' but there was no need to go past the abstract: "The increase in frequency of BNMN observed immediately after the glyphosate spraying was not consistent with the rates of application used in the regions and there was no association between self-reported direct contact with eradication sprays and frequency of BNMN."

DNA Repair

Overlooked by authors and expert review are considerations of DNA damage and repair kinetics, sampling times, and assay specific capabilities. To be brief: Paz-y-Miño (2007): "Venous blood (5 mL) was taken from the exposed individual between two weeks and two months after their exposure to aerial spraying and processed immediately after collection." Bolognesi (2009): regarding sampling: "… immediately (<5 d) after spraying," and Paz-y-Miño (2011): "Four months after spraying…"- this providing information on sampling times and study design. More information regarding sample handling was addressed in the expert panel review. Important aspects to any good study and the elements of: (1) dose-response and (2) temporal-response.

Oxidative damage to DNA is one leading biologically plausible explanation towards causation of hematopoietic cancers. The pharmacokinetics of glyphosate in humans was previously discussed. Formation of oxidative DNA damage would be linked to pharmacokinetics potentially rising above endogenous levels of damage, peaking within 1-3h after exposure and persisting for some time as a function of DNA repair. Studies would normally be designed to account for these parameters.

The kinetics of DNA damage in response to oxidative DNA damage is rapid, with processes starting within seconds, measured often in minutes and hours, and often fully complete within a single day (24h).[72] Exactly how sampling ~5 days, two weeks (14 days), months later, or even 2 years after

[71] David Brusick and others, 'Genotoxicity Expert Panel Review: Weight of Evidence Evaluation of the Genotoxicity of Glyphosate, Glyphosate-Based Formulations, and Aminomethylphosphonic Acid' (2016) 46 Critical reviews in toxicology 56 <https://pubmed.ncbi.nlm.nih.gov/27677670/> accessed 2 May 2022.

[72] Takashi Oizumi and others, 'Repair Kinetics of DNA Double Strand Breaks Induced by Simulated Space Radiation' (2020) 10 Life (Basel, Switzerland) 1 <https://pubmed.ncbi.nlm.nih.gov/33321941/> accessed 2 May 2022; M V. Lukina and others, 'Global DNA Dynamics of 8-Oxoguanine Repair by Human OGG1 Revealed by Stopped-Flow Kinetics and Molecular Dynamics Simulation' (2017) 13 Molecular bioSystems 1954 <https://pubmed.ncbi.nlm.nih.gov/28770925/> accessed 2 May 2022; Jakub A Kochan and others, 'Meta-Analysis of DNA Double-Strand Break Response Kinetics' (2017) 45 Nucleic acids research 12625

exposure provides any useful information regarding glyphosate-induced DNA damage in humans is questionable. Rhetorically, how does pharmacokinetics, sampling times, and DNA repair escape any review and analysis by IARC & other experts?

(Technical note: COMET would not likely be useful in these instances, the cytokinesis block micronucleus assay and variants may detect damage after extended periods given specifics and performance of the assay. Consideration of DNA repair kinetics and the half-life of detectable DNA damage appears lost without reason. For the cytokinesis block micronucleus study (CBMN), you'll need to go back to early literature by French in assay development and damage persistence data as intended for use in biomonitoring radiation exposures. CometChip™ with temporal sampling might be a technique to consider in future evaluations of glyphosate and formulations using 0-48h temporal windows.[73])

Unreliable Regulatory Studies

Recent commentaries and reports by some have suggesting regulatory studies submitted for glyphosate re-registration do not meet current guidelines and are 'unreliable' is a negligent misrepresentation. It would be obvious that updates to guidelines could cause previous studies not meet new requirements of current protocols. Declaring studies unreliable or invalid without discussion of technical aspects of genetic toxicology studies is misleading. Almost all glyphosate data is valuable regardless of source with careful review of materials and methods. These reviews fail to acknowledge some studies in registration or re-registration packages were conducted prior to the existence of OECD guidelines. Others met and exceeded internationally accepted protocols at time of conduct and submission. I would add that compilation of historical control data was not typically included in studies conducted >20 years ago and studies lacking such data are not unreliable and should not be 'invalidated.'

Separate guidelines for bacterial reverse mutations assay converged in 1999. The absence of one or more strains does not necessarily invalidate study results when reported accurately and judged accordingly by regulatory professionals. Any suggestion of additional bacterial reverse mutation studies is unwarranted. Guidelines for micronucleus testing have undergone multiple revisions and automated scoring has provided the ability to increase statistical power by increasing numbers of target cells scored. More uniform power of detection that minimizes counting errors and inter-animal variability was discussed by Kissling in a 2007 publication that compared 2000, 4000, 8000, and 20,000 of MN-RETs and probabilities of reducing counting error.[74] This contributed to the 2010 protocol meetings, and the 2015 Guidance Document of Revision to OECD Genetic Toxicology Test Guidelines implemented in 2016.[75] If guidelines for the micronucleus test again change in the near future requiring a cell scoring increase from 4000 to 8000, this will not invalidate or cancel results but again may lead some to claim

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<https://pubmed.ncbi.nlm.nih.gov/29182755/> accessed 2 May 2022; Anat Gafter-Gvili and others, 'Oxidative Stress-Induced DNA Damage and Repair in Human Peripheral Blood Mononuclear Cells: Protective Role of Hemoglobin' (2013) 8 PloS one <https://pubmed.ncbi.nlm.nih.gov/23874593/> accessed 2 May 2022; Anna R Poetsch, 'The Genomics of Oxidative DNA Damage, Repair, and Resulting Mutagenesis' (2020) 18 Computational and Structural Biotechnology Journal 207.

[73] Peter Sykora and others, 'Next Generation High Throughput DNA Damage Detection Platform for Genotoxic Compound Screening' (2018) 8 Scientific reports <https://pubmed.ncbi.nlm.nih.gov/29426857/> accessed 2 May 2022.

[74] Grace E Kissling and others, 'Sensitivity of the Erythrocyte Micronucleus Assay: Dependence on Number of Cells Scored and Inter-Animal Variability' (2007) 634 Mutation research 235 <https://pubmed.ncbi.nlm.nih.gov/17851117/> accessed 2 May 2022.

[75] 'Guidance Document on Revisions to OECD Genetic Toxicology Test Guidelines'.

studies as unreliable. False and misleading statements regarding reliability should be discussed with some competency regarding biological plausibility and statistical power. Incidentally, the OECD guidelines for chronic carcinogenicity testing were also updated in 2018 but these updates should not invalidate the cancer bioassay data for glyphosate. The COMET assay can be extremely powerful. Champions of this test might take the opportunity to explain assay significance in the context of DNA damage following acute aerobic exercise.[76] I think I will continue to exercise as failing to do so is a risk factor for cancer and cardiovascular disease. To conclude this section, I would just add that in the State of California, negligent or intentional misrepresentations as to opinions can result in liability when individuals are held out as "specially qualified" and the hearer is situated as to be regarded as reasonably relying on that expertise.

Glyphosate as an Endocrine Disruptor

There have been a number of scientific studies attempting to characterize glyphosate as an endocrine disruptor chemical (EDC).[77] The following should be considered as contrary evidence: (1) Chemical structure determines biological activity, glyphosate has little structural similarity to estrogens, androgens, or thyroid hormones; (2) in over 10 bioassays, there is little to no evidence of tumors associated with any endocrine responsive tissues; (3) Glyphosate was negative in Tier 1 of the endocrine screening disruptor program (EDSP21);[78] (4) EFSA concluded not an EDC following a comprehensive assessment.[79] Finally, cancer as an endpoint with glyphosate primarily concerns the hematopoietic/lymphoreticular system. A cursory review of literature indicates estrogen (the ultimate endocrine disruptor) when used in estrogen-replacement therapy does not appear associated with increases in Non-Hodgkin's Lymphoma or any hematopoietic cancer.

Glyphosate and Autism

Outside the scope of cancer labeling but within that of potential reproductive harm; there have been several recent publications linking glyphosate exposure to the causation of autism.[80] None of these

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[76] Despoina V. Tryfidou and others, 'DNA Damage Following Acute Aerobic Exercise: A Systematic Review and Meta-Analysis' (2020) 50 Sports medicine (Auckland, N.Z.) 103 <https://pubmed.ncbi.nlm.nih.gov/31529301/> accessed 2 May 2022.

[77] Juan P Muñoz, Tammy C Bleak and Gloria M Calaf, 'Glyphosate and the Key Characteristics of an Endocrine Disruptor: A Review' (2021) 270 Chemosphere <https://pubmed.ncbi.nlm.nih.gov/33131751/> accessed 2 May 2022; Laura N Vandenberg and others, 'Is It Time to Reassess Current Safety Standards for Glyphosate-Based Herbicides?' (2017) 71 Journal of epidemiology and community health 613 <https://pubmed.ncbi.nlm.nih.gov/28320775/> accessed 2 May 2022; John Peterson Myers and others, 'Concerns over Use of Glyphosate-Based Herbicides and Risks Associated with Exposures: A Consensus Statement' (2016) 15 Environmental Health </pmc/articles/PMC4756530/> accessed 2 May 2022.

[78] EDSP21, 'Glyphosate: Weight of Evidence Analysis of Potential Interaction with the Estrogen, Androgen, or Thyroid Pathways' <https://www.regulations.gov/document/EPA-HQ-OPP-2009-0361-0047> accessed 2 May 2022.

[79] European Food Safety Authority, 'Peer Review of the Pesticide Risk Assessment of the Potential Endocrine Disrupting Properties of Glyphosate' (2017) 15 EFSA Journal e04979 <https://onlinelibrary.wiley.com/doi/full/10.2903/j.efsa.2017.4979> accessed 2 May 2022.

[80] Yaoyu Pu and others, 'Maternal Glyphosate Exposure Causes Autism-like Behaviors in Offspring through Increased Expression of Soluble Epoxide Hydrolase' (2020) 117 Proceedings of the National Academy of Sciences of the United States of America <https://pubmed.ncbi.nlm.nih.gov/32398374/> accessed 3 May 2022; Ondine S Von

publications does justice to the autism community and those dedicated to autism research. Autism is primarily an inherited condition that like other neurodevelopmental disorders may involve hundreds of genetic loci.[81] In a "Large population-based multinational cohort study including more than 2 million individuals, 22,156 of whom were diagnosed with ASD," the heritability of autism spectrum disorder was estimated to be approximately 80%.[82] Remaining portions are unknown but leading theories include: (1) Repeat Expansion Disease – (i.e., Fragile X, FMR) where the phenomenon of 'anticipation' is receiving more attention; (2) viral infections (and treatment); (3) increasing maternal and paternal age; (4) improved diagnostics and genetic screening methods; and (5) environmental factors (both exogenous and endogenous).

Chemically induced autism remains the most controversial. Clearly thalidomide and valproic acid can elicit symptomology of what appears to be autism in animal models following high doses. Epidemiology data are mixed for some heavy metals, where copper has some interesting data. All the above areas need more targeted research.

Glyphosate Substitutes for Glycine in Proteins

Honestly, pretty much anything authored by Stephanie Seneff or Anthony Samsel should be treated "special". I will not link to any of these studies as effectively de-bunked by Antoniou[83] and Mesnage.[84] I would add that the 1991 published mass balance study of Brewster indicated a total recovery of glyphosate that ranged from 95 to 102% of an administered dose, where nearly 100% of the body burden of radioactivity was present as unmetabolized parent glyphosate. The total body burden 7 days after administration was approximately 1% of the administered dose and was primarily associated with the bone. One of the sites of highest protein synthesis in the body is bone marrow and the production of blood cells. If radiolabeled glyphosate were incorporated into proteins such as hemoglobin to any appreciably extent, radioactivity would appear and persist in peripheral blood with the average life of

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Ehrenstein and others, 'Prenatal and Infant Exposure to Ambient Pesticides and Autism Spectrum Disorder in Children: Population Based Case-Control Study' (2019) 364 BMJ (Clinical research ed.) <https://pubmed.ncbi.nlm.nih.gov/30894343/> accessed 3 May 2022; Kenji Hashimoto and Bruce D Hammock, 'Reply to Reeves and Dunn: Risk for Autism in Offspring after Maternal Glyphosate Exposure' (2021) 118 Proceedings of the National Academy of Sciences of the United States of America <https://pubmed.ncbi.nlm.nih.gov/33443192/> accessed 3 May 2022; William Reeves and S Eliza Dunn, 'Additional Observations Regarding Glyphosate-Based Herbicides and Developmental Toxicity' (2021) 118 Proceedings of the National Academy of Sciences of the United States of America <https://pubmed.ncbi.nlm.nih.gov/33443200/> accessed 3 May 2022.

[81] Kohei Hamanaka and others, 'Large-Scale Discovery of Novel Neurodevelopmental Disorder-Related Genes through a Unified Analysis of Single-Nucleotide and Copy Number Variants' (2022) 14 Genome medicine 40 <https://pubmed.ncbi.nlm.nih.gov/35468861/> accessed 2 May 2022.

[82] Dan Bai and others, 'Association of Genetic and Environmental Factors With Autism in a 5-Country Cohort' (2019) 76 JAMA psychiatry 1035 <https://pubmed.ncbi.nlm.nih.gov/31314057/> accessed 2 May 2022.

[83] Michael N Antoniou and others, 'Glyphosate Does Not Substitute for Glycine in Proteins of Actively Dividing Mammalian Cells' (2019) 12 BMC research notes <https://pubmed.ncbi.nlm.nih.gov/31395095/> accessed 2 May 2022.

[84] Robin Mesnage and Michael N Antoniou, 'Facts and Fallacies in the Debate on Glyphosate Toxicity' (2017) 5 Frontiers in Public Health 316 </pmc/articles/PMC5705608/> accessed 2 May 2022.

RBCs that in the rat this is about 60 days.[85] Again, glyphosate does not bioaccumulate and slower clearance from trabecular bone is not surprising considering the rich calcium microenvironment. The ASDTR review is the best complication of glyphosate pharmacokinetics that does not support significant persistence in any tissue.[86]

Epidemiology - Glyphosate

The human epidemiology on glyphosate is of little value considering: (1) recall bias, (2) selection bias, and (3) confounding by additional exposures associated with hematologic cancers. This is inclusive off all epidemiology where misuse contributed to outcomes of verdicts that is egregious in two instances:

- The work of Zhang and colleagues (2019)[87] in reporting "meta-relative risk (meta-RR) of NHL in GBH-exposed individuals was increased by 41% (meta-RR = 1.41, 95% confidence interval, CI: 1.13-1.75).
    - **["Common weed killer glyphosate increases cancer risk by 41%, study says"**][88]
    - **EPA HED "…does not believe Zhang et al. used appropriate methods" (2020)**
- The work of Pahwa and colleagues (2019)[89] suggesting a "statistically significant association for handling glyphosate >2 days/year (OR 1.73, 95% CI 1.02-2.94, P-trend=0.2)
    - [**"A Few Days of Roundup Use a Year Doubles Cancer Risk, Expert Says"**][90]
    - Compare and contrast to OEHHA NSRL –Pahwa ->no analytical support for exposure

A short history may be prudent. After the IARC determination in 2015, tort preparation immediately began, the EPA CARC (2016) finds "glyphosate not likely carcinogenic," that is followed by the EPA SAP panel in December 2016 that was summarized with mixed opinions in May 2017. Support and criticisms of the IARC monograph program are published and a congressional hearing is held Feb 2018.

Andreotti (2018) publishes the largest cohort study to date "Glyphosate Use and Cancer Incidence in the Agricultural Health Study" concluding "In this large, prospective cohort study, **no association was**

[85] Michael J Derelanko, 'Determination of Erythrocyte Life Span in F-344, Wistar, and Sprague-Dawley Rats Using a Modification of the [3H]Diisopropylfluorophosphate ([3H]DFP) Method' (1987) 9 Toxicological Sciences 271 <https://academic.oup.com/toxsci/article/9/2/271/1637817> accessed 2 May 2022.

[86] Zoller and others (n 65); David W Brewster, Jo Anne Warren and William E Hopkins, 'Metabolism of Glyphosate in Sprague-Dawley Rats: Tissue Distribution, Identification, and Quantitation of Glyphosate-Derived Materials Following a Single Oral Dose' (1991) 17 Fundamental and applied toxicology : official journal of the Society of Toxicology 43 <https://pubmed.ncbi.nlm.nih.gov/1916078/> accessed 2 May 2022; Atsdr (n 67).

[87] Luoping Zhang and others, 'Exposure to Glyphosate-Based Herbicides and Risk for Non-Hodgkin Lymphoma: A Meta-Analysis and Supporting Evidence.' (2019) 781 Mutation research 186 <http://www.ncbi.nlm.nih.gov/pubmed/31342895> accessed 19 July 2020.

[88] 'Glyphosate Weed Killers Increase Cancer Risk by 41%, Study Says | CNN' <https://www.cnn.com/2019/02/14/health/us-glyphosate-cancer-study-scli-intl/index.html> accessed 3 May 2022.

[89] Manisha Pahwa and others, 'Glyphosate Use and Associations with Non-Hodgkin Lymphoma Major Histological Sub-Types: Findings from the North American Pooled Project' (2019) 45 Scandinavian journal of work, environment & health 600 <https://pubmed.ncbi.nlm.nih.gov/31246262/> accessed 3 May 2022.

[90] 'A Few Days of Roundup Use a Year Doubles Cancer Risk, Expert Says | Courthouse News Service' <https://www.courthousenews.com/two-days-of-roundup-use-a-year-doubles-cancer-risk-expert-says/> accessed 3 May 2022.

apparent between glyphosate and any solid tumors or lymphoid malignancies overall, including NHL and its subtypes." https://pubmed.ncbi.nlm.nih.gov/29136183/

Sheppard (2019)[91] publishes a sharp criticism of the AHS study and multiple imputation procedures, Andreotti (2019)[92] respond "no meaningful bias" Despite sharp criticism of the AHS study, Zhang and colleagues (April, 2019)[93] select '*a priori*' a subset of data from AHS study and claim a 41% increase in NHL. [94] This same year Pahwa (2019)[95] publishes a statistically significant association for handling glyphosate >2 days/year. Leon (2019) shows increases in diffuse large B-cell lymphoma and glyphosate (with some remarkable negative associations with other pesticides).

US EPA releases interim decision (Jan 2020)[96], "glyphosate is not likely to be carcinogenic" (noting that this was not permitted entry as evidence during the concurrent trial), and the Health Effects Division (HED) EPA publishes a critique of Leon (2019) and Zhang (2019)[97]:

- "…does not believe Zhang et al. (2019) used appropriate methods to perform their meta analyses"
- "In summary, the a priori hypothesis that higher/longer exposures produce larger effect sizes advanced by Zhang et al. (2019) in their analysis does not appear to be supported by the new AHS data from Andreotti et al. (2018) which is the largest, best-designed high-quality study examined."

Sheppard as a self-described 'at-home organic gardener' takes to Forbes[98] to explain the nuances of glyphosate cancer risk conflating results with the IARC determination with her publication while it is well-known that IARC did not consider these results as available and wherein these may have altered IARC determinations.[99] Crump (April, 2020)[100] in reviewing the human data on glyphosate from five case-control studies makes the case that **case-controlled studies were plagued with recall and selection**

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[91] Lianne Sheppard and Rachel M Shaffer, 'Re: Glyphosate Use and Cancer Incidence in the Agricultural Health Study' (2019) 111 Journal of the National Cancer Institute 214 <https://pubmed.ncbi.nlm.nih.gov/30597026/> accessed 4 May 2022.

[92] Gabriella Andreotti and others, 'Response to Sheppard and Shaffer' (2019) 111 Journal of the National Cancer Institute 216.

[93] Zhang and others (n 87).

[94] Pahwa and others (n 89).

[95] ibid.

[96] 'Interim Registration Review Decision and Responses to Public Comments for Glyphosate | US EPA' <https://www.epa.gov/ingredients-used-pesticide-products/interim-registration-review-decision-and-responses-public> accessed 4 May 2022.

[97] US EPA - Glyphosate: Epidemiology Review of Zhang et Al. (2019) and Leon et Al. (2019) Publications for Response to Comments on the Proposed Interim Decision' <https://doi.org/10.1016/j.mrrev.2019.02.001> accessed 4 May 2022.

[98] 'Glyphosate Science Is Nuanced. Arguments About It On The Internet? Not So Much' <https://www.forbes.com/sites/thelabbench/2020/02/20/glyphosate-science-is-nuanced-arguments-about-it-on-the-internet-not-so-much/amp/> accessed 4 May 2022.

[99] 'The WHO's Cancer Agency Left in the Dark over Glyphosate Evidence' <https://www.reuters.com/investigates/special-report/glyphosate-cancer-data/> accessed 4 May 2022.

[100] Kenny Crump, 'The Potential Effects of Recall Bias and Selection Bias on the Epidemiological Evidence for the Carcinogenicity of Glyphosate.' (2020) 40 Risk analysis : an official publication of the Society for Risk Analysis 696 <https://pubmed.ncbi.nlm.nih.gov/31889327/> accessed 19 July 2020.

bias. Additional studies and meta-analysis are published in 2020 and 2021: Donato (2020),[101] Rana (2020),[102] Boffetta (2021),[103] Meloni (2021),[104] Kabat (2021),[105] and more.

It should not be lost upon the casual observers or experts that glyphosate epidemiology is capricious and that by using 'tricks of the trade,' 'careful selection of data,' and the ubiquitous phrase 'adjusted for' can produce different conclusions. Consider the following publications and associated data that add further complexities.

Confounding, Confounders, and more Confounders

Turning back the clock more than 25 years (1995), Aaron Blair of IARC working group distinction and glyphosate epidemiology opined in "Agricultural Exposures and Cancer" that farmers may have elevated rates leukemia, non-Hodgkin's lymphoma, multiple myeloma, soft-tissue sarcoma, and cancers of the skin, lip, stomach, brain, and prostate through exposure not only to pesticides, but also **(1) engine exhaust, (2) solvents, (3) dusts, and (4) zoonotic microbes**. Engine exhaust, solvents, dusts, and zoonotic microbes are confounders; variables, factors, or extraneous determinants that can influence both the dependent variable and independent variable causing spurious associations where correlation does not imply causation.

Dr. Blair was quite correct 27 years ago. Fast forwarding from 1995 almost 20 years to publications by the International Lymphoma Epidemiology Consortium (InterLymph. 2014): (1) Farming, as an occupation, has positive associations with NHL and DLBCL that is shared with women hairdressing, charworkers, spray-painters, electrical wiremen, and carpenters;[106] (2) Using 17,471 NHL cases and 23,096 controls, additional risk factors for NHL subtypes are associated with medical history, exposures, and occupation: (a) autoimmune diseases, (b) hepatitis C virus seropositivity, (c) eczema, (d) blood transfusions, (e) cigarette smoking, (f) B-cell activating autoimmune disease, and (5) occupation as a general farm worker or painter (note: teachers, alcohol are negatively associated).[107]

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[101] Francesca Donato and others, 'Exposure to Glyphosate and Risk of Non-Hodgkin Lymphoma and Multiple Myeloma: An Updated Meta-Analysis' (2020) 111 La Medicina del lavoro 63 <https://pubmed.ncbi.nlm.nih.gov/32096774/> accessed 4 May 2022.

[102] Zhang and others (n 87).

[103] Paolo Boffetta and others, 'Exposure to Glyphosate and Risk of Non-Hodgkin Lymphoma: An Updated Meta-Analysis' (2021) 112 Medicina del Lavoro 194.

[104] Federico Meloni and others, 'Occupational Exposure to Glyphosate and Risk of Lymphoma:Results of an Italian Multicenter Case-Control Study' (2021) 20 Environmental health : a global access science source <https://pubmed.ncbi.nlm.nih.gov/33910586/> accessed 4 May 2022.

[105] Geoffrey C Kabat, William J Price and Robert E Tarone, 'On Recent Meta-Analyses of Exposure to Glyphosate and Risk of Non-Hodgkin's Lymphoma in Humans' (2021) 32 Cancer causes & control : CCC 409 <https://pubmed.ncbi.nlm.nih.gov/33447891/> accessed 4 May 2022.

[106] Andrea t Mannetje and others, 'Occupation and Risk of Non-Hodgkin Lymphoma and Its Subtypes: A Pooled Analysis from the InterLymph Consortium' (2016) 124 Environmental health perspectives 396 <https://pubmed.ncbi.nlm.nih.gov/26340796/> accessed 4 May 2022; Lindsay M Morton and others, 'Rationale and Design of the International Lymphoma Epidemiology Consortium (InterLymph) Non-Hodgkin Lymphoma Subtypes Project' (2014) 2014 Journal of the National Cancer Institute. Monographs 1 <https://pubmed.ncbi.nlm.nih.gov/25174022/> accessed 4 May 2022.

[107] Lindsay M Morton and others, 'Etiologic Heterogeneity among Non-Hodgkin Lymphoma Subtypes: The InterLymph Non-Hodgkin Lymphoma Subtypes Project' (2014) 2014 Journal of the National Cancer Institute. Monographs 130 <https://pubmed.ncbi.nlm.nih.gov/25174034/> accessed 4 May 2022.

Welding and metal working also has a high occupational risk for lymphomas.[108] Occupational exposures to organic dust may carry elevated risks of lymphoma subtypes.[109] Diesel Exhaust is a known human carcinogen (IARC, class I, known [in agreement with EPA, NTP, ACS]) also has been associated with lymphomas in some but not other studies. Solvent exposures are clearly associated with NHL, and a recent systematic review of human studies (Rana,…Zhang, 2021) suggests a strong link between benzene exposure and non-Hodgkin's lymphoma, especially for diffuse large B-cell lymphoma (DLBCL).[110] Note: diesel as a fuel can contain significant amounts of benzene, with phenanthrene, fluoranthene, pyrene, benz(a)anthracene, chrysene, and benzo(a)pyrene.

Take note again of above potential factors within the vast farmer exposome and links to NHL/lymphomas: (1) solvents/benzene, (2) metals, (3) grain dust, (4) diesel exhaust, (5) painting, and (6) welding & equipment repair and then consider the publication of Coble (2002)[111] some 20 years ago. "Exposures to multiple chemical, physical, and biological agents in agricultural work environments can result in confounding that may obscure or distort risks observed in epidemiologic studies" – that concluded --"Confounding risk ratios calculated for these activities suggest that the magnitude of bias due to confounding is likely to be minimal." Today, some would respectively disagree that these exposures are not significant or minimal when the evidence was take-home questionaries and telephone surveys. There are no objective data reassuring or ruling out these confounding factors (and more unlisted) virtually all glyphosate studies:

- Members of the AHS study were exposed to solvents (25%, citing 71 different solvents in reference to previous studies and IARC), metals (68%), grain dusts (65%), and diesel exhaust fumes (93%).
- Most of the farmers in the AHS reported performing routine maintenance tasks at least once a month, such as painting (63%), welding (64%), and repair of pesticide equipment (58%)
- The majority of farmers (74% in North Carolina; 59% in Iowa) reported holding nonfarm jobs, of which the most frequent were construction and transportation.

In a recent study by Siegel (2017) [112] Forty-one percent (41%) of 692 males in the Agricultural Health Study (AHS) reported some solvent exposure where gasoline, paint/lacquer thinner, petroleum distillates, and any solvent were categorized and associated with depressive symptoms. Farmers are

[108] Omid Aminian and others, 'Evaluation of Occupational Risk Factors in Non-Hodgkin Lymphoma and Hodgkin's Disease in Iranian Men' (2012) 5 Iranian Journal of Cancer Prevention 189 </pmc/articles/PMC4209571/> accessed 4 May 2022.

[109] Pierluigi Cocco and others, 'Occupational Exposure to Organic Dust and Risk of Lymphoma Subtypes in the EPILYMPH Case-Control Study' (2021) 47 Scandinavian journal of work, environment & health 42 <https://pubmed.ncbi.nlm.nih.gov/33103203/> accessed 4 May 2022.

[110] Iemaan Rana and others, 'Benzene Exposure and Non-Hodgkin Lymphoma: A Systematic Review and Meta-Analysis of Human Studies' (2021) 5 The Lancet. Planetary health e633 <https://pubmed.ncbi.nlm.nih.gov/34450064/> accessed 4 May 2022.

[111] Joseph Coble and others, 'Prevalence of Exposure to Solvents, Metals, Grain Dust, and Other Hazards among Farmers in the Agricultural Health Study.' (2002) 12 Journal of exposure analysis and environmental epidemiology 418 <https://pubmed.ncbi.nlm.nih.gov/12415490/> accessed 29 April 2020.

[112] Miriam Siegel and others, 'Organic Solvent Exposure and Depressive Symptoms among Licensed Pesticide Applicators in the Agricultural Health Study' (2017) 90 International archives of occupational and environmental health 849 <https://pubmed.ncbi.nlm.nih.gov/28702848/> accessed 4 May 2022.

frequently exposed to diesel exhaust, burning biomass, and black carbon,[113] where fine atmospheric particulate matter ($PM_{2.5}$) and black carbon have been associated with an increase in childhood non-Hodgkin's lymphoma.[114]

Where is the data to assure us that confounding factors played no role in glyphosate epidemiology over the past decades? How can 21st century studies ignore significant risk factors? Quoting Leon (2019)[115]: "…we did not adjust for cigarette smoking, alcohol intake, or family history of any cancer but did adjust for animal production and for different pesticide active ingredients from those included in the AHS publication." Factors such as: (1) tobacco; (2) obesity; and (3) alcohol, and (4) genetic predispositions (i.e., family history) are critical and significant factors for most cancers. Alcohol uniquely so in these studies as positively associated with more than 6 cancer types but negatively associated with NHL. It is amazingly that few recognize alcohol as an important carcinogen (IARC Class I, known), and perhaps more amazing that it appears consistently negative in associations with NHL.

Lawyers and politicians more than most recognize that how you ask a question can determine outcome of response. Considering recall bias, selection bias, and confounders, the existing epidemiology studies with glyphosate strain scientific credibility. These studies are far from definitive evidence or proof that glyphosate CAN (support) or CANNOT (deny) be associated with any hematologic cancer.

Bad Luck – Cancer and glyphosate

Christian Tomasetti's testimony in Stephens -v- Monsanto regarding cancer incidence as 'bad luck' was likely a major factor that swayed the most recent jury decision. Idiopathic, "relating to or denoting any disease or condition which arises spontaneously or for which the cause is unknown," may not be the best term as there is overwhelming data supporting the Stem Cell Theory of Cancer as derived from the Somatic Mutation Theory of Carcinogenesis (SMTC). Additionally, the causes and processes of spontaneously arising cancers are not completely unknown. Tomasetti's testimony that >95% of NHL is caused by replication errors is supported by his work examining rates of stem cell division in tissues.[116] This may not accurately reflect all mechanisms involved with spontaneous hematologic cancers and it may be somewhat misleading to ascribe cancers as arising from 'errors in replication' or 'bad luck' in the same 'fashion' as those that arise from more solid and highly organized tissues using stem cell markers.

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[113] Jean François Sauvé and others, 'Diesel Exhaust Exposure during Farming Activities: Statistical Modeling of Continuous Black Carbon Concentrations' (2020) 64 Annals of work exposures and health 503 <https://pubmed.ncbi.nlm.nih.gov/32219300/> accessed 4 May 2022; Emma M Stapleton and others, 'A Task-Based Analysis of Black Carbon Exposure in Iowa Farmers during Harvest' (2018) 15 Journal of occupational and environmental hygiene 293 <https://pubmed.ncbi.nlm.nih.gov/29286870/> accessed 4 May 2022.

[114] Ulla Arthur Hvidtfeldt and others, 'Residential Exposure to PM 2.5 Components and Risk of Childhood Non-Hodgkin Lymphoma in Denmark: A Nationwide Register-Based Case-Control Study' (2020) 17 International journal of environmental research and public health 1 <https://pubmed.ncbi.nlm.nih.gov/33271946/> accessed 4 May 2022.

[115] Maria E Leon and others, 'Pesticide Use and Risk of Non-Hodgkin Lymphoid Malignancies in Agricultural Cohorts from France, Norway and the USA: A Pooled Analysis from the AGRICOH Consortium.' (2019) 48 International journal of epidemiology 1519 <http://www.ncbi.nlm.nih.gov/pubmed/30880337> accessed 19 July 2020.

[116] Cristian Tomasetti, Lu Li and Bert Vogelstein, 'Stem Cell Divisions, Somatic Mutations, Cancer Etiology, and Cancer Prevention' (2017) 355 Science 1330; Cristian Tomasetti and Bert Vogelstein, 'Cancer Etiology. Variation in Cancer Risk among Tissues Can Be Explained by the Number of Stem Cell Divisions.' (2015) 347 Science (New York, N.Y.) 78 <http://www.ncbi.nlm.nih.gov/pubmed/25554788> accessed 11 February 2020.

Non-Hodgkin lymphomas are malignancies that may arise spontaneously and in response to carcinogens in germinal centers from mature B Cells that display point mutations, larger genomic lesions, and clonality from genetic and epigenetic analysis. This is where immunoglobulin (Ig) class switching recombination (CSR) and somatic hypermutation (SHM) coupled with base excision repair play important roles. Errors during antigen-driven B cell differentiation associated with immunoglobulin gene remodeling through V(D)J recombination and errors in double-strand break repair with highly proliferating cells present in germinal centers are likely part of multi-step processes that can lead to transformation. Mutagenic processes and rates in germinal centers are high by design and necessary to rapidly generative immunologic diversity. This can be adverse when mutations activate oncogenes or inactivate tumor suppressor genes leading to uncontrolled cellular proliferation and cancers.[117] Epigenetic events are also likely involved and to add additional complexity, I'll will quote Stratigopoulu (2020) as excellent and invokes elements of endogenous DNA damage:

> *The integrity of the genome is under constant threat of environmental and endogenous agents that cause DNA damage. Endogenous damage is particularly pervasive, occurring at an estimated rate of 10,000–30,000 per cell/per day, and mostly involves chemical DNA base lesions caused by oxidation, depurination, alkylation, and deamination. The base excision repair (BER) pathway is primary responsible for removing and repairing these small base lesions that would otherwise lead to mutations or DNA breaks during replication. Next to preventing DNA mutations and damage, the BER pathway is also involved in mutagenic processes in B cells during immunoglobulin (Ig) class switch recombination (CSR) and somatic hypermutation (SHM), which are instigated by uracil (U) lesions derived from activation-induced cytidine deaminase (AID) activity. BER is required for the processing of AID-induced lesions into DNA double strand breaks (DSB) that are required for CSR and is of pivotal importance for determining the mutagenic outcome of uracil lesions during SHM. Although uracils are generally efficiently repaired by error-free BER, this process is surprisingly error-prone at the Ig loci in proliferating B cells. Breakdown of this high-fidelity process outside of the Ig loci has been linked to mutations observed in B-cell tumors and DNA breaks and chromosomal translocations in activated B cells*."[118]

My criticism of testimony on the grounds of failing to address additional mechanisms and stem cell theories of carcinogenesis should NOT be misconstrued. The likelihood that the majority of NHL, perhaps >95%, results from what can be characterized as 'copy errors' appears well supported when 'copy errors' include the 'natural' processes above. It is my opinion that Dr. Tomasetti's simplification of complex processes to 'bad luck' and 'errors in DNA copying' (perhaps only to make the complex more palatable) misleads as to the fidelity of DNA replication that is extremely high. I would emphasize that it is the presence of endogenous DNA damage from endogenous toxicants that increases copy errors that

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[117] Marc Seifert, René Scholtysik and Ralf Küppers, 'Origin and Pathogenesis of B Cell Lymphomas' (2019) 1956 Methods in Molecular Biology 1; Marc Seifert, René Scholtysik and Ralf Küppers, 'Origin and Pathogenesis of B Cell Lymphomas' (2013) 971 Methods in molecular biology (Clifton, N.J.) 1 <https://pubmed.ncbi.nlm.nih.gov/23296955/> accessed 3 May 2022; Clare C So and Alberto Martin, 'DSB Structure Impacts DNA Recombination Leading to Class Switching and Chromosomal Translocations in Human B Cells' (2019) 15 PLoS genetics <https://pubmed.ncbi.nlm.nih.gov/30946744/> accessed 3 May 2022.

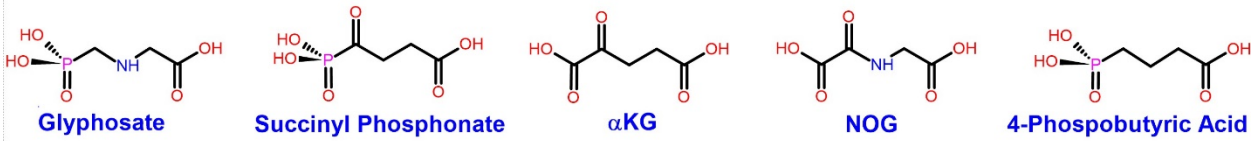
[118] Maria Stratigopoulou, Tijmen P van Dam and Jeroen EJ Guikema, 'Base Excision Repair in the Immune System: Small DNA Lesions With Big Consequences' <https://pubmed.ncbi.nlm.nih.gov/32547565/> accessed 24 October 2020.

is a significant source of genetic drift[119] and many if not most cancers.[120]
(worthwhile watching https://youtu.be/R4rxlRsNcs8)

Chemical Similarity – Where Future Research 'may' be Needed

Chemical structure determines biological activity, and all things are toxic.[121] At very high and extreme doses, glyphosate could disrupt pathways involving alpha-ketoglutarate ((αKG), 2-oxoglutaric acid (2OG)). The following set of compounds would be useful to study concurrently in future assays of glyphosate and glyphosate formulations to determine non-significant risk levels. Specifically, regarding mechanisms involving: (1) mitochondrial toxicity (complex I-IV interactions and or inhibition, and perhaps channels) with potential to generate reaction oxygen species (ROS); (2) Effects on DNA methylation, (i.e., members of the TET-family), that is involved in epigenetics; and (3) Effects on 2-Oxoglutarate-Dependent Oxygenases (with emphasis on proyl-hydroxylase interactions that is key to oxygen sensing, HIF-signaling, that could perhaps explain some aspects of aquatic species sensitivity). A lengthy discussion here clearly being outside scope of comment.

Again – emphasis - At high and or extreme doses (not a bad research proposal here)



Glyphosate	Succinyl Phosphonate	αKG	NOG	4-Phospobutyric Acid
PCID: 3496 CAS 1071-83-6 Glyphosate 2-(phosphonomethylamino) acetic acid C(C(=O)O)NCP(=O)(O)O	PCID 46209593 CAS 26647-82-5 Succinyl phosphonate 4-oxo-4-phosphonobutanoic acid C(CC(=O)P(=O)(O)O)C(=O)O	PCID 51 CAS 328-50-7 2-Oxoglutaric Acid 2-oxopentanedioic acid (alpha ketoglutaric acid) C(CC(=O)O)C(=O)C(=O)O	PCID 3080614 CAS 5262-39-5 N-Oxalylglycine 2-(carboxymethylamino)-2-oxoacetic acid C(C(=O)O)NC(=O)C(=O)O	PCID: 2773805 CAS 4378-43-2 4-Phosphonobutyric 4-Phosphonobutanoic Acid C(CC(=O)O)CP(=O)(O)O

The phenomenon of transgenerational inheritance is a subject of importance, however the work of Kubsad (2017)[122] on glyphosate and other toxicants recently published in the high-profile journals by

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[119] Motoo Kimura, 'Evolutionary Rate at the Molecular Level.' (1968) 217 Nature 624 <http://www.ncbi.nlm.nih.gov/pubmed/5637732> accessed 4 April 2020; Motoo Kimura, 'SOLUTION OF A PROCESS OF RANDOM GENETIC DRIFT WITH A CONTINUOUS MODEL' (1955) 41 Proceedings of the National Academy of Sciences of the United States of America 144 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC528040/> accessed 4 May 2022; Marcin Cieslik and Arul M Chinnaiyan, 'Global Cancer Genomics Project Comes to Fruition' <https://media.nature.com/original/magazine-assets/d41586-020-00213-2/d41586-020-00213-2.pdf> accessed 19 April 2020.

[120] Anthony Tubbs and André Nussenzweig, 'Endogenous DNA Damage as a Source of Genomic Instability in Cancer' (2017) 168 Cell 644 </pmc/articles/PMC6591730/> accessed 4 May 2022; Ivonne MCM Rietjens and others, 'The Role of Endogenous versus Exogenous Sources in the Exposome of Putative Genotoxins and Consequences for Risk Assessment' (2022) 96 Archives of Toxicology 1297 </pmc/articles/PMC9013691/> accessed 4 May 2022; Henrik Carlsson and Margareta Törnqvist, 'An Adductomic Approach to Identify Electrophiles In Vivo' (2017) 121 Suppl 3 Basic & clinical pharmacology & toxicology 44 <https://pubmed.ncbi.nlm.nih.gov/27889941/> accessed 4 May 2022.

[121] JF Borzelleca, 'Paracelsus: Herald of Modern Toxicology.' (2000) 53 Toxicological sciences : an official journal of the Society of Toxicology 2 <http://www.ncbi.nlm.nih.gov/pubmed/10653514> accessed 28 August 2019; Spyros N Michaleas and others, 'Theophrastus Bombastus Von Hohenheim (Paracelsus) (1493-1541): The Eminent Physician and Pioneer of Toxicology' (2021) 8 Toxicology reports 411 <https://pubmed.ncbi.nlm.nih.gov/33717994/> accessed 2 May 2022.

[122] Deepika Kubsad and others, 'Assessment of Glyphosate Induced Epigenetic Transgenerational Inheritance of Pathologies and Sperm Epimutations: Generational Toxicology' (2019) 9 Scientific reports <https://pubmed.ncbi.nlm.nih.gov/31011160/> accessed 4 May 2022.

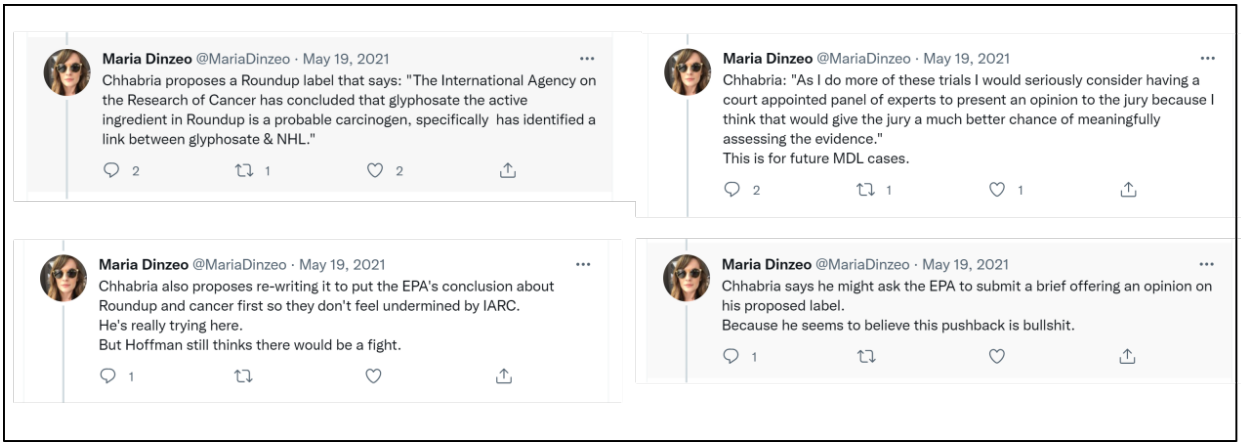
Nilsson (2022)[123] and Beck (2022)[124] using the phrase of Url – "is no way forward." Repeated intraperitoneal injections of toxicants at high levels (e.g., 25 mg/kg glyphsate) during sensitive developmental windows is not helpful.

In my opinion, the work of

- Ford (2017)[125] in "Mapping Proteome-wide Targets of Glyphosate in Mice" and observations that at high doses glyphosate can be metabolized *in vivo* reactive metabolites such as glyoxylate (albeit lacking dose-response data), and
- Duforestel (2019)[126] in "Glyphosate Primes Mammary Cells for Tumorigenesis by Reprogramming the Epigenome in a TET3-Dependent Manner" with some understanding of added ascorbic acid effects.

Deserve far more attention and further exploration.

Selected texts as reported by Maria Dizeo @Courthousenews
regarding the subject of 'labeling' by Judge Chhabria 19-May-2021



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[123] Eric E Nilsson, Millissia Ben Maamar and Michael K Skinner, 'Role of Epigenetic Transgenerational Inheritance in Generational Toxicology.' (2022) 8 Environmental epigenetics dvac001 <http://www.ncbi.nlm.nih.gov/pubmed/35186326> accessed 4 May 2022.

[124] Daniel Beck and others, 'Environmental Induced Transgenerational Inheritance Impacts Systems Epigenetics in Disease Etiology.' (2022) 12 Scientific reports 5452 <http://www.ncbi.nlm.nih.gov/pubmed/35440735> accessed 4 May 2022.

[125] Breanna Ford and others, 'Mapping Proteome-Wide Targets of Glyphosate in Mice' (2017) 24 Cell chemical biology 133 <https://pubmed.ncbi.nlm.nih.gov/28132892/> accessed 4 May 2022.

[126] Manon Duforestel and others, 'Glyphosate Primes Mammary Cells for Tumorigenesis by Reprogramming the Epigenome in a TET3-Dependent Manner.' (2019) 10 Frontiers in genetics 885 <https://pubmed.ncbi.nlm.nih.gov/31611907/> accessed 15 July 2020.

William Sawyer Expert Testimony (Pilliod -v- Monsanto)

Copied from transcript

> *Brett Wisner: Let's start off with the first one, glyphosate. What is glyphosate?*
>
> *William Sawyer: Well, glyphosate is what we call an organophosphorus compound. It's closely related to what we call organophosphates which there's a number of organophosphate that are of concern. Sarin is a war gas. It can penetrate right through clothing. It's lethal within a matter of a minute. There's other organophosphates that are used in farming that are tightly regulated because of neurotoxicity. Glyphosate is closely related, but it's not an organophosphate. It's an organophosphorus compound. And its chemical characteristic from a toxicological standpoint is that it like to what we call phosphorylate. You don't want to be phosphorylated. Okay. You would look like a twisted hot dog. Phosphorylating a protein or DNA results in damage. And that is the characteristic of glyphosate that causes more harm than just knocking out the shikimate pathway in the plant. That is one thing it can do. It can bind specifically to a plant enzymatic pathway that shuts down the life of that plant. And that is you know, an excellent characteristic of glyphosate. But what's not talked about is phosphorylation and the damage it causes."*

This is probably one of the best examples of a Rule 702 failure while also being illustrative of defense failure to challenge. Unless the laws of physics and physical chemical do not apply within the State of California, glyphosate is not a phosphorylating agent and glyphosate has no meaningful toxicological similarity to the chemical warfare agent sarin (CAS 107-44-8, PCID: 7871). Additionally, sarin shows no evidence of genotoxicity (i.e., mutagenesis, chromosomal damage, unscheduled DNA synthesis, or sister chromatid exchange) (Goldman et al., 1988 in toxicity Studies on Agents GB (Sarin, Types I and II) and GD (Soman). Available from the National Technical Information Service. NTIS AD-A187841 also available within Gulf War and Health: Volume 1. Depleted Uranium, Sarin, Pyridostigmine Bromide, Vaccines https://nap.nationalacademies.org/read/11064/chapter/4

Courtroom theatrics involving: (1) spray bottles, (2) reference to popping champagne corks, (3) stating regulatory professionals as literally having 'blood on their hands' and (4) highly animated lawyers telling jurys to "go-get-'em" is evidence that judicial verdicts are feckless proof of truth that lack scientific rigor.

I often wonder if regulatory professionals elsewhere in the world are watching.

END

I have not fully proofed this Appendix – and apologize in advance for any typos or lack of reference where appropriate. Also, I recognize "There are more things in heaven and earth, than are dreamt of in this philosophy" Again, thank you for the opportunity to comment…