October 19, 2015

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Re: Support for Prop 65 Glyphosate Listing

Dear Ms. Barajas-Ochoa and Ms. Robinson,

The undersigned food, farming, public health and environmental organizations support the Office of Environmental Health Hazard Assessment's (OEHHA's) determination to list glyphosate as a substance known to the State of California to cause cancer under the Safe Drinking Water and Toxic Enforcement Act of 1986 (aka Proposition 65[1]).

On September 4, 2015, OEHHA issued a notice of intent to list glyphosate as a chemical known to the state to cause cancer under Proposition 65.[2] OEHHA has determined that glyphosate meets the requirements for listing pursuant to the Labor Code listing mechanism. Under this mechanism, the law requires that "[s]ubstances listed as human or animal carcinogens by the International Agency for Research on Cancer (IARC)" be listed under Proposition 65.[3] IARC is an arm of the World Health Organization, and the world's leading authority on cancer. Thus, the only relevant question for OEHHA is whether IARC has, in fact, determined that glyphosate is a human or animal carcinogen. We agree with the agency that the answer is yes.

Glyphosate is an animal carcinogen

Near the end of IARC's exhaustive, 92-page monograph on glyphosate, the Agency concludes: "There is *sufficient evidence* in experimental animals for the carcinogenicity of glyphosate."[4] This sufficient evidence derives from multiple studies in which glyphosate, when administered in the diet,

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[1] Health and Safety Code section 25249.5 et seq.
[2] CA EPA OEHHA (2015). Notice of intent to list chemicals by the Labor Code mechanism: tetrachlorvinphos, parathion, malathion, glyphosate. CA Environmental Protection Agency, Office of Environmental Health Hazard Assessment, September 4, 2015.
[3] Labor Code section 6382(b)(1); Health and Safety Code section 25249.8(a). Health and Safety Code section 25249.8(a) incorporates Labor Code section 6382(b)(1).
[4] IARC (2015a). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112. Glyphosate. IARC, World Health Organization, Lyon, France, p. 78. http://monographs.iarc.fr/ENG/Monographs/vol112/mono112-02.pdf

caused carcinomas or other tumors in the kidneys, pancreas, liver and other organs of experimental mice and rats.[5]

In IARC's evaluation system, "sufficient evidence" is evidence that: 1) Meets a specific set of formal scientific criteria; and 2) Establishes "a causal relationship" between the agent in question and cancer.[6] With respect to studies in animals and humans, IARC distinguishes four categories of evidence, "sufficient" being the strongest. Other categories are "limited evidence," "inadequate evidence" and "evidence suggesting lack of carcinogenicity."[7] Thus, there is no dispute that glyphosate has been listed an "animal carcinogen" by the International Agency for Research on Cancer. Under Health and Safety Code section 25249.8(1)'s plain language, therefore, we agree with OEHHA's decision to list glyphosate as a substance known to the State of California to cause cancer under Proposition 65.

Additional evidence that glyphosate is carcinogenic

While unnecessary for listing under Proposition 65, it is important to note that IARC found additional evidence of glyphosate's carcinogenicity in two other areas. First, well-designed human epidemiology studies in the U.S., Canada and Sweden found associations between exposure to glyphosate and increased incidence of the immune system cancer non-Hodgkin's lymphoma in farmers.[8] Because some but not all epidemiology studies found this association, IARC classified the human evidence as "limited" rather than "sufficient."[9] Second, IARC found strong mechanistic evidence that glyphosate causes damage to DNA and chromosomes as well as oxidative stress – pathways by which chemicals are known to cause cancer in human beings.[10] This additional evidence – from real-world studies of farmers and studies on tissue damage caused by glyphosate – corroborates IARC's separate "animal carcinogen" finding. IARC's overall assessment of glyphosate, which weighs evidence from all three areas – animal studies, human epidemiology and mechanistic research – resulted in assignment of glyphosate to Group 2A, "probably carcinogenic to humans."[11] Group 2A is the second highest of five IARC categories for carcinogenic potential, exceeded only by Group 1, which includes agents such as tobacco smoking, plutonium and asbestos.[12] Other substances classified by IARC as Group 2A, probable human carcinogens, that are also listed under Proposition 65 include DDT and inorganic lead compounds.[13]

IARC's classification of glyphosate has been criticized by Monsanto,[14] individuals and organizations funded by Monsanto and other chemical companies,[15] and bloggers.[16] While these criticisms are

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[5] IARC (2015a), op. cit., p. 76. Note that haemangiosarcoma

[6] IARC (2006). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Preamble. IARC, World Health Organization, Lyon, France, p. 20. http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf.

[7] IARC (2006), op. cit., p. 21.

[8] IARC (2015a), op. cit., pp. 75-76.

[9] Pollack A (2015). Weed killer, long cleared, is doubted. The New York Times, 3/27/15.

[10] IARC (2015a), op. cit., pp. 76-78.

[11] Guyton KZ, Loomis D, Grosse Y, El Ghissassi F, Benbrahim-Tallaa L, Guha N, Scoccianti C, Mattock H, and Straif K, on behalf of the International Agency for Research on Cancer Monograph Working Group (2015). Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. The Lancet Oncology 16(5): 490-491. http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045%2815%2970134- 8/fulltext.

[12] See IARC's searchable List of Classifications, Volumes 1-113, http://monographs.iarc.fr/ENG/Classification/latest_classif.php.

[13] For DDT, see: Loomis D, Guyton K, Grosse Y, El Ghissai F, Bouvard V, Benbrahim-Tallaa L, Guha N, Mattock H, Straif K, on behalf of the International Agency for Research on Cancer Monograph Working Group (2015). Carcinogenicity of lindane, DDT, and 2,4-dichlorophenoxyacetic acid. The Lancet Oncology 16(8): 891-892. For lead compounds, see IARC List of Classifications, cited in last footnote. Compare OEHHA's Proposition 65 list (August 25, 2015) at http://oehha.ca.gov/prop65/prop65_list/files/P65single082515.pdf.

[14] Monsanto (2015). Monsanto disagrees with IARC classification for glyphosate. March 20, 2015. http://news.monsanto.com/news/monsanto-disagrees-iarc-classification-glyphosate.

entirely irrelevant to OEHHA's statutory duty to list glyphosate under Proposition 65, we nevertheless here respond to three points frequently raised by critics.

Rebutting criticisms of IARC's glyphosate determination

1) IARC's determination was biased

IARC has been recognized as the world's leading authority on cancer for four decades. IARC's Monograph Programme is funded mainly by the U.S. National Cancer Institute, a division of the National Institutes of Health. Additional support is provided by organizations such as the European Commission, the U.S. National Institute of Environmental Health Sciences and the U.S. Environmental Protection Agency.[17] IARC has put in place rigorous protocols both for the selection of agents to assess and to ensure that members who serve on the Working Groups that make carcinogenicity classifications are both qualified and free from conflicts of interest.[18] In a remarkable defense of IARC's program, 124 medical scientists from universities and government health institutes around the world co-authored an article rebutting misinformed criticisms of its carcinogenicity determination process.[19]

The 17-member IARC Working Group that made the glyphosate determination was composed of qualified scientists from a wide range of countries and disciplines, including seven from the U.S. The Working Group chair, Dr. Aaron Blair, is a scientist emeritus at the U.S. National Cancer Institute,[20] and he is a distinguished epidemiologist who has spent over three decades exploring environmental causes of cancer. Significantly, the 17 members of the Working Group were unanimous in their determination that glyphosate is "probably carcinogenic to humans."[21] This remarkable unanimity reflects the strength of the evidence, and contrasts with some other determinations, in which "significant minorities" may dissent from the majority opinion.[22]

2) IARC's assessment is at odds with that of the U.S. Environmental Protection Agency (EPA)

In 1985, EPA classified glyphosate as a possible carcinogen based on a long-term feeding study, in which male mice fed glyphosate developed kidney tumors.[23] EPA initially defended its determination,[24] but, reclassified glyphosate as non-carcinogenic in 1991 after input from Monsanto led to a dubious re-evaluation of the evidence.[25] IARC disputes EPA's reinterpretation, noting that an EPA Scientific Advisory Panel found that the reevaluation of the mouse study still demonstrates

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[15] Robinson, C (2015). Kevin Folta is "wrong," over cancer-glyphosate link, says expert. GM Watch, August 27, 2015. http://www.gmwatch.org/news/latest-news/16374-kevin-folta-exposed-again-for-making-false-claims.

[16] Johnson N (2015). So Roundup "probably" causes cancer. This means what, exactly? GRIST, March 24, 2015. http://grist.org/business-technology/so-roundup-probably-causes-cancer-this-means-what-exactly/.

[17] Pearce N et al. (2015). IARC Monographs: 40 years of evaluating carcinogenic hazards to humans. Environmental Health Perspectives 123(6): 507-514.

[18] Ibid., see also IARC (2006), op. cit.

[19] Pearce et al (2015), op. cit.

[20] Gillam C (2015). Scientist defends WHO group report linking herbicide to cancer. Reuters, 3/26/15.

[21] Pollack A (2015). Weed killer, long cleared, is doubted. The New York Times, 3/27/15.

[22] Loomis D, Guyton K, Grosse Y, El Ghissai F, Bouvard V, Benbrahim-Tallaa L, Guha N, Mattock H, Straif K, on behalf of the International Agency for Research on Cancer Monograph Working Group (2015). Carcinogenicity of lindane, DDT, and 2,4-dichlorophenoxyacetic acid. The Lancet Oncology 16(8): 891-892. This Working Group classified 2,4-D as "possibly carcinogenic to humans" (Group 2B), although "significant minorities" found the animal and human evidence to be stronger; if the minority views had prevailed, 2,4-D would likely have been classified as "probably carcinogenic" (Group 2A), the same category as glyphosate.

[23] EPA (1985a). Consensus review of glyphosate. Memorandum co-signed by 8 members of EPA's Toxicology Branch, March 4, 1985. For review of other toxicity studies, see: Cox, C (1995). Glyphosate, Part 1: Toxicology. Journal of Pesticide Reform 15(3), Fall 1995. http://www.1hope.org/glyphos8.htm.

[24] EPA (1985b). Memorandum on Use of historical data in determining the weight of evidence from kidney tumor incidence in the glyphosate two-ear feeding study; and some remarks on false positives. EPA, 2/26/85. Formerly available at http://www.epa.gov/pesticides/chemicalsearch/chemical/foia/cleared-reviews/reviews/103601/103601-170.pdf.

[25] EPA (1991). Memorandum on Second Peer Review of Glyphosate, U.S. Environmental Protection Agency, 10/30/91.

that glyphosate causes kidney tumors in mice according to IARC protocols. Based on this and more recent studies, IARC concluded that "there is sufficient evidence of carcinogenicity in experimental animals."[26] Since IARC's determination, EPA has removed from its website (or relocated) many key studies, which are no longer available at the web addresses listed in the IARC monograph.[27]

IARC's assessment is up-to-date, analyzing all of the credible research, while EPA's last comprehensive assessment of glyphosate occurred in 1993. IARC considered a broad range of evidence, including human epidemiology and other peer-reviewed studies, while EPA did not assess human epidemiology and relied almost entirely on unpublished industry studies.[28] IARC is an independent agency whose sole mission is human health. While EPA is charged with protecting human health as well, its practice of relying excessively on industry-submitted studies introduces conflicts of interest and excludes pertinent evidence from peer-reviewed studies by independent scientists.[29] EPA is currently re-assessing glyphosate, and has said it will consider IARC's findings.

3) IARC's hazard assessment incorporates elements of human exposure

A formal risk assessment evaluates both the inherent toxicity of a substance (called hazard) and our exposure to it. While a toxic substance is always hazardous, the risk it poses depends upon the circumstances of exposure.[30] While IARC's listing determination is a hazard assessment and does not directly evaluate exposure it does consider the results of qualified epidemiological studies, which evaluate risk from actual exposure under real-world conditions. As noted above, IARC found that epidemiology studies of farmers in three countries show an association between exposure to glyphosate and increased risk of non-Hodgkin's lymphoma (NHL), an often-fatal immune system cancer. Another finds a "suggestive association" between glyphosate and multiple myeloma, now considered a subtype of NHL, and recommends follow-up given the herbicide's widespread use.[31] Because there is typically a time lag of decades between exposure to a carcinogen and elevated cancer rates, and glyphosate use has risen dramatically over the past 10-15 years, the full effects of glyphosate's rising use remain to be discovered.

Glyphosate use and exposure on the rise

There is no doubt that both the use of and exposure to glyphosate has increased tremendously over the past two decades. In the U.S., agricultural use of glyphosate exceeded 280 million lbs. in 2012, exceeding by more than four times the amount of the second most heavily used conventional pesticide, atrazine.[32] This represents a 10-fold increase in use since 1995, driven primarily by the

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[26] IARC (2015b). IARC Monographs Volume 112: evaluation of five organophosphate insecticides and herbicides. International Agency for Research on Cancer, Lyon, France, 3/20/15. http://www.iarc.fr/en/media-centre/iarcnews/pdf/MonographVolume112.pdf.

[27] See IARC (2015a), pp. 82-83. Studies no longer accessible at the websites listed in IARC's References section include EPA 1980a, 1980b, 1985a, 1985b, 1986, 1991a, 1991b and 1991d.

[28] EPA (1993). Glyphosate Reregistration Eligibility Decision. U.S. Environmental Protection Agency, Sept. 1993, Appendix. C. Appendix C lists studies relied upon by EPA in its assessment of glyphosate for reregistration.

[29] Boone MD, Bishop CA, Boswell LA, Brodman RD, Burger J, Davidson C, Gochfeld M, Hoverman JT, Neuman-Lee LA, Relyea RA, Rohr JR, Salice C, Semlitsch RD, Sparling D, Weir S (2014). Pesticide regulation amid the influence of industry. BioScience 64: 917-922.

[30] Key factors include the timing and level of exposure. Children and fetuses are generally more susceptible to harm than adults; and while greater exposure is generally thought to mean greater risk, lower levels of hormone-disrupting chemicals sometimes cause more harm than higher levels. See e.g. Vandenberg LN et al 2012. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. Endocrine Reviews 33(3): 378-455.

[31] De Roos AJ et al (2005). Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. Environmental Health Perspectives 113(1): 49-54. IARC (2015a), op. cit., notes that: "Multiple myeloma is now considered to be a subtype of NHL" (p. 16).

[32] For 2012 agricultural use of glyphosate (>280 million lbs.) and atrazine (70 million lbs.) in the U.S., see U.S. Geological Survey charts below maps at pertinent links on http://water.usgs.gov/nawqa/pnsp/usage/maps/compound_listing.php?year=2012&hilo=L

widespread planting of glyphosate-resistant corn, soybeans and cotton, which each represent roughly 90% of respective crop acres.[33] Total U.S. glyphosate use exceeds 300 million lbs./year.[34] Use and exposure will increase still more if glyphosate-resistant turfgrasses currently being developed for lawns, playing fields and golf courses are introduced.[35] In California, glyphosate is sprayed on more acres than any other non-adjuvant pesticide, and is the fifth most heavily used pesticide. Major uses are in almond and wine grape orchards as well as on glyphosate-resistant varieties of cotton and alfalfa.[36]

With such massive use, it is not surprising that glyphosate is frequently detected in the air, rainfall and surface waters of the U.S.[37] Although there is very little testing for glyphosate residues in food, especially in the U.S., tests that have been conducted frequently detect it in foods, including bread.[38] Glyphosate is found at similar frequencies and levels in the urine of farm and non-farm family members, including children, suggesting similar levels of exposure.[39] Glyphosate has also been detected in human blood.[40] EPA's maximal "safe" level of chronic glyphosate exposure is six times higher than Europe's,[41] and 17.5-fold higher than the level that EPA itself set in the early 1980s.[42] EPA's latest high-end estimate of infant exposure to glyphosate exceeds the level it regarded as safe in the 1980s;[43] and is five times higher than the maximum level suggested by independent scientists.[44]

Conclusion

For all of the above reasons, we support the listing of glyphosate as a chemical known to the State of California to cause cancer. OEHHA is required by law to make this listing under Proposition 65's Labor Code listing mechanism, because glyphosate has been deemed to be an animal carcinogen by the World Health Organization's International Agency for Research on Cancer.

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[33] USDA ERS (2015). Adoption of genetically engineered crops in the U.S. USDA Economic Research Service. http://www.ers.usda.gov/data-products/adoption-of-genetically-engineered-crops-in-the-us/recent-trends-in-ge-adoption.aspx.

[34] In addition to annual use of over 280 million lbs. glyphosate in U.S. agriculture (see footnote 26), non-farm uses total 18-23 million lbs./year. See: EPA (2011). Pesticide Industry Sales and Usage: 2006 and 2007 Market Estimates, EPA, Feb. 2011, Tables 3.7 & 3.8.

[35] Keim B (2011). Genetically modified grass could make superweed problem worse. Wired 7-11-11. http://www.wired.com/2011/07/engineered-bluegrass/. Snow AA (2012). Illegal gene flow from transgenic creeping bentgrass: the saga continues. Molecular Ecology 21: 4663-4664.

[36] CA DPR (2015). Summary of Pesticide Use Report Data 2013: Indexed by Chemical. California Department of Pesticide Regulation, May 2015. http://www.cdpr.ca.gov/docs/pur/pur13rep/chmrpt13.pdf.

[37] For glyphosate in air, rain and surface water, see Chang F-C et al (2011). Occurrence and fate of the herbicide glyphosate and its degradate aminomethylphosphonic acid in the atmosphere. Environ Toxicol Chem 30(3): 548-555; and Coupe RH et al (2011). Fate and transport of glyphosate and aminomethylphosphonic acid in surface waters of agricultural basins. Pest Manag Sci 68(1): 16-30.

[38] For glyphosate in food, see FoEE (2013). Human contamination by glyphosate. Friends of the Earth Europe, June 2013. https://www.foeeurope.org/sites/default/files/press_releases/foee_4_human_contamination_glyphosate.pdf. For lack of testing in U.S., see: Gillam C (2015). Regulators may recommend testing food for glyphosate residues, Reuters, 4/20/15.

[39] Curwin BD et al (2007a). Urinary pesticide concentrations among children, mothers and fathers living in farm and non-farm households in Iowa. Ann. Occup. Hyg. 51(1): 53-65; and Curwin BD et al (2007b). Pesticide dose estimates for children of Iowa farmers and non-farmers. Environmental Research 105: 307-315. For Europe, see FoEE (2013), op. cit.

[40] Aris A, Leblanc S. Maternal and fetal exposure to pesticides associated to genetically modified foods in Eastern Townships of Quebec, Canada. Reprod Toxicol. 2011: 31(4): 528-533.

[41] "Acceptable daily intake" (ADI) or the equivalent "chronic population adjusted dose" (cPAD), expressed as milligrams glyphosate per kilogram body weight per day: 0.3 in Europe vs. 1.75 mg/kg/day in the U.S. For Europe, see http://ec.europa.eu/food/plant/protection/evaluation/existactive/list1_glyphosate_en.pdf, Appendix II; for US, see EPA (2006). Glyphosate human health risk assessment for proposed use on Indian mulberry and amend use on pea. EPA, 9/29/06, p. 21.

[42] For EPA's setting of the glyphosate ADI at 0.1 mg/kg/day in the early 1980s (vs. 1.75 today), see EPA (1983). Glyphosate (Roundup) on wheat. March 3, 1983.

[43] See EPA (2006), op. cit., in footnote 34, Table 6.1.2, maximum infant exposure = 0.127562 mg/kg/day, 28% higher than the 1980's ADI of 0.1 mg/kg/day (see EPA (1983), op. cit., in last footnote).

[44] Antoniou M et al. (2012). Teratogenic effects of glyphosate-based herbicides: divergence of regulatory decisions from scientific evidence. J Environ Anal Toxicol S4:006. doi:10.4172/2161-0525.S4-006, suggesting an ADI of 0.025 mg/kg/day based on teratogenic rather than carcinogenic effects.

Please contact Rebecca Spector, West Coast Director at the Center for Food Safety (rspector@centerforfoodsafety, 415-826-2770) with any questions.

Sincerely,

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