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October 20, 2015

Ms. Esther Barajas-Ochoa
Office of Environmental Health Hazard Assessment
P.O. Box 4010, MS-19B
Sacramento, California 95812-4010

Re: Notice of Intent to List Chemicals by the Labor Code Mechanism: Tetrachlorvinphos, Parathion, Malathion, Glyphosate

Dear Ms. Barajas-Ochoa,

We are writing to support California's intention to list glyphosate and its salts as a chemical known to the state to cause cancer under Proposition 65. Beyond Pesticides is a national not-for-profit organization that works to advance improved protections from pesticides and alternative pest management strategies that reduce or eliminate a reliance on toxic pesticides. We are submitting these comments on behalf of our large membership in California.

The California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) intends to list glyphosate as a substance known to the state to cause cancer under the Safe Drinking Water and Toxic Enforcement Act of 1986, also known as Proposition 65. According to OEHHA, this action is being proposed pursuant to the Labor Code listing mechanism, which requires that certain substances identified by the International Agency for Research on Cancer (IARC) be listed as known to cause cancer under Proposition 65. OEHHA is requesting that comments be limited to whether IARC has identified the specific chemical or substance as a known or potential human or animal carcinogen.

We believe glyphosate meets the requirements for listing as causing cancer specified in Health and Safety Code section 25249.8(a) and 'Labor Code' section 6382(b)(1).[1] Glyphosate, the active ingredient in the popular Roundup, manufactured by Monsanto, is a herbicide that is widely used on agricultural and non-agricultural sites. It has been linked to numerous adverse human and environmental health issues.

[1] OEHHA. 2015. Notice of Intent to List Chemicals by the Labor Code Mechanism: Tetrachlorvinphos, Parathion, Malathion, Glyphosate. Proposition 65. http://oehha.ca.gov/prop65/CRNR_notices/admin_listing/intent_to_list/090415LCset27.html

In March 2015, the World Health Organization's IARC found that there was *sufficient evidence of carcinogenicity* in experimental organisms to classify glyphosate as "probably carcinogenic to humans" (Group 2A).[2] IARC finds sufficient mechanistic evidence in animals for genotoxicity and oxidative stress. Based on the available scientific evidence, we believe IARC has appropriately identified glyphosate as a potential human or animal carcinogen, and should be listed under California's Proposition 65.

IARC Cancer Classification and Criteria:

Group 2A. IARC has a well-defined cancer classification scheme that takes into account available human and animal data. Substances can be placed in one of six groups; Group 1 "carcinogenic to humans," Group 2A "probably carcinogenic," Group 2B "possibly carcinogenic," Group 3 "not classifiable as to its carcinogenicity," and Group 4 "probably not carcinogenic."[3]

Accordingly, Group 2A, "probably carcinogenic to humans," is used when there is *limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals.* In some cases, a substance may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and ***sufficient evidence of carcinogenicity in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans***. A substance may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. A substance may also be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

For IARC, *sufficient evidence of carcinogenicity* is defined as where a *causal relationship has been established between the agent and human cancer.* That is, *a positive relationship has been observed between the exposure and cancer in studies* in which chance, bias and confounding could be ruled out with reasonable confidence. For experimental animal data, *a causal relationship is established between the substance and an increased incidence of malignant tumors/abnormal growth (neoplasms) or of an appropriate combination of benign and malignant neoplasms* in, (a) two or more species of animals, or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumors in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*. A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree

[2] IARC. IARC Monographs Volume 112: evaluation of five organophosphate insecticides and herbicides. 20 march 2015. http://www.iarc.fr/en/media-centre/iarcnews/pdf/MonographVolume112.pdf

[3] IARC. Preamble: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. World Health Organization (WHO) 2006. http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf

with regard to incidence, site, type of tumor or age at onset, or when there are strong findings of tumors at multiple sites.

Mechanistic evidence. Mechanistic and other relevant data may provide evidence of carcinogenicity and also help in assessing the relevance and importance of findings of cancer in animals and in humans. Specifically, IARC may identify the possible mechanisms by which the substance may increase the risk of cancer that can include (i) changes in physiology, (ii) changes at the cellular level, and (iii) changes at the molecular level (including genotoxicity). IARC then assesses whether that particular mechanism is likely to be operative in humans.

With these in mind, IARC concluded, "there is sufficient evidence of carcinogenicity in experimental animals. Glyphosate also caused DNA and chromosomal damage in human cells, although it gave negative results in tests using bacteria. One study in community residents reported increases in blood markers of chromosomal damage (micronuclei) after glyphosate formulations were sprayed nearby."[4] Specifically, IARC's review of glyphosate's data states,

> *"*In male CD-1 mice, *glyphosate induced a positive trend in the incidence of a rare tumor, renal tubule carcinoma. A second study reported a positive trend for haemangiosarcoma in male mice. Glyphosate increased pancreatic islet-cell adenoma in male rats in two studies. A glyphosate formulation promoted skin tumors in an initiation-promotion study in mice. Glyphosate has been detected in the blood and urine of agricultural workers, indicating absorption. Soil microbes degrade glyphosate to aminomethylphosphoric acid (AMPA). Blood AMPA detection after poisonings suggests intestinal microbial metabolism in humans. Glyphosate and glyphosate formulations induced DNA and chromosomal damage in mammals, and in human and animal cells in vitro. One study reported increases in blood markers of chromosomal damage (micronuclei) in residents of several communities after spraying of glyphosate formulations.Bacterial mutagenesis tests were negative. Glyphosate, glyphosate formulations, and AMPA induced oxidative stress in rodents and in vitro."*[5]

We support OEHHA's listing of glyphosate as a substance known to the state to cause cancer based on IARC's classification. Additionally, although not requested by OEHHA, there is a growing body of science that finds that glyphosate can cause serious adverse effects in humans. One recent study finds that low dose exposure of glyphosate leads to changes in gene expression associated with organ damage (liver, kidney) observed in the rats.[6] A paper by scientists at Massachusetts Institute of Technology (MIT), examining the toxic effects of glyphosate, links the herbicide to a wide range of diseases and suggests that more research is

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[4] Ref #2
[5] Guyton, K, Loomis Dana, Grosse, Y, et al. 2015. Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. The Lancet Oncology. 16(5):490-491.
[6] Mesnage R, Arno, M, Costanzo M, et al. 2015. Transcriptome profile analysis reflects rat liver and kidney damage following chronic ultra-low dose Roundup exposure. *Environ Health*. 14:70

needed.[7] Here the scientists argue that glyphosate's inhibition of cytochrome P450 (CYP) enzymes is an overlooked component of its toxicity to mammals.

A 2013 study entitled, "Glyphosate induces human breast cancer cells growth via estrogen receptors," finds that low and environmentally relevant concentrations of glyphosate possess estrogenic activity.[8] Glyphosate, in another study, was observed to promote hematological and hepatic alterations, even at sub-acute exposure.[9] In 2002, a study of Swedish men showed that glyphosate exposure was *significantly* associated with an increased risk of Non-Hodgkin's lymphoma (NHL), and hairy cell leukemia, a rare subtype of NHL.[10] Further, a 2003 review of studies conducted on farmers by researchers at the National Cancer Institute shows that exposure to glyphosate is associated with an increased incidence of NHL.[11] Additionally, formulated glyphosate products, which include the surfactant polyethoxylated tallowamine (POEA), have been found to be more toxic than glyphosate itself. Glyphosate formulated products kill human cells, particularly embryonic, placental and umbilical cord cells, even at very low concentrations, according to another study.[12] Other studies have found that the formulated glyphosate products reduces human placental JEG3 cell viability at least two times more efficiently than glyphosate, disrupts aromatase activity and mRNA levels,[13] induce a dose-dependent formation of DNA adducts in the kidneys and liver of mice[14] (a process that can lead to carcinogenesis), and induce developmental retardation of the fetal skeleton, a decrease in sperm number and increase in the percentage of abnormal sperms.[15]

We look forward to glyphosate inclusion under Proposition 65 and welcome any further questions relating to glyphosate's toxicity.

Respectfully,

Nichelle Harriott

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[7] Samsel A, Seneff S. Glyphosate's Suppression of Cytochrome P450 Enzymes and Amino Acid Biosynthesis by the Gut Microbiome: Pathways to Modern Diseases. *Entropy*. 2013; 15(4):1416-1463.
[8] Thongprakaisang S, Thiantanawat A, et al. 2013. Glyphosate induces human breast cancer cells growth via estrogen receptors. Food Chem Toxicol. pii: S0278-6915(13)00363-3. doi: 10.1016/j.fct.2013.05.057.
[9] Jasper R, et al. 2012. Evaluation of biochemical, hematological and oxidative parameters in mice exposed to the herbicide glyphosate-Roundup(®). Interdiscip Toxicol. 5(3):133-40
[10] Hardell L, Eriksson M, & Nordstrom M. 2002. Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies. *Leuk Lymphoma*, 43(5), 1043-1049.
[11] De Roos, et al. 2003. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. *Occup Environ Med*, 60(9).
[12] Benachour, N., & Seralini, G.-E. 2008. Glyphosate Formulations Induce Apoptosis and Necrosis in Human Umbilical, Embryonic, and Placental Cells. *Chemical Research in Toxicology*, 22(1), 97-105.
[13] Richard S, Moslemi S, Sipahutar H, Benachour N, & Seralini GE. 2005. Differential effects of glyphosate and roundup on human placental cells and aromatase. *Environ Health Perspect*, 113(6), 716-720.
[14] Marco, P., Armelle, M., Claudia, B., & Silvio, P. 1998. ^{32}P-postlabeling detection of DNA adducts in mice treated with the herbicide roundup. *Environmental and Molecular Mutagenesis*, 31(1), 55-59.
[15] Dallegrave, E., et al. 2003. The teratogenic potential of the herbicide glyphosate-Roundup® in Wistar rats. *Toxicology Letters*, 142(1-2), 45-52.; Dallegrave, E., et al. (2007). Pre- and postnatal toxicity of the commercial glyphosate formulation in Wistar rats. *Arch Toxicol*, 81(9), 665-673.

Science and Regulatory Director