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NEBRASKA'S HEALTH SCIENCE CENTER

PATHOLOGY AND MICROBIOLOGY

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October 9, 2015

RE: NOIL Glyphosate

Ms. Barajas-Ochoa:

Please accept these comments in opposition to the Office of Environmental Health Hazard Assessment's (OEHHA) intention to list glyphosate under the Label Code Provision of the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65).

Glyphosate-based herbicides are widely used throughout the world and are amongst the most thoroughly tested herbicides. The history of safe use is supported by one of the most extensive worldwide human health, crop residue and environmental databases ever compiled on a pesticide product.

The International Agency for Research on Cancer's (IARC) misclassification of glyphosate should not be used by OEHHA to list glyphosate under Proposition 65. IARC's evaluation was based on limited and selective use of data without consideration of established toxicological principles which are key elements of the thorough risk assessments conducted by global regulatory agencies. It utilized numerous studies that do not meet standards set by the Organization for Economic Co-operation and Development (OECD) guidelines. Regulatory authorities and independent experts around the world have reviewed numerous long-term carcinogenicity and genotoxicity studies as well as epidemiology and basic research investigations and agree that there is no evidence that glyphosate causes cancer, even at very high doses, and that it is not genotoxic. IARC overlooked decades of thorough and robust analyses by regulatory agencies, including a multi-year assessment just completed on behalf of the pesticide regulatory authority in the European Union.

The IARC monograph does not present new research or data. All of the key studies considered by IARC in their monograph had been previously reviewed and considered by regulatory agencies, most recently in 2015 in a comprehensive toxicology assessment by the EU Rapporteur Member State and by the Canadian PMRA for their re-registration processes in the EU and Canada, respectively. Neither of these agencies found glyphosate to pose a carcinogenic or genotoxic risk.

IARC did not consider the total weight of scientific evidence available for glyphosate, being highly selective in the studies that were chosen for review. It is clear from the limited references listed in the monograph that the information actually selected for consideration by the panel represents only a subset of the data available on glyphosate. Evaluation of the complete dataset, as performed by regulators globally, overwhelmingly supports the conclusions of safety and lack of carcinogenic potential of glyphosate.

IARC's selective data evaluation made basic errors in data interpretation within each of the four areas of evidence they considered (animal carcinogenicity, exposure, genotoxicity, and epidemiology), reflecting a non-critical evaluation of many of the studies published. I would like to address several issues under each of these.

With respect to animal carcinogenicity, the IARC panel came to the conclusion of "sufficient evidence" of carcinogenicity in animals. The panel re-interpreted isolated findings of tumor incidence in particular studies, focusing on numerical increases in tumor incidence in treatment groups, but ignoring the lack of a dose-response, background tumor incidences in historical control animals and pathology experts' opinions. All of these typically provide context to toxicologists in their assessment of whether there is a possible relationship to treatment. IARC's approach is non-standard and at odds with basic toxicological practices. They did not appear to account for the lack of reproducibility between studies. Such lack of concordance provides additional evidence that the tumors identified were not related to glyphosate treatment. Other experts and regulators have long concluded that all of the isolated tumors discussed by IARC were spontaneous and not related to glyphosate treatment. Moreover, multiple long-term toxicology studies conducted according to international standards were not reviewed by IARC but clearly corroborate the lack of carcinogenic potential of glyphosate. The review by the IARC regarding renal tumors in mice is against the interpretation of all other regulatory agencies as well as an expert Pathology Working Group (PWG). The bias of the IARC panel is reflected in their statements regarding their interpretation of the animal data, as well as in their statements in a number of other aspects, which I will detail later.

Their interpretation of the pancreatic tumors in rats also goes against several decades of research, not only on glyphosate but on the historical background of these tumors and overall mechanistic understanding of their development. The pancreatic tumors in rats are acinar cell tumors, mostly benign, not the ductal carcinomas that are usually seen in humans. Acinar cell tumors in humans are quite rare. Furthermore, the development of these tumors in rats was shown more than two decades ago to be related to a mechanism that is not relevant to humans. It involves the induction of cholecystokinin (CCK), which acts as a mitogenic hormone for pancreatic acinar cells in the rat. In humans, CCK is not mitogenic to acinar cells. In the rat, this unique circumstance leads to induction of pancreatic acinar cell tumors by a variety of means that are not related to human carcinogenesis, such as administration of corn oil by gavage, high fat diets, as well as soy protein. I am astonished that the panel appears to be completely unaware of the extensive research background on these tumors, resulting in an interpretation of the

data in the glyphosate studies which cannot be substantiated by basic science and basic research. In addition, the incidence of pancreatic acinar cell tumors in the rat studies of glyphosate were well within historical controls.

An additional indication of the bias of this panel is their inclusion of a recent publication by Seralini et al, which was republished in Environmental Sciences Europe after being retracted from a previous publication in Food and Chemical Toxicology. I am astonished that the panel appears to be completely unaware of the numerous deficiencies of this study which resulted in its retraction from publication in Food and Chemical Toxicology. The details of the deficiencies of the Seralini et al study were broadly documented in the literature with Letters to the Editor and a variety of other means.

In their evaluation of other carcinogenicity results, they also appear to ignore more recent developments regarding specific tumors. With respect to hemangiosarcomas in male CD-1 mice, the IARC panel appears to be unaware of the broad range of incidences seen in historical controls. This is a tumor that appears at very high incidence in certain strains of mice, such as CD-1, with frequent spontaneous incidences of 4 to 12 percent, but as high as 25 percent. The incidences in the studies with glyphosate were all well within these historical controls. It is alarming that IARC appears to completely ignore the issue of historical controls except when they need to demonstrate that a tumor is infrequent. Furthermore, recent evidence strongly suggests that the hemangiosarcomas in mice are not relevant to humans. Hemangiosarcomas in humans appear to arise from a completely different cell of origin than in mice, and it is an exceedingly rare tumor in humans. For example, it is estimated that there are only approximately 100 cases of hemangiosarcoma in the United States yearly.

In their evaluation of skin-tumor promotion, the panel appears to completely ignore the fact that the glyphosate caused dermal irritation, which is a known cause of so-called tumor promotion in these mice, unrelated to the chemical itself. In fact, in the Tg.AC strain of mice, which was designed to be a more sensitive system for detection of mouse tumor skin promotion, it is explicitly stated by the National Toxicology Program (who developed the mice) that the maximum tolerated dose should be below a dose which causes skin irritation since skin irritation by itself will result in the positive finding. To even consider the results of the mouse tumor promotion finding in skin as relevant to the evaluation of cancer risk for humans is highly inappropriate.

The IARC Monograph evaluation of exposure also reflected an incomplete literature review, citing old references despite more recent ones existing. It appears that the cited literature is highly selective. IARC cites detection of glyphosate in different matrices (urine, serum, soil, air, water, and food) without putting the levels and potential exposures into proper context. Regulatory authorities and JMPR establish ADIs and/or AOELs which account for potential human exposure and which establish safe exposure levels. When exposure is put into context, it is consistently clear that there are no health concerns with exposure to glyphosate.

The interpretation of genotoxicity was particularly inadequate. In reaching their conclusion of strong evidence that commercial formulations can be genotoxic and produce oxidative damage, the IARC panel selectively relied on non-standard studies with adverse effects, which used methods that have not been validated and/or not conducted according to international guidelines. Several of these studies were performed at doses that approached lethality, and do not meet guidelines for any type of dose-setting for genotoxicity testing, or for that matter, any other standard toxicology investigation. The results are essentially related to severe toxicity, including cell death, which are known confounding factors in interpretation of genotoxicity studies. The IARC report does not even mention such possibilities. Furthermore, IARC disregarded a plethora of more relevant data, peer reviewed literature reviews, and opinions of numerous other scientists who have carefully considered all of the available data and concluded glyphosate is not genotoxic. OECD has set guidelines for performance of genotoxicity studies, because of the types of issues that IARC is completely ignoring in their review of some of the genotoxicity data. These include dose setting parameters, evaluation of cytotoxicity, the number of replicas that need to be evaluated, as well as standardization of methods. Furthermore, many of the studies which are referred to in the IARC report have not been validated with respect to an assessment of genotoxicity in any aspect. It is astonishing that IARC would consider these without statements of their limitations.

In their evaluation of the epidemiology studies regarding glyphosate, the IARC panel reached their conclusion of "limited evidence" in humans for the carcinogenicity of glyphosate. They relied heavily on case-control studies with design limitations and diverse methods for the estimation of glyphosate exposure and inappropriate statistical models. IARC appeared to undervalue the findings from the largest and most important study on the health of pesticide applicators (Agricultural Health Study, AHS) in the United States which found no link between glyphosate and non-Hodgkin's lymphoma or any other cancer. There are several aspects of the interpretation of the panel that deserve specific comment. To begin with, the case control studies are retrospective, and recall bias is a major difficulty with such studies. In contrast, the AHS study was prospective in nature, and exposure was much more carefully documented. Furthermore, the case-control studies lumped together non-Hodgkin's lymphomas rather than subdividing them into their appropriate categories. The bias of the panel again was demonstrated in their statement regarding multiple myeloma. They try to include this as a non-Hodgkin's lymphoma, which is a stretch of the definition. More importantly, they indicate that the incidence of myeloma was increased in some of these studies, whereas in fact, the studies did not show any statistical increase for myeloma. In the AHS, there was no evidence of an increased risk of myeloma or any other type of tumor, including non-Hodgkin's lymphoma.

To lump all of the types of non-Hodgkin's lymphoma together in an epidemiology study is inappropriate, and reflects the older nature of the studies that were cited. This is particularly astonishing since one of the champions of attempting to address this issue in the epidemiology community, Dr. Aaron Blair, was a panel member. Non-Hodgkin's

lymphoma is actually a combination of a wide variety of diseases, which have very distinct pathologic, molecular, clinical, etiologic, and therapeutic aspects. As Dr. Blair has indicated in numerous publications, to evaluate them all as a single disease is highly inappropriate.

IARC appears to be classifying substances on the basis of a non-standard cancer hazard identification process. In addition, it would appear that they are evaluating selected studies and selected data, and the publications appear to be evaluated in a non-critical manner. Apart from glyphosate, over the years IARC has classified many other substances, professions, foods, and objects of every-day use to varying degrees of "evidence" for carcinogenicity. Some of these have been based on sound evaluations of excellent studies. However, some, like the evaluation of glyphosate, have been based on a non-critical evaluation of studies, and a lack of overall appreciation of the issues involved in the evaluation. In this instance, they have come to a conclusion that is the exact opposite of numerous other agencies around the world, including other agencies within the World Health Organization (WHO). A consideration of the weight of evidence in a full set of studies on exposure are not all taken into account. Furthermore, they do not appear to utilize what has become a standard for evaluation of both epidemiology and animal studies, the International Programme on Chemical Safety (IPCS) framework for analysis of mode of action and human relevance of animal studies. Overall, with respect to glyphosate, IARC's 2A classification does not reflect the comprehensive evaluation of carcinogenicity hazard, and does not represent a thorough exposure or risk assessment.

IARC is only one of four programs within the WHO that have reviewed the safety of glyphosate, and the IARC classification is inconsistent with the assessments of all of the other programs. Two of the WHO programs (the Core Assessment Group of JMPR and the IPCS) previously concluded that glyphosate is not carcinogenic. WHO Guidelines for Drinking-Water Quality concluded that glyphosate does not represent a hazard to human health. In addition, other regulatory agencies, such as Health Canada, the United States Environmental Protection Agency, and the European Union have all concluded that glyphosate does not represent a genotoxicity or carcinogenicity risk to humans.

Other recent instances of inappropriate evaluation of studies have led to a level of concern regarding the IARC Monograph process overall. One instance, for example, was the evaluation of aloe vera extract. Despite extensive literature on the subject, IARC refused to describe the fact that the major animal study that was used for coming to its conclusion (by the National Toxicology Program, NTP, study on aloe vera) utilized a type of extract that is completely unrelated to the commercial specifications of aloe worldwide. The extract utilized for the NTP study included a high concentration of anthraquinones, known animal carcinogens for a number of target tissues. In contrast, commercial specifications require that the aloe extract be devoid (less than 1 ppm) of anthraquinones. Other recent instances of inappropriate classifications have been described in the literature. Despite the defense of the monograph process by numerous individuals, there is a deep concern about the quality of these evaluations. The evaluation by IARC of

glyphosate will only add to this controversy, as it is a glaringly inappropriate and is in complete contradiction to the evaluations by agencies around the world, including other agencies within the WHO.

In closing, I would reiterate that regulatory authorities around the world agree that there is no evidence that glyphosate causes cancer, even at very high doses, and that it is not genotoxic. I strongly disagree with the OEHHA's intention to list glyphosate under Proposition 65.



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