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**COMMENTS ON NOTICE OF INTENT TO LIST CHEMICALS BY THE LABOR  
CODE MECHANISM: TETRACHLORVINPHOS, PARATHION,  
MALATHION, GLYPHOSATE [09/04/15]**

Dear Ms. Barajas-Ochoa:

Ramboll Environ appreciates the opportunity to provide the following comments at the request of The Scotts Company LLC regarding the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) intent to list the chemicals malathion and glyphosate as known to the state to cause cancer under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65).

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**1.0 Comments on Intent to List Malathion**

Under OEHHA's interpretation of California law, certain substances identified by the International Agency for Research on Cancer (IARC) must be listed as known to cause cancer under Proposition 65 through reference to Labor Code section 6382(b)(1). OEHHA noted that on IARC's website malathion is classified in Group 2A ("probably carcinogenic to humans"). Although OEHHA is correct in noting that this designation already appears on IARC's website, publication of the basis for the designation has yet to be released to the public in a comprehensive, transparent source consistent with the norms of scientific communication; e.g., an IARC monograph.

On July 29, 2015, IARC noted on its website<sup>1</sup> that the glyphosate portion of Monograph Volume 112 ("Some Organophosphate Insecticides and Herbicides") was publically available, but that those portions of Volume 112 pertaining to other pesticides, including malathion "will be published subsequently." These have yet to be made available for review. As Volume 112 is the cited documentation source for the classification of malathion, and as IARC's classification cannot be considered

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<sup>1</sup> See <http://monographs.iarc.fr>.

complete in the absence of release for evaluation and review of the corresponding parts of Monograph Volume 112, OEHHA's designation of these compounds under Proposition 65 is premature. An action on listing should be withheld until IARC releases the evaluations for these compounds. Otherwise, OEHHA would be making a Proposition 65 listing decision in response to a press release and website notice while the scientific analysis cited remains withheld from the agency, as well as the public and scientific community.

This may appear to be a technicality were it not for the fact that the information on IARC's classification of malathion that is publically available for review – a May, 2015 summary article<sup>2</sup> – contains errors illustrating how initial announcements may be incomplete or inaccurate representations of comprehensive evaluations. For example, the May, 2015 summary cited a study by Eriksson et al. (2008)<sup>3</sup> as one of those relied on for IARC's classification of malathion as a Group 2A carcinogen. This study does **not** address malathion carcinogenicity and did not present analyses of risks for malathion or any related pesticides. The study reported associations between non-Hodgkin lymphoma and herbicides as a group and with some specific herbicides, but did not examine risks for organophosphate pesticides as a class and did not report significant associations for insecticides in general. Malathion is not mentioned in the data tables in this study, nor are organophosphate pesticides. Given this, it is clear that the summary information released to date is in error, incomplete, or in some other way not reflective of the scientific basis by which IARC made a determination about malathion, and thus, is an unreliable basis for OEHHA to move ahead with listing.

## 2.0 Comments on Intent to List Glyphosate

Unlike the situation for malathion, the basis of IARC's classification of glyphosate as a Group 2A carcinogen has been presented in a released portion of Monograph Volume 112. We provide comment regarding glyphosate in the context of 1) IARC's basis for classification – i.e., the studies considered by IARC in their classification; 2) contradictory conclusions by IARC's parent authority and other scientific/regulatory organizations (e.g., U.S. EPA) upon review of the same studies [note: IARC is a technical advisory body for the United Nations-affiliated World Health Organization]; and 3) additional scientific opinions of IARC's classification of glyphosate.

### 2.1 IARC's Basis for Classification

IARC's classification of glyphosate in Group 2A was based on five principal studies of glyphosate:

- DeRoos et al. (2003)<sup>4</sup> – "Integrative Assessment of Multiple Pesticides as Risk factors for Non-Hodgkin's Lymphoma Among Men";

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<sup>2</sup> See [http://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045\(15\)70134-8.pdf](http://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045(15)70134-8.pdf).

<sup>3</sup> See <http://onlinelibrary.wiley.com/doi/10.1002/ijc.23589/epdf>.

<sup>4</sup> DeRoos, A.J., Zahm, S.H., Cantor, K.P., Weisenburger, D., Holmes, F., Burmeister, L., and Blair, A. 2003. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. *Occup Environ Med* 60:E11.

- McDuffie et al. (2001)<sup>5</sup> – “Non-Hodgkin’s Lymphoma and Specific Pesticide Exposures in Men: Cross-Canada Study of Pesticides and Health”;
- Eriksson et al. (2008)<sup>6</sup> – “Pesticide Exposure as Risk Factor for Non-Hodgkin Lymphoma Including Histopathological Subgroup Analysis”;
- Bolognesi et al. (2009)<sup>7</sup> – “Biomonitoring of Genotoxic Risk in Agricultural Workers from Five Colombian Regions: Association to Occupational Exposure to Glyphosate”;
- WHO (2006)<sup>8</sup> – “Pesticide Residues in Food - 2004, Joint FAO/WHO Meeting on Pesticide Residues, Evaluations, 2004, Part II – Toxicological.”

The study by DeRoos et al. (2003) was based on pooled data from three 1980’s-era National Cancer Institute population-based case-control studies of Non-Hodgkin’s Lymphoma (NHL) in Nebraska, Iowa, Minnesota, and Kansas. Each of these studies focused on farming exposure to pesticides. The DeRoos study reported that the use of specific pesticides, including glyphosate, was more frequent among NHL cases than controls. The odds ratio (OR) for glyphosate was 1.6, with a 95% confidence limit = 0.9 to 2.8. The lower bound of this confidence limit is not above 1 and, thus, is not statistically significant by the generally accepted criterion for this type of study.

DeRoos et al. noted that the incidence and mortality rates for NHL have been generally increasing in the United States and in most industrialized countries for several decades, with an 85-100% increase in mortality among whites and non-whites from the late 1940s to the late 1980s, a time period relevant for this study. However, the authors also noted that this increase may be partially attributed to improved diagnosis and in later years to AIDS-related lymphomas. The authors also recognized that their findings were confounded by multiple and simultaneous pesticide exposures that may have occurred in the study populations.

DeRoos et al. concluded that their exposure metric of having ever used a pesticide was “rather crude, offering no distinctions based on use by the number of years or the number of days per year.” In addition, they concluded that their analysis provided no information on the timing of pesticide use in relation to disease onset or in conjunction with the timing of other pesticides used.

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<sup>5</sup> McDuffie, H.H., Pahwa, P., McLaughlin, J.R., Spinelli, J.J., Fincham, S., Dosman, J.A., Robson, D., Skinnider, L.F., and Choi, N.W. 2001. Non-Hodgkin’s Lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. *Cancer Epidemiol Biomarkers Prev.* 10(11):1155-1163.

<sup>6</sup> Eriksson, M., Hardell, L., Carlberg, M., and Akerman, M. 2008. Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis. *Int J Cancer* 123:1657-1663.

<sup>7</sup> Bolognesi, C., Carrasquilla, G., Volpi, S., Solomon, K.R., Marshall, E.J. 2009. Biomonitoring of genotoxic risk in agricultural workers from five Colombian regions: Association to occupational exposure to glyphosate. *J Toxicol Environ Health* 72:986-997.

<sup>8</sup> WHO. 2006. Pesticide residues in food – 2004, Joint FAO/WHO Meeting on Pesticide Residues, Evaluations – 2004, Part II – Toxicological. International Programme on Chemical Safety. World Health Organization. WHO/PCS/06.1

The study by McDuffie et al. (2001) looked at possible associations of specific pesticides with NHL in a Canadian multicenter population-based incident, case-control study among men in a diversity of occupations. The study involved an initial postal questionnaire followed by a telephone interview for those reporting pesticide exposure of 10 hours per year or more, and a 15% random sample of the remainder. Odds ratios (ORs) were reported after adjustment for statistically significant variables, including a history of measles, mumps, cancer, and allergy desensitization shots and a positive history of cancer in a first-degree relative. For glyphosate, the OR for frequency of exposure was not significant (OR = 1.20; 95% CI = 0.83 - 1.74). When ORs were stratified by the average number of days per year of exposure, the OR for glyphosate was shown to be not significant for >0 to ≤2 days (OR = 1.00; 95% CI = 0.63 - 1.57) but significant for ≥2 days (OR = 2.12; 95% CI = 1.20 - 3.73).

McDuffie et al. noted that few study subjects were limited in exposure to just one pesticide or to one class of pesticides. It was also noted that the study was limited by the case-control design itself – specifically, by the potential for recall bias and for misclassification of pesticide exposure – and that as a consequence of conducting multiple comparisons, a small number of statistically significant results may have been attributable to chance alone.

Eriksson et al. (2008) conducted a population-based case-control study of exposure to pesticides as risk factors for NHL. The subjects were men and women aged 18-74 years who lived in Sweden from December 1, 1999, to April 30, 2002. Controls were selected from the national population registry. Exposure to different agents was assessed by questionnaire. Exposure to glyphosate produced an OR of 2.02 (95% CI = 1.10 - 3.71) and with >10 years latency period, the glyphosate OR was 2.26 (95% CI = 1.16 - 4.40).

Eriksson et al. noted that exposures were assessed by questionnaires with information supplemented over the phone, but that no registries exist in Sweden on individual pesticide exposure/use, which is a weakness of the study. It was concluded that exposure to pesticides was difficult to assess, and some misclassification regarding quantity of exposure probably occurred in the study population.

Bolognesi et al. (2009) studied possible human effects associated with glyphosate formulations used in the Colombian aerial spray program for control of illicit crops. Via cytogenetic biomonitoring, the study was carried out on subjects from five Colombian regions characterized by different exposure to glyphosate and other pesticides. Women of reproductive age (137 persons, 15 - 49 years old) and their spouses (137 persons) were interviewed to obtain data on current health status, history, lifestyle, including past and current occupational exposure to pesticides, and factors including those known to be associated with increased frequency of micronuclei (MN). In regions where glyphosate was being sprayed, blood samples were taken prior to spraying (indicative of baseline exposure), 5 days after spraying, and 4 months after spraying. Study results indicated that the highest frequency of binucleated cells with micronuclei (BNMN) was in Boyacá, where no aerial eradication spraying of glyphosate was conducted, and in Valle del Cauca, where glyphosate was used for maturation of sugar cane. It was also reported that the increase in frequency of BNMN observed 5 days 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.

Bolognesi et al. concluded, "Evidence indicates that the genotoxic risk potentially associated with exposure to glyphosate in the areas where the herbicide is applied for coca and poppy eradication is low." It was also concluded that a major drawback of environmental epidemiology studies like this one is the accurate characterization of exposures to the agents being investigated. Further, the authors concluded that, based on the Bradford-Hill guidelines (Hill 1965),<sup>9</sup> it was not possible to assign causality to the increases in frequency of BNMN observed in the study.

Mouse and rat studies summarized by WHO (2006) are cited as evidence of the carcinogenicity of glyphosate. Specifically, in male CD-1 mice, glyphosate induced a "positive trend" in the incidence of 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; and a glyphosate formulation promoted skin tumors in an initiation-promotion study in mice.

A careful examination of the WHO (2006) report reveals a number of inconsistencies and errors in IARC's reliance on this report. First, regarding the "positive trend" in the incidence of renal tubule carcinoma in mice discussed by IARC, there is no actual description of this effect attributable to glyphosate anywhere in the WHO report.

Second, regarding the "positive trend" of haemangiosarcoma in male mice described by IARC – the WHO report noted as follows:

"Haemangiosarcoma was evident in 4/50 males at the highest dose, in 2/50 females at the lowest dose, and in 1/50 females at the highest dose, but in none of the 50 animals of the control group. . . . Owing to the lack of a dose–response relationship, the lack of statistical significance and the fact that the incidences recorded in this study fell within the historical ranges for controls, these changes are not considered to be caused by administration of glyphosate."

The WHO analysis, thus, determined that tumor incidence did not exceed controls and did not exhibit a dose-response relationship (based on the results from females). These are substantially different conclusions than characterizing the study as reporting a "positive trend," particularly as no statistical test for trend was discussed or apparently undertaken by IARC.

Third, regarding the reference by IARC to glyphosate causing increased pancreatic islet-cell adenoma in male rats in two studies, the WHO report actually stated:

"Regarding neoplastic lesions, the only statistically significant difference between control and treated animals was an increase in the incidence of pancreatic islet cell adenomas in males at the lowest dose. The incidences of this lesion were 1 out of 58 (2%), 8 out of 57 (14%), 5 out of 60 (8%), and 7 out of 59 (12%) in males in the control group and at the lowest, intermediate and highest dose, respectively. The historical-control range for this tumour at the testing laboratory was 1.8–8.5%, but a partial review of studies reported recently in the literature revealed a prevalence of 0–17% in control males with

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<sup>9</sup> Hill, A. B. 1965. The environment and disease: association or causation? Proc. R. Soc. Med. 58:295-300.

several values being  $\geq 8\%$ . More importantly, the incidences of islet cell adenomas clearly did not follow a dose-related trend in the treated groups of males, as indicated by the lack of statistical significance in the Peto trend test. It should be noted that there was also considerable intergroup variability in the numbers of females with this tumour (5 out of 60, 1 out of 60, 4 out of 60 and 0 out of 59 in the control group and at the lowest, intermediate and highest doses, respectively). There was no evidence of dose related pancreatic damage or pre-neoplastic lesions. The only pancreatic islet cell carcinoma found in this study occurred in a male in the control group, thus indicating a lack of treatment-induced neoplastic progression. Taken together, the data support the conclusion that the occurrence of pancreatic islet cell adenomas in male rats was spontaneous in origin and unrelated to administration of glyphosate.”

Again, the WHO analysis made clear that the results were not dose related, noting that a test for trend was completed and supported this conclusion, and that the results were not outside the expected control range. Further, the WHO authors concluded the tumors were spontaneous and unrelated to glyphosate. Accordingly, the description by IARC of these results is not reflective of the results or findings by WHO.

Fourth, like the renal tubule carcinomas in mice, there is no actual description of skin tumors attributable to glyphosate anywhere in the WHO report.

Finally, none of the purported carcinogenic effects of glyphosate observed in animals – i.e., renal tubule carcinomas, haemangiosarcomas, pancreatic islet-cell adenomas, and skin tumors – have been observed in human populations that may have experienced glyphosate exposure.

## 2.2 Previous WHO and Other Evaluations of Glyphosate Prior to 2015

IARC classified glyphosate regarding carcinogenicity for the first time in 2015. The World Health Organization (WHO), the parent authority of IARC, as well as other authoritative regulatory and scientific organizations, have included glyphosate in other evaluations of the carcinogenicity of glyphosate. For example, WHO’s International Programme on Chemical Safety (IPCS) published “Environmental Health Criteria 159” on glyphosate in 1994.<sup>10</sup> In this evaluation, WHO concluded the following:

“Bioassays in mice and rats did not indicate that technical glyphosate was carcinogenic.”

and

“Animal studies show that glyphosate is not carcinogenic, mutagenic or teratogenic.”

And, more recently, evaluating the same studies cited by IARC, the aforementioned WHO (2006) report offered the following conclusions regarding glyphosate carcinogenicity:

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<sup>10</sup> See <http://www.inchem.org/documents/ehc/ehc/ehc159.htm>.

“Long-term studies of toxicity and carcinogenicity were conducted in mice and rats. In the study of carcinogenicity in mice, no toxic effects were observed at up to the highest dose tested (1,000 mg/kg bw per day), and there was no evidence of carcinogenicity. In a 1-year study of toxicity in rats, the NOAEL was 2,000 ppm (equal to 141 mg/kg bw per day) on the basis of a reduction in body weight and clinical chemistry findings at 8,000 ppm. Three new long-term studies in rats were evaluated. In the first study, the NOAEL was 8,000 ppm (equal to 362mg/kg bw per day) on the basis of a reduction in body weight in females and an increased incidence of cataracts and lens abnormalities in males at 20000 ppm. In the second study, the NOAEL was 100 mg/kg bw per day on the basis of more pronounced alterations of the parotid and submaxillary salivary glands at  $\geq 300$ mg/kg bw per day. In the most recent 2-year study in rats, the NOAEL was 6.000 ppm (equal to 361 mg/kg bw per day) on the basis of a reduction in body weight and food consumption, and indications of kidney, prostate, and liver toxicity at 20,000ppm. There was no evidence of a carcinogenic response to treatment in rats.”

and

“The genotoxic potential of glyphosate has been extensively tested in a wide range of assays both in vitro and in vivo, including end-points for gene mutation, chromosomal damage and DNA repair. Negative results were obtained in studies performed in compliance with current test guidelines. The Meeting concluded that glyphosate is unlikely to be genotoxic.”

and

“In view of the absence of a carcinogenic potential in animals and the lack of genotoxicity in standard tests, the Meeting concluded that glyphosate is unlikely to pose a carcinogenic risk to humans.”

In reaching its conclusions, IARC specifically considered six mouse studies (and only relied on two of them). Only one of those six studies post-dated the WHO (2006) report. However, the design of this one study (a skin-painting study) was deemed by IARC as “inadequate for the evaluation of glyphosate.” IARC also considered seven rat studies (and, again, only relied on two of them). Only two of those rat studies were published after the WHO (2006) report. In the first, a 2000 study of glyphosate in drinking water, IARC noted that there occurred no significant increases in tumor incidence in any of the treatment groups, and that the study was deficient in reporting dosing regimens and histopathological examination methods. In the second rat study, a 2014 study also of glyphosate in drinking water, IARC reported that histopathology was poorly described, that tumor incidences in individual animals were not described in detail, and that the study used small numbers of animals per treatment group. This led IARC to conclude that the 2014 rat study was “inadequate for the evaluation of glyphosate carcinogenicity.”

Thus, the difference in conclusions between IARC and WHO cannot be attributed to the passage of time and newly emerged studies, since the same underlying studies were evaluated and additional, newer studies were concluded by IARC to be inadequate for their evaluation. Since WHO is the parent authority for IARC, OEHHA should treat their conclusion, which contradicts IARC, as the more authoritative and withhold listing until the discrepancy between conclusions by the parent and subordinate organizations are resolved. As demonstrated above, IARC’s most recent determination was not based on new data or improved analysis,

but heavily based on misconstruing the conclusions by WHO. For post-hoc re-characterization to take precedence over the more authoritative report by original analysts, a clear and compelling rationale and explanation should be required.

Looking at other reviewing bodies, a 2002 regulatory review conducted by the European Commission's Health and Consumer Protection Directorate-General, after which glyphosate was re-registered for use in Europe, concluded that there was "no evidence of carcinogenicity" for glyphosate, and that it was "not genotoxic."

In 2000, an international panel of toxicology experts published a peer-reviewed assessment of glyphosate studies (Williams et al. 2000). The panel concluded:

"The genotoxicity data for glyphosate and Roundup were assessed using a weight-of-evidence approach and standard evaluation criteria. There was no convincing evidence for direct DNA damage in vitro or in vivo, and it was concluded that Roundup and its components do not pose a risk for the production of heritable/somatic mutations in humans."

and

"Multiple lifetime feeding studies have failed to demonstrate any tumorigenic potential for glyphosate. Accordingly, it was concluded that glyphosate is noncarcinogenic."

and

"It was concluded that, under present and expected conditions of use, Roundup herbicide does not pose a health risk to humans."

In July 2013, the Australian Pesticides and Veterinary Medicines Authority (APVMA) conducted a review of the Earth Open Source report "Roundup and Birth Defects: Is the Public Being Kept in the Dark?" and concluded:

"The APVMA currently has no data before it suggesting that glyphosate products registered in Australia and used according to label instructions present any unacceptable risks to human health, the environment and trade. . ."

and

"The weight and strength of evidence shows that glyphosate is not genotoxic, carcinogenic or neurotoxic."

In a recent (March 23, 2015) communication entitled "Does glyphosate cause cancer?" (BfR Communication No 007/2015), the German Federal Institute for Risk Assessment (BfR) commented on IARC's classification of glyphosate as follows:

"In the opinion of BfR, the classification of glyphosate as "carcinogenic in Group 2A" (probably carcinogenic to humans) as published in the 20 March 2015 issue of the "Lancet" journal comes as a surprise, since other evaluations performed by supranational bodies such as the WHO-Panel of the Joint Meeting of Pesticide Residues. . . and also by national regulatory agencies such as the U.S.EPA had concluded the contrary, i.e., that glyphosate was not carcinogenic."

and

"The new IARC classification for glyphosate as a carcinogenic substance is based firstly on 'limited evidence' in humans. This risk is derived from three epidemiological studies in the USA, Canada and Sweden based on a statistical correlation between exposure to glyphosate and an increased risk of non-Hodgkin lymphoma. However, this assessment was not confirmed in a very large cohort of the also cited 'Agricultural Health Study' or in other studies. A recent publication from 2012 has reviewed the epidemiologic literature to evaluate whether exposure to glyphosate is associated causally with cancer risk in humans and the relevant methodological and biomonitoring studies of glyphosate. The review found non-consistent patterns of positive associations indicating a causal relationship between total cancer or any site-specific cancer and exposure to glyphosate. The current report of BfR to the EU based on the evaluation of over 30 epidemiological studies came to the overall assessment that there is no validated or significant relationship between exposure to glyphosate and an increased risk of non-Hodgkin lymphoma or other types of cancer."

and

". . . IARC points to findings of studies based on animal experiments submitted by the producers of glyphosate as evidence for the carcinogenic effect of glyphosate. All these findings were also considered in the glyphosate assessments of BfR, which did support the conclusion of the Joint Meeting on Pesticide Residues (JMPPR) of the FAO/WHO responsible for the assessment of active substances in pesticides: 'In view of the absence of a carcinogenic potential in animals and the lack of genotoxicity in standard tests, the Meeting concluded that glyphosate is unlikely to pose a carcinogenic risk to humans.'"

In its Proposed Re-evaluation Decision PRVD2015-01 for glyphosate, Health Canada stated:

"The World Health Organization's (WHO) International Agency for Research on Cancer (IARC) recently assigned a hazard classification for glyphosate as 'probably carcinogenic to humans'. It is important to note that a hazard classification is not a health risk assessment. The level of human exposure, which determines the actual risk, was not taken into account by WHO (IARC). Pesticides are registered for use in Canada only if the level of exposure to Canadians does not cause any harmful effects, including cancer." [Note: after a re-evaluation of the herbicide glyphosate, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the Pest Control Products Act and Regulations, is proposing continued registration of products containing glyphosate for sale and use in Canada.]

In summary, the European Commission's Health and Consumer Protection Directorate-General, the Australian Pesticides and Veterinary Medicines Authority, the German Federal Institute for Risk Assessment, Health Canada, and an international scientific review panel consistently reached conclusions contradicting IARC. Canada and Germany's reaffirmations came after the IARC classification and specifically addressed this determination. Again, the timing makes clear that IARC was not acting upon newly available information and its conclusions are not supportable.

### **2.3 EPA's Evaluations of the Carcinogenicity of Glyphosate**

The EPA is the overall regulatory authority in the United States concerning the use of glyphosate as a pesticide. Despite the EPA's online Integrated Risk Information System's (IRIS) listing of glyphosate as a Group D carcinogen (inadequate animal evidence of carcinogenic potential), this information is outdated and does not reflect the EPA's updated determination (since 1991) that there is sufficient evidence of non-carcinogenicity for glyphosate and corresponding listing as Group E (evidence of non-carcinogenicity). Below is a brief review of the EPA's classification of glyphosate.

Glyphosate's carcinogenic potential was first considered by the EPA's Toxicology Branch Ad Hoc Committee in 1985. At that time, glyphosate was considered a Group C carcinogen. These findings were referred to the Scientific Advisory Panel (SAP), and in 1986 glyphosate was classified as a Group D carcinogen. The SAP concluded that the carcinogenic potential of glyphosate could not be determined from existing data and proposed that the studies on rats be repeated. Upon receipt of the second rat chronic/carcinogenicity study, all findings were referred to the Health Effects Division Carcinogenicity Peer Review Committee. In 1991, the Peer Review Committee updated the classification of glyphosate to Group E based on findings of a lack of treatment related carcinogenicity in adequate studies with two different species (mice and rats).<sup>11</sup>

Thus, while IRIS continues to list glyphosate as classified in Group D<sup>12</sup>, the current profile refers to the 1989 determination, not the agency's updated 1991 determination. The most current classification, and the classification based upon the most comprehensive set of studies, remains that the agency determined there is evidence of a lack of carcinogenicity, i.e. Group E.

Since 2005, it is important to note that, unlike IARC, EPA has no longer used the term "probable" or "probably" in its carcinogen classification scheme.<sup>13</sup> Instead, it uses the following four classification categories:

- "Likely to be carcinogenic to humans";
- "Suggestive evidence of carcinogenic potential";
- "Inadequate information to assess carcinogenic potential"; and
- "Not likely to be carcinogenic to humans."

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<sup>11</sup> See USEPA, Reregistration Eligibility Decision (RED) Glyphosate (1993), Office of Prevention, Pesticides and Toxic Substances, EPA 738-R-93-015, September, 1993.

<sup>12</sup> See <http://www.epa.gov/iris/subst/0057.htm>.

<sup>13</sup> See <http://www.epa.gov/pesticides/health/cancerfs.htm#a>.

EPA has stated that it does not necessarily re-evaluate every chemical under the new classifications, unless there is some new information that could change the basic understanding of that chemical. Given this, it should be understood that EPA has not been compelled by any more recent information to classify glyphosate as anything other than Group E. It should also be noted that there is no statutory or other requirement for EPA to change its designation in response to IARC.

## 2.4 Additional Scientific Opinions of IARC's Classification of Glyphosate

A number of prominent experts have offered opinions on IARC's classification of glyphosate as a Group 2A carcinogen, including a co-author of one of the human studies papers (Bolognesi et al. 2009) relied on by IARC to classify glyphosate, a chemical review manager for the Office of Pesticide Programs at U.S. EPA, and others. Their reported opinions are listed below.

- K.R. (Keith) Solomon, Centre for Toxicology and Department of Environmental Biology, University of Guelph, Guelph, Ontario, Canada, co-author of the Bolognesi et al. (2009) study (reviewed previously)<sup>14</sup>:

"They [IARC] stated there was evidence of genotoxicity and they quoted one paper to support that statement. . . They (IARC) got this totally wrong. They said the study showed there was a relationship. . . It's certainly a different conclusion than the one we came to."

- Carissa Cyran, chemical review manager for the Office of Pesticide Programs at U.S. EPA<sup>15</sup>:

"Our review concluded that this body of research does not provide evidence to show that glyphosate causes cancer, and it does not warrant any change in EPA's cancer classification for glyphosate. This is the same conclusion reached in 2004 by the United Nations' Food and Agriculture Organization and affirmed this year by Germany's pesticide regulatory officials."

- Dr. Oliver Jones, Senior Lecturer in Analytical Chemistry at RMIT University in Melbourne, Australia<sup>16</sup>:

"This sounds scary and IARC evaluations are usually very good, but to me the evidence cited here appears a bit thin. . . People might be interested to know that there are over 70 other things IARC also classifies as 'probably carcinogenic', including night shifts. In the highest category of known carcinogens are 'alcoholic beverages' and 'solar radiation' (sunlight) – along with plutonium. . . So yes, pesticides can be dangerous, but [sic] are many other common things which are also dangerous in sufficient amounts or over long periods of time – the dose makes the poison. While absence of evidence is not evidence of absence this does seem to me to be a precautionary rather than a reactionary change."

<sup>14</sup> See <http://www.geneticliteracyproject.org/2015/03/30/globally-recognized-epidemiologist-pans-whos-glyphosate-cancer-designation>.

<sup>15</sup> See <http://www.monsanto.com/iarc-roundup/pages/third-party-responses-iarc.aspx>.

<sup>16</sup> See <http://www.sciencemediacentre.org/expert-reaction-to-carcinogenicity-classification-of-five-pesticides-by-the-international-agency-for-research-on-cancer-iarc>.

- Prof. Alan Boobis, Professor of Biochemical Pharmacology at Imperial College London<sup>16</sup>:

“The IARC process is not designed to take into account how a pesticide is used in the real world – generally there is no requirement to establish a specific mode of action, nor does mode of action influence the conclusion or classification category for carcinogenicity. . . The IARC process is not a risk assessment. It determines the potential for a compound to cause cancer, but not the likelihood. Exposure assessment in epidemiological studies on the effects of pesticides is notoriously difficult. Agricultural workers, the most commonly studied group, are almost never exposed to just a single pesticide and it is very difficult to establish cause and effect. . . The UK Committee on Carcinogenicity has evaluated possible links between pesticide exposure and cancer on several occasions. It has found little evidence for such a link. At most, the evidence was inconsistent and was considered insufficient to call for regulatory action. . . These conclusions of IARC are important and should be taken into account when evaluating these pesticides, but that must also take into account how the pesticides are used in the real world. In my view this report is not a cause for undue alarm.”

- Prof. Sir Colin Berry, Emeritus Professor of Pathology at Queen Mary University of London<sup>16</sup>:

“I have served on a number of regulatory bodies for the UK, EU and WHO and I am well used to sifting wheat from chaff in the analysis of pesticides. What is missing in this new assessment is balance in the consideration of the studies. . . There are over 60 genotoxicity studies on glyphosate with none showing results that should cause alarm relating to any likely human exposure. For human epidemiological studies there are 7 cohort and 14 case control studies, none of which support carcinogenicity. . . The authors have included non-Hodgkin lymphoma (NHL), but that diagnosis is no longer used in pathology because it’s far too imprecise. Even if you do include NHL there are still 7 studies, only one of which is positive – and that one is not a good study in my view. . . The weight of evidence is against carcinogenicity. . . This assessment has looked at a group of 43 diseases lumped into one category, multiple pesticides with very different chemistry, and has failed to include critical data. There is nothing here to suggest that the variety of genetic changes in these diseases could be caused by these pesticides. This appears to be a rather selective review.”

- Prof. David Coggon, Professor of Occupational and Environmental Medicine at the University of Southampton<sup>16</sup>:

“Given the large number of epidemiological studies that have been carried out on pesticides and cancer, many of them looking at multiple types of malignancy, it is to be expected that some positive associations will occur simply by chance. Thus, when evaluating the epidemiological evidence, one is looking for a consistent pattern of increased risk for one or more tumour types, which is unlikely to be explained by biases (often unavoidable) in the study methods. It is clear from the summary table in the Lancet report that clear and consistent evidence of this type was not found for any of the pesticides that were considered. . . Regulatory risk assessment for pesticides,

both in the EU and the USA, routinely considers evidence on potential carcinogenicity, both from animal studies (including some that may not have been published in the peer-reviewed literature, but which have been conducted to specified exacting standards) and also, where available, from epidemiological research. The approach adopted is precautionary. . . The IARC report does not raise immediate alarms.”

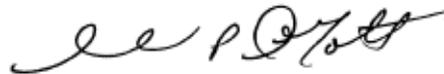
Thank you for considering these comments.

Yours sincerely,



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