Glyphosate and Cancer:

A Review of the Epidemiological Literature Related to the Development of Non-Hodgkin Lymphoma

by

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Charge 2d. Please comment on the strengths and limitations of the available studies to inform the association between glyphosate and non-Hodgkin lymphoma (NHL). Please comment on the agency's conclusion as described in Section 3.6.

I. Summary of NHL risks in the six studies cited by EPA on page 64 of the review document (substituting for the HR analysis in DeRoos et al. 2003)

a) 5/6 studies cited by EPA indicate RR > 1.0: (**DeRoos et al. 2003; DeRoos et al. 2005; Eriksson et al. 2008; Hardell et al. 2002; McDuffie et al. 2001)**

b) 3/6 studies demonstrate significantly elevated risk in relation to glyphosate exposure: (**DeRoos et al. (2003)** indicate an overall OR = 2.1 (95% CI = 1.10-4.03.71); **Erickkon et al. (2008)** > 10 days total exposure, OR = 2.36 (95% CI = 1.04-5.37 and **McDuffie et al. (2001**) > 2 days/year exposure, OR = 2.12 (95% CI = 1.20-3.73)

c) 2/3 studies that evaluated an exposure-response demonstrate an exposure-response relationship: In the **Eriksson et al. (2008)** study, for those exposed to ≤ 10 days total, the OR = 1.69 (95% CI 0.70-4.07); those exposed for > 10 days total, OR = 2.36 (95% CI = 1.04-5.37). In the **McDuffie et al. (2001**) study, as compared to those with no exposure to glyphosate, those exposed for ≤ 2 days/year, the NHL OR = 1.00 (95% CI = 0.63-1.57); for those exposed for > 2 days/year, OR = 2.12 (95% CI = 1.20-3.73).

d) Data indicate an increase in NHL risk by latency period:

The only study **(Eriksson et al. 2008)** to evaluate latency, indicates an increase in risk of NHL related to latency period. For those with a latency period of < 10 years, the NHL OR = 1.11 (95% CI = 0.24-5.08); for those with a latency period of > 10 years, NHL OR = 2.26 (95% CI = 1.16-4.40).

Thus, 5/6 studies show a NHL risk of > 1.0; 3/6 studies demonstrate significantly elevated risk of NHL in relation to glyphosate exposure; 2/3 studies indicate an exposure-response between glyphosate exposure and NHL.

II. Comments on Four Epidemiological studies that Received the Most Review in the EPA (2016) report

Eriksson et al. (2008) (EPA high quality study rank)

On page 65 of the Glyphosate Issue Paper, **EPA (2016)** states that the apparent lack of adjustment for co-exposure to other pesticides in the **Erickson et al. (2008**) study may have confounded the exposure-response relationship for glyphosate. The ability to observe an exposure-response related to a single chemical exposure (glyphosate) in the presence of other pesticide exposures makes it less likely, however, that the exposure-response is related to confounding from several other pesticide exposures. The other pesticide exposures are likely to dampen the exposure-response being evaluated for a single chemical. Thus, identification of an exposure-response relationship in an epidemiological study such as **Eriksson et al. (2008)** is usually a strong indication of causality because and most errors in exposure classification will bias results toward finding no association. The observation of a significantly increased risk for NHL among those with greater than 10 years latency (the only latency analysis provided in any of the 6 studies that EPA considered of high or medium quality in relation to glyphosate exposure and risk of NHL) is dismissed by EPA because of "lack of statistical power." This statement is incorrect.

Statistical power in a study is related to the ability to detect an effect or association if one is present (beta-error). A positive association is evaluated by the strength of the association and the probability that the association did not occur by chance (alpha error). Alpha error can be determined by the estimate of relative risk accompanied with a confidence interval. The EPA document seems to dismiss positive associations in some cases because relatively less power was present. This aspect of EPA's evaluation process needs to be reconsidered.

Eriksson et al. (2008) also demonstrated elevated risk for glyphosate exposure in relation to several categories of NHL: B-cell lymphoma OR = 1.87 (95% CI = 0.998-3.51); lymphocytic lymphoma/B-CLL OR = 3.35 (95% CI = 1.42-7.89); unspecified lymphoma OR = 5.63 95% CI = 1.44-22.0). **EPA (2016)** again dismisses these findings because of lack of statistical power. It is unlikely that the risk from every sub-type of NHL would be identical to the overall risk. Thus, the findings of some subtypes of NHL demonstrating significantly elevated risks that are greater than the risk with all subtypes combined, is to be expected. I recommend that EPA consider sub-types of NHL in its evaluation of NHL risks to glyphosate-exposed populations.

McDuffie et al. (2001) (EPA medium quality study rank)

EPA (2016) stated that the authors carried out a well-conducted exposure assessment, but then criticized the study because of potential recall bias, exposure misclassification and concern about controls, e.g., controls were selected from different sources and their participation rate was 48%. Differential information bias is a concern in case-control studies. **McDuffie et al. (2001)**, however, conducted a pilot validation study by comparing the questionnaire results from farmers with records from their local agrochemical supplier. They stated that the concordance was excellent though specific data were not provided in the report. On this same issue, **Blair and Zahm (1993)** also evaluated agreement between farmers and suppliers for use of pesticides and found little disagreement for cases and controls in questionnaire responses and supplier records. See **Blair and Zahm (1993)** Table 4.

EPA's (2016) comment about exposure misclassification in the **McDuffie et al. (2001)** does not seem to be supported by any data analysis, and it contradicts its own statement that exposure assessment was well-conducted in the study. **EPA (2016)** goes on to further criticized the finding of a exposure-response relationship in the **McDuffie et al. (2001)** study because the observation was based on two dose groups only in the analysis. In dose response analysis, a concern should be placed on the amount of separation that is present in the exposure groups being evaluated. If there is little difference in exposure, there is more difficulty in observing a dose response. The fact that a dose response was observed negates any concern regarding the number of dose groups used in the analysis. [Note: Three dose groups were actually used in the analysis because the odds ratios in the < 2 days exposure and the > 2 days exposure/year groups were compared to those exposed to no glyphosate.] The issue of control participation rate is a concern in any case-control study.

DeRoos et al. (2003 (EPA medium quality study rank)

As can be seen from the data in Table 3 of the study, the logistic regression analysis, adjustment for exposure to all other pesticides (N=47), resulted in a NHL OR = 2.1 (95% CI = 1.1-4.0). A second analysis, "hierarchial regression analysis," that further adjusted for prior evidence that any of the 47 pesticides may cause "any type of cancer" according to IARC or the EPA resulted in a NHL OR = 1.6 (95% CI = 0.9-2.8). The use of a "carcinogenic probability factor" that is not related

specifically to NHL for an adjustment to the results of the logistic regression analysis has little scientific merit. First, the adjustment is related to prior evidence that any of the 47 pesticides may cause any cancer, not whether they may cause NHL. Second, opinions on the carcinogenicity of pesticides change over time which would lead to different results for the same analysis depending upon when in time the hierarchial analysis is performed. A cursory review of the carcinogenic probability factors shown in Table 1 of **DeRoos et al. (2003)** indicates that the potency factor for glyphosate would change from 0.3 to 0.6, the factor for 2,4-D would change from 0.5 to 0.8 and the factor for lindane would change from 0.3 to 1.0 as **IARC (Monographs 112 and 113)** has recently classified the first two pesticides as likely to be carcinogenic to humans and lindane as a human carcinogen.

EPA (2016) chose the hierarchial regression analysis based on prior opinions about carcinogenicity as the preferred analysis rather than the logistic regression analysis. In my opinion, reliance upon study results related to actual data from the study should be preferred. Thus, the logistic regression analysis that adjusted for exposure to 47 pesticides and indicated an OR = 2.1 should have been selected to represent the risk of NHL from glyphosate exposure in the study.

On page 66, the **EPA (2016)** Issue Paper notes that epidemiological studies that rely upon questionnaires can be subject to exposure misclassification and recall bias. While these forms of bias are always a concern in such studies in general, **EPA (2016**) reports no evidence of exposure misclassification in the **DeRoos et al. (2003)** study.

Regarding recall bias, **EPA (2016)** speculates that "proxy respondents including next-of-kin were used for deceased individuals, and although these family members may have been in close contact with the study participant while living, it may have been hard for them to recall specific pesticide exposure(s), especially in the occupational setting. This specific issue of recall bias in the **DeRoos et al. (2003**) had previously been evaluated **(Blair and Zahm 1993)**. Cases did not report any more overall pesticide exposure than controls, and the pesticides reported by the surrogates were the same as reported by subjects themselves, but with less frequency. Based upon several analyses provided in the study, the authors concluded "Comparison of reporting by cases and controls provided no evidence of case-response (differential) bias; thus inaccurate recall of pesticide use by subjects or surrogates would tend to diminish risk

estimates and dilute exposure-response gradients." Therefore, the EPA's speculation about recall bias from proxy responders in the **DeRoos et al. (2003)** study has no merit.

DeRoos et al. (2005) (EPA high quality study rank)

The **DeRoos et al. (2005**) study, also referred to as the Agricultural Health Study (AHS) was reviewed in detail because of the numerous comments received by the Glyphosate Docket about the quality of the study and the study results. The review provides evidence of a) a young cohort that has not been followed for a sufficient period to time to allow for a meaningful evaluation of cancer risk; b) an inability to determine latency in relation to glyphosate exposure and risk of NHL; c) use of a comparison group known to have an elevated risk of NHL; d) exposure misclassification. As a result, the study should be considered "**uninformative**" at this point in follow-up.

A. The follow-up period is too short

Pesticide "applicators" were enrolled in the study between 1993-1997 and were followed to 2001 which equates to a follow period ranging from 4-8 years. The median follow-up period is reported in the study is 6.7 years. The age distribution of the cohort being followed indicates that 70% were below the age of 60 years and 46% were younger than age 50 years at the time of enrollment. These data suggested that the cohort may be too young to adequately evaluate cancer risk. Cancer incidence does not increase very rapidly until the ages of 50-55 years when the cancer incidence begins an exponential rise (**Cancer Research UK 2016**). Thus, trends in total cancer incidence support the opinion that the cohort will need to be followed for a much longer period of time in order to adequately evaluate cancer risk from glyphosate exposure.

Further analyses of the cohort data were then made to verify whether the cohort may, in fact be "too young" to evaluate cancer risk. Toward this end, data in Table 1 of the report allow one to calculate the number of glyphosate exposed cohort members as 40,376. Data presented in Table 3 of the report indicate there were between 1309 (intensity-weighted exposure days analysis) and 1324 (cumulative exposure days analysis) deaths from all cancers in the study. Using the larger number of deaths, 3.3% (1,324/40,375) of the cohort has been diagnosed with a cancer. Data from the **American Cancer Society (2016a)** indicate that the lifetime risk of developing an invasive cancer for US males is 42.0%. When one contrasts the 3.3% who have been diagnosed with a

cancer in the cohort with the lifetime risk for males to develop cancer (40%), it is clear from these data that the cohort has not been followed long enough to evaluate the risk of any cancer, including NHL.

B. Inability to Determine the Latency Period for NHL in the AHS:

Several documents submitted to the glyphosate docket have discussed the adequacy of the latency period to evaluate cancer risk in the **DeRoos et al. (2005**) study. The study provides no analysis of NHL risk by latency period. While information of glyphosate exposure was determined during the enrollment period (1993-1997), the time period of the initial exposure is not reported. Thus, it is not possible to estimate the latency period from data in the report.

C. Control Group Likely has an Elevated Risk of NHL

The comparison group used in the analysis for "ever/never" exposed to glyphosate (Table 2 of the report) would be expected to have an elevated risk of NHL for the following reasons. First, a number of epidemiological studies, including **Orsi et al. (2009)** and the recent study by **Morton et al. (2014)** demonstrate a significantly elevated risk of NHL among farmers, who comprised 91% of the comparison group in the **DeRoos et al. (2005)** study. Second, the **Hardell et al. (2002)** study indicates that exposure to "all herbicides" is a risk factor for NHL, OR = 1.75 (95% CI = 1.26-2.41). If farmers had not yet switched to glyphosate (those assigned to the comparison group in **DeRoos et al. 2005**), they are likely to have used other herbicides and hence have an elevated risk of NHL. Third, and more specifically, 53.3% of the comparison group in DeRoos et al. (2005) was exposed to 2,4-D, known to be associated with an elevated risk of NHL. The **Schinasi and Leon (2014**) study indicates a NHL meta-risk of 1.40 (95% CI = 1.0-1.9) for 2,4-D exposure and **IARC (2015a)** classified 2,4-D as likely to be carcinogenic to humans (category 2A). Therefore, the use of farmers as a control group for the glyphosate cohort in the AHS will result in an underestimate of NHL risk in the "ever/never" analysis.

D. Exposure Misclassification

In the AHS, intensity of exposure to glyphosate was determined from questionnaire data for the pesticide applicators only at the time of enrollment (1993-1997). The cohort was followed until 2011. As there was a dramatic increase in glyphosate production and use with the introduction of

genetically engineered crops in 1996, individuals already using glyphosate are likely to have had a corresponding dramatic increase in their glyphosate exposure beginning in 1996, including their intensity of exposure. This increase in glyphosate exposure over time, and particularly in 1996 was also pointed out by EPA on page 66 of the Glyphosate Issue Paper. Any such increase in exposure intensity that occurred subsequent to enrollment period would not be accounted for in the AHS "intensity-weighted cumulative exposure days analysis," e.g., "intensity-weighted cumulative exposure" was calculated as the product of intensity of exposure X years of use X days per year. Therefore, an unknown number of cohort members who continued to use glyphosate through 2001 are likely to have had their cumulative exposure underestimated for the period of exposure that occurred subsequent to enrollment into the study, and particularly subsequent to 1996 as glyphosate use had been continuously on the rise for the decade prior to 1996.

The analysis by "cumulative exposure days" (years of use X days per year) also would be adversely effected because length of exposure is only a meaningful surrogate of dose if the exposure levels during the exposure periods are similar **(Infante (1988).** To illustrate: 10 days of exposure to glyphosate between 1985 and 1990 would constitute a lesser exposure than 10 days of exposure between 1995 and 2000 because of the surge in glyphosate use after 1995. Yet, data for applicators exposed for 10 days during these two separate time-periods would be assigned to the same "cumulative exposure days" category. This methodology results in misclassification of glyphosate exposure in the study and biases a dose response analysis toward the null.

III. Meta-risk analyses for glyphosate exposure and NHL (all used same 6 studies included in EPA Glyphosate Issue Paper, Fig 3.2, page 64)

The studies are: **DeRoos et al. 2003; DeRoos et al. 2005; Eriksson et al. 2008; Hardell et al. 2002; McDuffie et al. 2001; Orsi et al. 2009.** The results from five meta-analyses published in the literature, plus the Infante (2016, this paper) are presented in Table 2.

A. **EPA (2016**) presented point estimates from the 6 studies in a Forest plot related to glyphosate exposure and NHL as shown on page 65 of the EPA Issue Paper, but did not calculate a meta-risk from the data. As shown in Table 2, the NHL meta-risk is 1.29 (95% CI = 1.04–1.60). This is virtually the same result as the IARC (2015a) meta-analysis which is not surprising since the same

studies and data points were used.

B. Using the same data points rom the same 6 studies, the **(2015a)** results indicate a NHL meta-risk = 1.3 (95% CI = 1.03-1.665

C. The **Schinasi and Leon(2014)** study demonstrates a NHL meta-risk of 1.5)95% CI = 1.1-2.2) using the **Hardell et al. (2002)** unadjusted result (3.04) and the unadjusted result (2.0) from **Eriksson et al. (2008).**

D. **Chang and Delzell (2016),** using the same six studies and data points as selected by EPA (page 64), calculated a NHL meta-risk = 1.3; 95% CI = 1.0-1.60 (model #1). When they substituted the logistic regression results of the **DeRoos et al. (2003)** for the hierarchial regression results and used the updated data from **McDuffie et al. (2001)** by **Hohenadal et al. (2011),** the NHL meta-risk = OR 1.4 (95% CI = 1.0-1.8).

E. **Infante (2016),** this presentation) applied both fixed effects and random effects models to the same data points as used by **Chang and Delzell (2016)** model 4. The results (shown for fixed effects models) indicate a meta-risk = 1.37 (95% CI = 1.04-1.82). When the **Cocco et al. (2013)** study of B-cell lymphoma were added to the model, the NHL meta-risk = 1.40 (95% CI = 1.06-1.85). One may question including the data from **Cocco et al. (2013)** on B-cell lymphoma in relation to glyphosate exposure in a meta-analysis of NHL. B-cell lymphoma, however, comprises 85% of NHL in the US (**American Cancer Society 2016b**) and it was the only category of NHL evaluated in the study. Finally, a meta-analysis of NHL was done that included the five case-control studies used by EPA in its evaluation, adding the **Cocco et al. (2013)** study and excluding the **DeRoos et al. (2005)** study that was considered informative at this point in cohort follow-up. The NHL meta-risk = 1.57 (95% CI = 1.12-2.18).

All of the meta-analyses demonstrate statistically significant elevated risk of NHL in relation to glyphosate exposure. The highest meta-risk is seen when the DeRoos et al. Study is excluded. This is not surprising as the OR was 1.1 and the study contributed 31 to the weight of the combined studies as shown in Table 1. [Note: All meta-analysis estimates were calculated using both the fixed- and random-effects models. Tests for heterogeneity between the individual study results were all clearly non-significant, and both models gave nearly identical results in all cases. The results using the fixed-effects models are presented in Table 2.]

IV. Summary of Meta-analyses Related to Glyphosate Exposure and NHL

The **EPA (2016)** Issue Paper on pages 63 and 64 concludes that only the **IARC (2015a)** meta-analysis for NHL was statistically significant. This is not the case. A meta-analyses based specifically on the data points for the 6 studies EPA presents in Figure 3.2 on page 64 of the Issue Paper indicate a significant NHL meta-risks ranging between 1.3 and 1.4 as reported by **Chang and Delzell (2016)**. The meta-analysis including the **Cocco et al. (2013)** study and also the meta-analysis excluding the **DeRoos et al. (2005)** additionally demonstrate statistically significant meta-risks for NHL ranging from 1.40 to 1.57. The meta analyses by **Schinasi and Leon (2014)** using slightly different data points for the **Hardell et al. (2002)** and **McDuffie et al. (2001)** indicate a NHL meta risk of 1.5 (95% CI - 1.1-2.0). Replacing the hierarchial regression analysis with the logistic regression analysis results **(Infante 2016)**, indicates a NHL meta-risk = 1.37 (95% CI =1.04-1.82).

The summary of the data for NHL on pages 64 and 65 of the **EPA (2016)** issue paper should include the results not only from the **IARC (2015a)** meta-analysis for NHL, but also the results of the **Chang and Delzell (2016)** meta-analysis from all four models presented in Table 3 of their report. Additionally, the meta-analysis **(Infante 2016)** that includes the Cocco et al. (2013) study and excludes the **DeRoos et al. (2005)** study should be considered in the evaluation of meta-analyses related to glyphosate exposure and risk of NHL.

V. EPA Cancer Guidelines (2005) for categorizing cancer risk of chemical substances and agents (pages 2-54 to 2-57)

On page 140, regarding epidemiological study results, the document states that "due to conflicting results and various limitations identified in studies investigating NHL, a conclusion regarding the association between glyphosate and risk of NHL cannot be determined based on the available data." If one accepts EPA's "quality of study methodology" which has limitations as pointed out below, it is difficult to understand this designation in the face of the **EPA 2005** Guidelines for Carcinogen Risk Assessment as related to the epidemiological data available to the Agency.

Figure 3.2 on page 64 of the document indicates that 6 studies were found to be of high or moderate quality. Of these six studies, 5 indicate a relative risk of greater than 1.0 and

three studies (**DeRoos et al. 2003; Eriksson et al. 2008; McDuffie et al. 2001**) demonstrate a statistically significant increase in risk of NHL. For the **DeRoos et al. (2003)** study preference should be given to the results based on the logistic model (RR = 2.1 (95% CI = 1.1-4.0) over the hierarchical regression (HR) analysis results, RR = 1.6 (95% CI = 0.9-2.8).

A fourth study (**Hardell et al. 2002**) indicated a RR of 1.85 (95% CI 0.55-6.27) with multivariate analysis, while univariate analysis indicated a RR = 3.04 (95% CI 1.08-8.52). Two of the six studies also demonstrated an exposure-response by days of exposure **(Eriksson et al. 2008; McDuffie et al. 2001**) and EPA considered these studies of high quality, and of and moderate quality, respectively. The **Eriksson et al. (2008)** study also demonstrated a significant increase in risk of NHL with an increase in latency.

The **EPA (2005)** Guidelines for Cancer Risk Assessment, on pages 2-52 to 2-58 define the following descriptors for carcinogen evaluation. They are listed going from the strongest evidence to the weakest:

"Carcinogenic to Humans"
"Likely to be Carcinogenic to Humans"
"Suggestive Evidence of Carcinogenic Potential"
Inadequate Information to Assess Carcinogenic Potential"
"Not Likely to be Carcinogenic to Humans"

Of these descriptors, the EPA Office of Pesticides has selected the descriptor "Not Likely to be Carcinogenic to Humans" to describe the result of its evaluation for glyphosate exposure and risk of cancer. Three of these categories are presented below.

<u>EPA designation: "Not Likely to be Carcinogenic to Humans</u>"

"This descriptor is appropriate when available data are considered robust for deciding that there is no basis for human hazard concern."

* "animal evidence that demonstrates lack of carcinogenic effect in both sexes in well-designed and well-conducted studies in a least two appropriate animal species (<u>in the absence of</u> other animal or <u>human data suggesting a potential for cancer effects</u>." (underline added)

EPA Designation "Suggestive Evidence of Carcinogenic Potential"

"a concern for potential carcinogenic effects in humans is raised, but the data are judged not sufficient for a stronger conclusion. This descriptor covers.... varying levels of concern for carcinogenicity, ranging from a positive cancer result in the only study on an agent to a single positive cancer result in an extensive database that includes negative studies in other species." (Underlines added)

Some examples include:

* "a small, and possibly not statistically significant, increase in tumor incidence observed in a single animal or human study that does not reach the weight of evidence for the descriptor "Likely to Be Carcinogenic to Humans. The study generally would not be contradicted by other studies of equal quality in the same population group or experimental system."

EPA designation "Likely to Be Carcinogenic to Humans"

"Adequate evidence consistent with this descriptor covers a broad spectrum....the use of the term "likely as a weight of the evidence descriptor does not correspond to a quantifiable probability. The examples below are meant to represent the broad range of data combinations that are covered by this descriptor."

* "an agent demonstrating a plausible (but not definitely causal) association between human exposure and cancer, in most cases with some supporting biological, experimental evidence, though not necessarily carcinogenicity data from animal experiments." (underlines added)

Conclusion: Based upon a review of the 6 studies that EPA relies upon for its evaluation of NHL risk in relation to the criteria presented in its Guidelines for Cancer Risk Assessment, the data for Glyphosate exposure and risk of NHL, clearly exceed the descriptor of "Suggestive Evidence of Carcinogenic Potential." I would argue that they easily meet the descriptor "Likely to Be Carcinogenic to Humans."

VI. Risk for Subtypes of NHL in relation to glyphosate exposure

Regarding NHL, the EPA **(2016)** document only includes analyses related to NHL with all sub-types combined. On page 55 of the document, **EPA (2016)** states that "there are analyses available for particular subtypes of NHL; however, these are particularly limited by the small sample sizes. As a result, this

evaluation only presents results for total NHL." If an elevated risk of NHL is observed for all types combined, it is likely that some subtypes would indicate relative risks higher than the overall NHL risk and these risks should be considered for evaluation. For example, the **Eriksson et al. (2008**) study demonstrates elevated risks for B-cell lymphomas (OR = 1.87; 95% CI = 0.99-3.51), lymphocytic lymphoma/B-CLL (OR = 3.35; 95% CI = 1.42-7.89) and for unspecified NHL (OR = 5.63; 95% CI= 1.44-22.0) in relationship to glyphosate exposure. The **Schinasi and Lyon (2014)** and **Chang and Delzell (2016)** meta-analyses both indicate a meta-risk of 2.0 (95% CI 1.1-3.6) for "b-cell" lymphoma in relation to glyphosate exposure. Data from the abstract of the study being conducted by researchers from the Occupational Cancer Research Center in Toronto and the US National Cancer Institute **(Pahwa 2016)** as presented at the IARC 50th Anniversary Meeting in Lyon, France in May 2016 suggests elevated risks for several sub-types of NHL in relation to glyphosate use. Thus, EPA should consider evaluating the data for glyphosate exposure and risk of sub-types of NHL.

VII. Request Current Glyphosate Study Results from the National Cancer Institute Related to NHL

The SAP should ask EPA to request any new study results that may be available from the current studies being performed by researchers from the Occupational Cancer Research Center in Toronto and the US National Cancer Institute **(Pahwa 2016).**

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Table 1. Publications Used in Various Meta-Analyses to Estimate Relative Risks for Exposure to Glyphosate and Non-Hodgkin's Lymphoma. Estimates Unadjusted and adjusted (multivariate) for other Pesticides. Slide 2

Study Publication	Type of Study	Estimates of Relative Risk (95% C.I)		Comments	Rel. Weights, Fixed Effects Model
		Unadjusted	Multivariate Adj		100%
De Roos (2003)	CC	N.A.	2.1 (1.1 – 4.0)	1.6 (0.9 - 2.8) Hier. Regression – Adj.	18.48
De Roos (2005)	Cohort	1.2 (0.7 – 1.9)	1.1 (0.7 – 1.9)		30.76
Erikkson (2008)	CC	2.02 (1.10 –3.71)	1.51 (.77 – 2.94)		17.10
Hardell (2002)	CC	3.04 (1.08–8.52)	1.85 (0.55 – 6.2)		5.25
McDuffe2001 Hohendal (2011)	CC	1.20 (0.8 – 1.74) 1.40 (0.62- 3.15)	N. A.	Hohendal corrects McDuffie's	11.67
Orsi (2009)	CC	1.0 (0.5 – 2.2)	N.A.		14.00
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Coco (2013)	CC	3.1 (0.6 – 17.1)	N.A.	B-Cell Lymphoma	2.74

Table 2. Various Meta-Analysis Results of Relative Risk Estimates from Agencies and Publications based on Six Studies of Glyphosate Exposure and NHL. Results from Fixed Effects Models. Slide 3

PUBLICATIONS with Meta-Analyses: Ever vs. Never	RR est. (95% C.I.)	Number of Studies Adjusted for Other Pesticides	Comments
EPA (2016)	1.29 (1.04 – 1.60)	4	Used DeRoos (2003) Hier. Regression; Used McDuffie.
IARC (2015)	1.3 (1.03 – 1.65)	4	IARC Vol. 112 Pg. 30
Schinasi (2014)	1.5 (1.1 – 2.0)	2	Used Hardell unadjusted, Erikkson unadj., McDuffie
Chang (2016)	1.4 (1.0 – 1.8)	4	Hohenadel (2011) replaces McDuffie (2001): Model 4.
Infante: This presentation	1.37 (1.04 – 1.82)	4	Hohenadel, DeRoos (2003) with standard reg. 6 studies
Infante: With Cocco (2013)	1.40 (1.06 – 1.85)	4	Includes Cocco (2013) B-Cell Lymphoma. 7 studies
Without DeRoos (2005)	1.57 (1.12-2.18)	3	Includes 6 case-control studies