

Epidemiologic evidence

Evidence describing the association between glyphosate exposure and the risk of developing non-Hodgkin lymphoma (NHL) was available from 14 epidemiologic studies - 13 case-control studies (Cocco et al., 2013; Hohenadel et al., 2011; Orsi et al., 2009; Eriksson et al., 2008; Lee et al., 2004; De Roos et al., 2003; Hardell et al., 2002; and McDuffie et al. 2001; Hardell and Eriksson, 1999; Nordstrom et al., 1996; Cantor et al., 1992; Zahm et al., 1990; Hoar et al., 1986) and one cohort study (De Roos et al., 2005). These are the only studies that specifically evaluated the risk of NHL associated with exposure to glyphosate. As De Roos et al. (2003) is a pooled analysis of three case-control studies by Cantor et al. (1992), Zahm et al. (1990), and Hoar et al. (1986), and Lee et al. (2004) is a pooled analysis of Cantor et al. (1992) and Zahm et al. (1990), the results of De Roos et al. (2003) are considered to be the most representative findings among this group of studies. Similarly, Eriksson et al. (2008) is a pooled analysis of Hardell and Eriksson (1999) and Nordstrom et al. (1996) and the results of Eriksson et al. (2008) are considered to be the most representative of that group of studies. McDuffie et al. (2001) and Hohenadel et al. (2011) report on the same case-control study population; however, the results of McDuffie et al. were considered to be more specific to glyphosate. The synthesis of the epidemiologic evidence is therefore based on seven studies (Cocco et al., 2013; Orsi et al., 2009; Eriksson et al., 2008; De Roos et al., 2005; De Roos et al., 2003; Hardell et al., 2002; and McDuffie et al. 2001).

Consistency of the observed association

Most of the studies reported more than one result describing the relationship between exposure to glyphosate and the risk of NHL. For studies reporting results on multiple metrics of exposure, each metric is included in Figure G; however, only the highest category of each exposure metric is presented. The most commonly evaluated exposure was for a crude measure of 'ever' been exposed to glyphosate. All seven of the studies reported results adjusted for standard demographic covariates. Five studies reported at least some results further adjusted for co-exposures to other pesticides or evaluated if there was potential confounding (Eriksson et al., 2008; De Roos et al., 2005; De Roos et al., 2003; Hardell et al., 2002; McDuffie et al., 2001). All five of these studies reported elevated risks of NHL ($OR > 1$) following adjustment for co-exposures including other pesticides: Eriksson et al. (2008) reported $OR=1.51$ (95% CI: 0.77-2.94); De Roos et al. (2005) reported $OR=1.1$ (95% CI: 0.7-1.9); De Roos et al. (2003) reported $OR=1.6$ (0.9-2.8)¹; Hardell et al. (2002) reported $OR=1.85$ (95% CI: 0.55-6.2); McDuffie et al. (2001) reported $OR=1.20$ (95% CI: 0.83-1.74). Of the two studies which did not control for co-exposures to other pesticides, Cocco et al. (2013) reported $OR=3.1$ (95% CI: 0.6-17.1) and Orsi et al. (2009) reported a null result with $OR=1.0$ (95% CI: 0.5-2.2).

Overall, six of the seven studies reported at least some increased risk of NHL associated with exposure to glyphosate, but all of the seven reported relative effect estimates for 'ever' been exposed

¹ Hierarchical regression model results. Note that the standard logistic regression results yielded $OR=2.1$ (95% CI: 1.1-4.0).

to glyphosate had 95% confidence intervals which included the null value of 1.0 (see Figure G). Three meta-analyses of studies reporting on glyphosate and the risk of NHL have been published. Chang and Delzell (2016) discussed Cocco et al. (2013) but did not include that study in the meta-analysis, presumably because that study reported glyphosate-specific results only for B-cell lymphomas; however, these B-cell lymphoma cases constitute 90% of all NHL cases. Chang and Delzell (2016) reported a Meta-OR=1.3 (95% CI: 1.0-1.6). Schinasi and Leon (2014) reported a Meta-OR=1.5 (95% CI: 1.1-2.0) for the same studies in Chang and Delzell and further reported a Meta-OR for B-cell lymphomas of 1.8 (95% CI: 0.9-3.5) and a Meta-OR for diffuse large b-cell lymphomas of 2.0 (95% CI: 1.1-3.7) based on specific results from Eriksson et al. (2008) and Orsi et al. (2013). IARC (2016) reviewed the meta-analysis by Schinasi and Leon (2014) and noted that for two studies (Eriksson et al., 2008 and Hardell et al., 2002), the effect estimates used in the meta-analysis were not the most fully adjusted values. IARC (2016) reported a revised Meta-OR of 1.3 (95% CI: 1.03-1.65). None of the three reported meta-analyses reported significant statistical heterogeneity among the study results as measured by the I² statistic which were all lower the typical threshold of 50% (i.e., 0%, 0% and 33%). Table G shows the results of the three published meta-analyses (Chang and Delzell, 2016; IARC, 2016; Schinasi and Leon, 2014).

In summary, the results of seven epidemiologic studies reporting on the association between exposure to glyphosate and risk of NHL were consistent in reporting elevated risks of NHL associated with exposure to glyphosate.

Strength of the observed association

Relative effect estimates from the seven studies for the association between ‘ever’ having been exposed to glyphosate and the risk of NHL ranged from 1.0 (Orsi et al., 2009) to 3.1 (Cocco et al., 2013) with a median value of 1.51 (Eriksson et al., 2008). A standard inverse variance weighted meta-analysis of the five ‘ever/never’ results which controlled for other pesticides (Eriksson et al., 2008; De Roos et al., 2005; De Roos et al., 2003; Hardell et al., 2002; and McDuffie et al. 2001) yielded an overall effect of OR=1.30 (95% CI: 1.02-1.65) which is essentially the same as the meta-analysis result reported by Chang and Delzell (2016) and IARC (2016) although those analyses included the results from Orsi et al. (2009) which did not control for other pesticide exposures.

Table G. Results of meta-analyses of glyphosate exposure and risk of NHL

Meta-analysis	Studies included	Overall OR (95% CI)
Schinasi and Leon, 2014	Orsi et al., 2009; Eriksson et al., 2008; De Roos et al., 2005; De Roos et al., 2003; Hardell et al., 2002; and McDuffie et al. 2001	1.5 (1.1-2.0)
IARC, 2016	Orsi et al., 2009; Eriksson et al., 2008; De Roos et al., 2005; De Roos et al., 2003; Hardell et al., 2002; and McDuffie et al. 2001	1.3 (1.03-1.65)
Chang and Delzell, 2016	Orsi et al., 2009; Eriksson et al., 2008; De Roos et al., 2005; De Roos et al., 2003; Hardell et al., 2002; and McDuffie et al. 2001	1.3 (1.0-1.6)
This evaluation	Eriksson et al., 2008; De Roos et al., 2005; De Roos et al., 2003; Hardell et al., 2002; and McDuffie et al. 2001	1.30 (1.02-1.65)

Temporal relationship of the observed association

Two related aspects of time are encompassed in the consideration of temporality. One aspect is the necessity for the exposure to precede the onset of the disease. In each of the studies, the glyphosate exposures among the study participants started prior to their diagnoses of NHL. The second aspect involves the time course of glyphosate exposures in relation to the incidence of NHL. Hardell and Eriksson (1999) reported that for herbicides as a group and for phenoxyacetic acids (e.g., MCPA, '2,4,5-T', '2,4-D'), the highest risks were associated with first herbicide exposures 10-20 years prior to diagnosis of NHL. Only one study evaluated the impact of the time since first exposure (Ericksson et al., 2008) and reported that for glyphosate exposure in a 10 year period prior to diagnosis of NHL, the OR=1.11 (95% CI: 0.24-5.08), but for glyphosate exposure that occurred more than 10 years prior to diagnosis of NHL, the OR=2.26 (95% CI: 1.16-4.40). This finding, while limited to a single study, is consistent with a biologically relevant induction/latency period for NHL. This finding suggests that cohort studies without sufficient follow-up time, or other case-control studies which did not stratify by time since first exposure could be insensitive to the detection of risk.

Exposure-response relationship

Of the seven studies which provided evidence to evaluate the association between exposure to glyphosate and the risk of NHL, three studies (Ericksson et al., 2008; De Roos et al., 2005; McDuffie et al., 2001) reported the results assessing a potential exposure-response relationship. De Roos et al. (2005) analyzed exposure-response by tertile of cumulative exposure and by tertile of intensity-weighted cumulative exposure and found no evidence of an exposure-response relationship. While there were 92 cases of NHL included in the 'ever' exposed to glyphosate analysis, in order to control for co-exposures to other pesticides in the exposure-response analyses, cases and controls were excluded if any study participant's data on exposure duration or exposure frequency was missing or incomplete. This exclusion resulted in an approximate loss of 25% of all cases and controls (see De Roos et al., 2003) leaving 61 glyphosate exposed cases for the exposure-response analyses in De Roos et al. (2005). Compared to people in the lowest tertile of cumulative glyphosate exposure (n=29 with 20 or fewer exposed days), those in the highest tertile (n=17 with more than 57 exposed days) had an OR=0.9 (95% CI: 0.5-1.6) and the trend p-value was 0.73. Compared to people in the lowest tertile of intensity-weighted cumulative glyphosate exposure (n=24), those in the highest tertile (n=22) had an OR=0.8 (95% CI: 0.5-1.4) and the trend p-value was 0.99. These results were from analyses that did not control for co-exposures to other pesticides; however, the investigators did check that inclusion of co-exposures in the model did not change the effect estimates so these results can be viewed as being without meaningful confounding. Additional exposure-response analyses also showed no sign of an exposure-response relationship: these analyses included using those unexposed to glyphosate as the reference group; comparing those in the highest quintile of glyphosate exposure (>108 days) to those in the lowest quintile of glyphosate exposure (0-9 days); and, a using a linear function of cumulative exposure days.

McDuffie et al. (2001) assessed the potential for an exposure-response relationship by stratifying by the average number of days individuals were exposed each year; however, these analyses did not control for exposures to other pesticides. Compared to people who were unexposed to glyphosate, but may have been exposed to other pesticides (n=1,839), those whose glyphosate exposures less than or equal to 2 days per year (n=125) had an OR=1.00 (95% CI: 0.63-1.57) and those whose glyphosate exposures exceeded 2 days per year (n=59) had an OR=2.12 (95% CI: 1.20-3.73).

Eriksson et al. (2008) used the median number of days exposed to glyphosate among the controls to stratify results in their exposure-response analysis which also did not control for exposures to other pesticides. Compared to people who were unexposed to glyphosate, those who were exposed for 10 or fewer days had an OR=1.69 (95% CI: 0.70-4.07) while those who were exposed for more than 10 days had an OR=2.36 (95% CI: 1.04-5.37). To provide context for this results, the 'ever' exposed result without adjustment for co-exposures was OR=2.02 (95% CI: 1.10-3.71) and the 'ever' exposed result with adjustment for co-exposures was OR=1.51 (95% CI: 0.77-2.94).

Two interpretations of these three evaluations of the potential exposure-response relationships are possible. First, there may be an exposure-response relationship, but only if sufficient time since first exposure has elapsed. Eriksson et al. (2008) reported a marked increase in glyphosate-associated risk of NHL, but only among those study participants with greater than 10 years' time since first exposure. The cohort studies by De Roos et al. (2005) had a median follow-up time of 6.7 years up through 2001. Since the range of enrollment dates spanned from 1993-1997, the range of follow-up was from 4-8 years. While it is likely that cohort members were exposed to glyphosate prior to enrollment, because cohort members were checked against state cancer registries as a criteria for inclusion in the cohort, the study design of De Roos et al. (2005) does not allow time prior to the enrollment date to be considered to be 'at risk' and thus any prior glyphosate exposure is not the exposure of interest in this study. So it is possible that the seemingly conflicting results simply reflect a lack of detectable risk of NHL within the 10 years following first exposure to glyphosate, with increased, exposure-dependent risks after 10 years. This is a common pattern in studies of occupational or environmental exposures and would be a simple explanation for these findings.

A second interpretation could be that people exposed to glyphosate are co-exposed to other risk factors for NHL in a correlated manner such that higher exposures to glyphosate were associated with higher exposures to other pesticides and that those other causes of NHL were confounding the exposure-response relationship between glyphosate and risk of NHL. De Roos et al. (2005) evaluated the effect of glyphosate on the risk of NHL both in the presence and absence of other co-exposures and did not find a meaningful difference. This generally indicates a lack of confounding, and since they did not identify an association between glyphosate and risk of NHL in the analyses that did not control for co-exposures, De Roos et al. (2005) provides no evidence of confounding. Eriksson et al. (2008) did provide evidence of potential confounding which is seen by comparing the results with and without control of co-exposures. The unadjusted effect of glyphosate was OR=2.02 (95% CI: 1.10-3.71) while the same effect adjusted for all co-exposures ('ever' exposed) which themselves had unadjusted ORs>1.5

yielded an herbicide adjusted OR for glyphosate of 1.51 (0.77-2.94). Comparing the magnitude of those effect sizes on the natural log scale, the unadjusted effect was $\beta=0.70$ (95% CI: 0.10, 1.31) while the adjusted effect was $\beta=0.41$ (95% CI: -0.26, 1.08), suggesting a difference compatible with a degree of confounding by those herbicide co-exposures which appeared to have inflated the unadjusted effect upwards by 70% on the natural log scale (or upwards by 46% on the OR scale). Since accurate statistical control of confounding requires high quality exposure information on the potential confounders and Eriksson et al. (2008) did not include quantitative estimates of co-exposures, it is possible that there remains some degree of residual confounding – even in the adjusted effect estimate.

In summary, there was limited evidence of an exposure-response relationship between increased glyphosate exposure and increased risk of NHL, however the evidence was heterogeneous. The heterogeneity may be explained as either an insufficiency of follow-up time for NHL in De Roos et al. (2005) or the potential for residual confounding by other pesticides that themselves cause NHL.

Potential impact of selection bias, information bias, confounding bias, and chance

Selection bias is an unlikely alternative explanation for the consistent evidence of increased risk of NHL in people exposed to glyphosate. Loss to follow-up in the only cohort study (De Roos et al., 2005) was less than 1% of participants over the course of follow-up. Selection bias is unlikely in the majority of the case-control studies of NHL as participation rates for both cases and controls were high (80-99%) and well-balanced with differences in participation rates between cases and controls of <10% (Orsi et al., 2009; Eriksson et al., 2008; De Roos et al., 2003; Hardell et al., 2002). In two case-control studies with lower or unbalanced participation rates, there was potential for selection bias. Cocco et al. (2012) had a high participation rate among cases (88%) but controls were recruited differently in some of the participating counties. From the European countries which contributed hospital controls, participation rates were high (81%) but from the countries which contributed population controls, only 52% of selected controls participated. Participation rates for cases in McDuffie et al. (2001) were low (67%) and substantially different from controls (48%) which increased the potential for selection bias. However, both studies (Cocco et al., 2012 and McDuffie et al., 2001) used trained interviewers working from standardized questionnaires, there is no indication that participation rates would be related to glyphosate exposure and thus the potential for selection bias due to participation rates is considered to be unlikely to explain the observed results.

Information bias is an unlikely alternative explanation for the consistent evidence of increased risk of NHL in people exposed to glyphosate. Information bias may distort epidemiologic findings when subjects' true exposures are inaccurately assigned at the individual or group level. A differential misclassification, in which exposure status influences disease classification by the investigator (or disease status influences exposure classification), can lead to spurious (i.e., "false positive") associations. However, information bias is considered unlikely among these studies of NHL incidence because the likelihood of differential misclassification based on these study designs is low. The assignment of exposure status or calculation of exposure measures in the cohort study was independent of any cancer

diagnosis by design. In the case-control studies, exposure assessment to glyphosate is extracted from detailed occupational histories based on interview data and subjects were unlikely to be aware of specific chemical exposures of interest in the study. Each of the case-control studies was designed to evaluate the risk of multiple pesticides and other agricultural risk factors for NHL. There is no apparent basis to support the idea that NHL cases would recall exposures to glyphosate differently than they would recall exposures to other common herbicides such as MCPA (2-methyl-4-chlorophenoxyacetic acid), '2,4,5-T' or '2,4-D'. Therefore, a glyphosate-specific exposure-related bias in their recall of their occupational histories is unlikely.

Additional exposure measurement error may arise in circumstances when the time period of exposure assessment is not well aligned with the time period when glyphosate exposure could induce carcinogenesis that develops to a detectable stage (incident cancer). Epidemiology studies regularly explore the analytic impact of different lengths of 'latency periods' which may exclude from the analyses the glyphosate exposure most proximal to each individual's cancer incidence. For analyses of the exposure-related risks of cancer, it is commonplace to evaluate latency periods by presenting results stratified by time since first exposure, or to exclude (or in the parlance of epidemiology, to 'lag') exposures in the years immediately prior to cancer diagnosis from the analyses so as to potentially more accurately describe what may be the more biologically relevant exposure window that could have caused carcinogenesis (sometimes called the etiologically relevant time period). Analyses which do not evaluate latency, may be inducing exposure measurement error by including biologically irrelevant exposures and yielding results somewhat biased towards the null. Among the epidemiologic studies of glyphosate and NHL, only the study by Eriksson et al. (2008) included a latency analysis of glyphosate which showed markedly higher risks for glyphosate exposure more than 10 years prior to NHL diagnosis (OR=2.26; 95% CI: 1.16-4.40) compared to the specific risk for exposures in the 10 years immediately preceding NHL diagnosis (OR=1.11; 95% CI: 0.24-5.08). While this latency analysis did not control for co-exposures to other pesticides and thus may be confounded, such potential confounding does not explain the doubling of risk by time since first exposure. This pattern of higher risk associated with lagged exposure suggests that the other studies may have systematically underestimated the risk of NHL associated with exposures to glyphosate by assuming the risk of exposure is unrelated to the timing of exposure. The same pattern of stronger effects in the 10-20 year period following first exposure was also reported by Hardell et al. (2002) for all herbicides, phenoxyacetic acids as a group as well as individually for MCPA and '2,4-D + 2,4,5-T'.

The potential for confounding was evaluated based on exposures to identified risk factors for NHL, or related cancers, whether those other exposures were found to be risk factors in the specific study and whether there was a known or likely correlation between those exposure and glyphosate. Risk factors for lymphohematopoietic cancers, which includes NHL, include pharmaceuticals (chemotherapeutic drugs), biological agents (e.g., viruses), radiation, and chemical exposures (Cogliano et al., 2011). The primary agents of interest that were considered in the study quality review are the potential occupational and environmental co-exposures that may be associated with glyphosate

exposure as well as NHL. Chemotherapeutic drug exposures were not expected to be correlated with glyphosate exposures and were not considered as potential confounders. Similarly, viral exposures and radiation exposures were also not expected to be correlated with glyphosate exposures. Each of the chemical and occupational exposures which were reported to be associated with risks of lymphohematopoietic cancers (i.e., benzene, 1,3-butadiene, 2,3,7,8-tetrachlorodibenzo-para-dioxin, ethylene oxide, magnetic fields, paint, petroleum refining, polychlorophenols, radioisotopes and fission decay products, styrene, tetrachloroethylene, tobacco smoking, trichloroethylene; Coglianò et al., 2011) was examined in the study quality review and evaluated as a potential confounder as were the specific risk factors in each of the study analyses.

Of the seven epidemiologic studies of glyphosate and NHL, four higher quality studies included analyses controlling for co-exposure to other pesticides (Eriksson et al., 2008; De Roos et al., 2005; De Roos et al., 2003; Hardell et al., 2002). As mentioned in the exposure-response section, Eriksson et al. (2008) provided evidence of potential confounding by comparing the results with and without control of co-exposures. The unadjusted effect of glyphosate was OR=2.02 (95% CI: 1.10-3.71) while the same effect adjusted for all co-exposures ('ever' exposed) which themselves had ORs>1.5 yielded an OR=1.51 (0.77-2.94). Those co-exposures were MCPA, '2,4,5-T and/or 2,4,-D', mercurial seed dressing, arsenic, creosote, and tar. Of these, MCPA, mercurial seed dressing, and creosote were somewhat stronger risk factors for NHL than was glyphosate in the multivariate analysis. Compared to the adjusted result, the regression coefficient from the unadjusted analysis was 71% larger, an analytic finding consistent with confounding although there may be another explanation. Eriksson et al. (2008) note that in Sweden glyphosate has replaced MCPA as the most widely used agricultural herbicide and that many people exposed to glyphosate were likely to have been exposed to MCPA earlier. In the context of the multivariate regression, control of another co-exposure is essentially a stratification of the results by each factor. Therefore, if glyphosate is a replacement for MCPA then the information available to estimate the specific effect of glyphosate without MCPA is limited to those people who only recently applied a broad-spectrum herbicide and thus that group would have a shorter period of follow-up which Eriksson et al. (2008) showed was associated with lower risk of NHL.

De Roos et al. (2005) evaluated evidence of potential confounding by adjusting for co-exposures which were most highly correlated with glyphosate exposure ('2,4-D', alachlor, atrazine, benomyl, carbaryl, diazinon, maneb, metolachlor, paraquat, and trifluralin), but did not find that the adjusted effect estimate differed from the unadjusted effect estimate by more than 20%. Likewise, De Roos et al. (2003) reported that multivariate adjustment for 47 pesticides ('ever' exposed) provided few examples of substantial confounding and no mention of confounding of the effect of glyphosate was mentioned. Conversely, Hardell et al. (2002) reported that the effect of glyphosate without adjustment for co-exposures to other pesticides was OR=3.04 (95% CI: 1.08-8.52) while the effect adjusted for all co-exposures ('ever' exposed) shown to be risk factors for NHL yielded an OR=1.85 (95% CI: 0.55-6.20). A key difference in the methodology used by De Roos et al. (2003) and Hardell et al. (2002) was in the definition of the reference group which, in Hardell et al., was composed of only those individuals who

had no pesticide exposures – a particular strength of this study. This categorization of the reference group increases the contrast and precision of effect estimates between those exposed to glyphosate and those unexposed to any pesticide compared to those exposed to glyphosate and those not exposed to glyphosate but exposed to other pesticides – even if those other pesticides are included in the model.

There is clearly a strong potential for confounding by co-exposures to other pesticides since many are highly correlated and have been reported to be risk factors for NHL. In each instance where a study controlled for other pesticides, the adjusted effect estimate decreased in magnitude. This finding suggests that those reported results of the effect of glyphosate on the risk of NHL which did not control for other pesticides, may be confounded upwards (Cocco et al., 2013; Orsi et al., 2009; and McDuffie et al. 2001) and is why these studies were considered to be of relatively lower quality. However, the four higher quality studies (Eriksson et al., 2008; De Roos et al., 2005; De Roos et al., 2003; Hardell et al., 2002) all reported elevated risks of NHL associated with exposure to glyphosate even after controlling for other pesticide exposures.

The results of seven independent epidemiologic studies reporting on the association between exposure to glyphosate and risk of NHL were consistent in reporting elevated risks of NHL associated with exposure to glyphosate with little statistical heterogeneity. Consistency across multiple studies was demonstrated by a pattern of increased risk in different populations, exposure scenarios, and time periods. Such consistency makes selection bias, information, bias and confounding less likely alternative explanations for the observed associations. This consistency also reduces the likelihood of chance as an alternative explanation, and although many of the individual results did not exclude the null value of 1, the meta-analysis by IARC (2016) had a summary estimate of OR=1.3 (1.03-1.65) and the meta-analysis for this evaluation based only on the five studies which did control for exposure to other pesticides had a summary estimate of OR=1.30 (95% CI: 1.02-1.65). The observations of two exposure-response relationships somewhat reduce the likelihood that chance, confounding, or other biases can explain the observed association – although incompletely confounding may have inflated some results.

Causal Evaluation

The causal evaluation for glyphosate exposure and the risk of developing NHL placed the greatest weight on five particular considerations:

- 1)** The overall consistency of the observed increases in risk across a set of seven *High* and *Medium* confidence independent results with varied study designs and populations clearly suggests carcinogenic potential;
- 2)** The only study to evaluate the potential impact of cancer latency showed a biologically coherent temporal relationship consistent with a pattern of exposure to glyphosate and increased risk of NHL allowing time for cancer latency. While this specific result did not control for exposures to other

pesticides, the more than doubling of risk among those exposures to glyphosate more than 10 years prior to getting NHL compared to those with less than 10 years (OR=2.26 95% CI 1.16-4.40 vs. OR=1.11 95% CI: 0.24-5.08) is evidence supportive of carcinogenic potential;

3) The strength of the association from a meta-analysis of the five studies which controlled for exposures to other pesticides shows a 1.3-fold increase in risk (95% CI: 1.02-1.65) although may still have been both confounded upward due to incompletely controlled exposures to other pesticides that were risk factors for NHL, as well as biased downward due to information bias due to non-differential exposure measurement error;

4) There was limited evidence from two studies reporting results consistent with an exposure-response relationships which is supportive evidence of a causal association, however, another study with more extensive analyses did not detect any exposure-response relationship – although this study had a relatively short median follow-up period for cancer incidence at 6.7 years (maximum of 8 years);

5) Based on the available epidemiologic evidence from seven studies, only five of which controlled for exposures to other pesticides, and only three of which evaluated potential dose-response relationships –with conflicting results, alternative explanations for the observed associations between glyphosate and the risk of NHL cannot be ruled out.

Conclusion

- The available epidemiologic studies provide **suggestive** evidence of carcinogenic potential between glyphosate exposure and increased risk of non-Hodgkin lymphoma.
- According to the EPA Cancer Guidelines (2005), “this descriptor of the database is appropriate when the weight of evidence is suggestive of carcinogenicity; a concern for potential carcinogenic effects in humans is raised, but the data are judged not sufficient for a stronger conclusion. This descriptor covers a spectrum of evidence associated with 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.”

All Studies Reporting Non-Hodgkin Lymphoma Risk Estimates

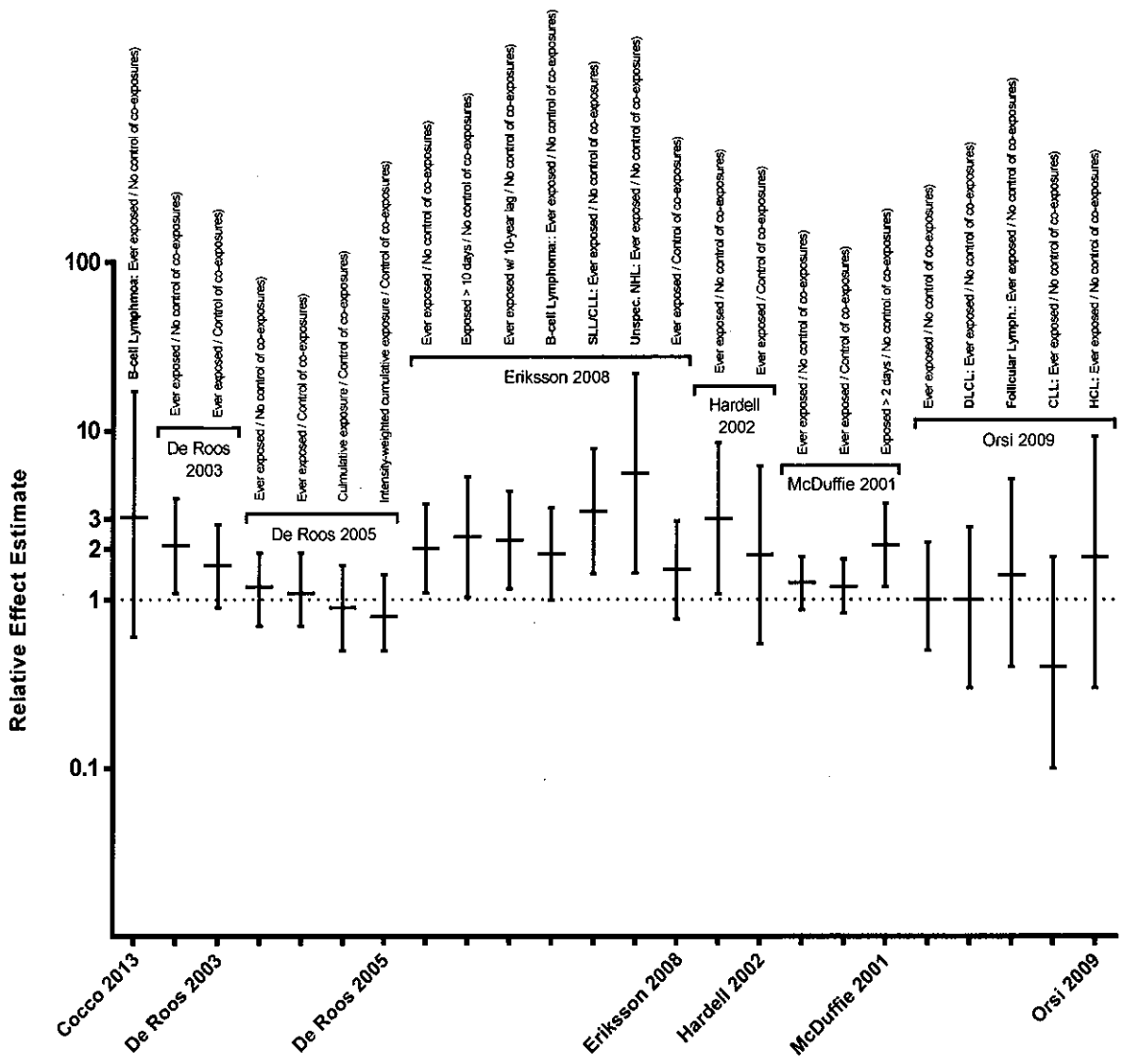


Figure G. Epidemiologic studies reporting NHL risk estimates associated with exposure to glyphosate. For studies reporting results on multiple metrics of exposure, each metric is included; however, only the highest category of each exposure metric is presented in the figure.