UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: **October 1, 2015**

SUBJECT: **GLYPHOSATE:** Report of the Cancer Assessment Review Committee

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On September 16, 2015, the Cancer Assessment Review Committee (CARC) of the Health Effects Division, of the Office of Pesticide Programs evaluated the carcinogenic potential of Glyphosate in accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005). Attached please find the final Cancer Assessment Document.

CANCER ASSESSMENT DOCUMENT

EVALUATION OF THE CARCINOGENIC POTENTIAL OF
Glyphosate

FINAL REPORT
October 1, 2015

CANCER ASSESSMENT REVIEW COMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS
U.S Environmental Protection Agency

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EXECUTIVE SUMMARY

Glyphosate is a nonselective herbicide that is currently registered for pre- and post-emergence application to a variety of fruit, vegetable, and field crops.

In 1985, the agency, in accordance with the Proposed Guidelines for Carcinogen Risk Assessment, classified glyphosate as a Group C chemical (Possible Human Carcinogen) based on the presence of kidney tumors in male mice. There was no evidence for carcinogenicity in male or female rats. Furthermore, there were no mutagenicity concerns (TXR No. 0052067).

In 1986, the agency requested the FIFRA Scientific Advisory Panel (SAP) to evaluate the carcinogenic potential of glyphosate. On February 24, 1986, the SAP recommended that glyphosate should be categorized as a Group D chemical: Not Classifiable as to Human Carcinogenicity. The panel determined that the data on renal tumors in male mice were equivocal: they were only adenomas, and the increase did not reach statistical significance. The panel also advised the agency to issue a data call-in notice for further studies in rats and/or mice to clarify unresolved questions (SAP Report, 02/24/1986). This review is available at http://www.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-103601_24-Feb-86_209.pdf

In 1991, the Carcinogenicity Peer Review Committee (CPRC) of the Health Effects Division (HED), of the Office of Pesticide Programs (OPP), of the U.S. Environmental Protection Agency (USEPA) evaluated the carcinogenic potential of glyphosate. In accordance with the agency's 1986 *Draft Guidelines for Carcinogen Risk Assessment,* the CPRC classified glyphosate as a Group E Chemical: "Evidence of Non-Carcinogenicity for Humans" based upon lack of evidence for carcinogenicity in mice and rats and the lack of concern for mutagenicity (TXR# 0008897).

Earlier this year (March 2015), the International Agency for Research on Cancer (IARC), Lyon, France, assessed the carcinogenic potential of glyphosate. The IARC reviewed the available epidemiological studies and carcinogenicity studies for glyphosate in experimental animals. The IARC concluded that there is *limited evidence* in humans for the carcinogenicity of glyphosate based on a positive association for non-Hodgkin lymphoma (NHL). The IARC also concluded that there is *sufficient evidence* in experimental animals based on significant positive trends for kidney tumors in one study and for hemangiosarcomas in another study in male mice. IARC determined that there is strong evidence for genotoxicity. Overall, IARC classified glyphosate as "*probably carcinogenic to humans (Group 2A)* (IARC, 2015).

IARC's conclusion was based on epidemiologic studies available in the open literature and carcinogenicity studies in rats (4 studies) and mice (2 studies) by dietary administration. Of these six studies reviewed by IARC, two studies in rats and one study in mice were previously not available to OPP. The conclusion by IARC and the additional studies not available to OPP, prompted the agency to re-evaluate the carcinogenic potential of glyphosate.

On September 16, 2015, HED's Cancer Assessment Review Committee (CARC) evaluated all available epidemiological studies published in the open literature that examined the association between glyphosate exposure and one or more cancer outcomes. This included one cohort study, seven nested case-control studies based on the cohort study population, and 25 case- control studies. The CARC also evaluated 11 chronic toxicity/carcinogenicity studies in rats (7) and mice (4) following dietary administration for up to two years. Six of the studies (4 rat and 2 mouse) were submitted to OPP to support registration/re-registration requirements, including two studies in rats and one study in mice which were not previously available to OPP (but reviewed by IARC). Data for review of the other five studies (3 rat and 2 mouse) were obtained from a review article and its supplement published in the open literature (Greim *et al.,* 2015) that also had not been previously reviewed by the agency (IARC did not evaluate the five studies cited in the Greim *et al.* 2015 review article). The CARC also evaluated the mutagenicity/genotoxicity studies submitted to OPP as well as studies summarized in two review articles (Williams *et al*., 2000, and Kier and Kirkland, 2013) published in the open literature.

The CARC concluded that the epidemiological studies in humans showed no association between glyphosate exposure and cancer of the following: oral cavity, esophagus, stomach, colon, rectum, colorectum, lung, pancreas, kidney, bladder, prostate, brain (gliomas), soft-tissue sarcoma, leukemia, or multiple myelomas.

The CARC concluded that there is conflicting evidence for the association between glyphosate exposure and NHL. No association between glyphosate exposure and NHL was found in population-based case-control studies in the United States, Canada or France. Additionally, the large prospective Agricultural Health Study (AHS) with 54,315 licensed pesticide applicators in Iowa and North Carolina did not show a significantly increased risk of NHL. A population-based case-control study from Sweden suggested an association between glyphosate exposure and NHL; however, this finding was based on only 4 glyphosate-exposed cases and 3 controls.

When data from two case-control studies in Sweden (one on NHL and the other on hairy cell leukemia) were pooled, a univariate analysis showed an increased risk (odds ratio (OR) = 3.04; 95% confidence interval (CI) = 1.08–8.52); however, when study site, vital status, and exposure to other pesticides were taken into account in a multivariate analysis, the risk was attenuated (OR=1.85; 95% CI=0.55–6.20). In another case-control study in Sweden, among the 29 glyphosate-exposed cases, a multivariate analysis showed an increased risk for NHL (OR=1.51; 95% CI=0.77–2.94) and B-cell lymphoma (OR=1.87; 95% CI=0.998–3.51). A meta-analysis of the six separate studies showed an association between glyphosate exposure and NHL with a meta-risk ratio of 1.5 (95% CI=1.1–2.0) (Schinasi and Leon, 2014). The CARC noted that most of the studies in the database were underpowered, suffered from small sample size of cancer cases with glyphosate exposure, and had risk/odds ratios with large confidence intervals. Additionally, some of the studies had biases associated with recall and missing data.

In an attempt to address the noted power/sample size issues across studies, IARC used adjusted weighting estimates of the two Swedish studies (Hardell *et al*. 2002 and Eriksson *et al*. 2008) and

reported an lower odds ratio in a second meta-analysis of the same data (OR=1.3; 95% CI=1.03–1.65). Given the limitations of the studies used and uncertainty in the analytical methods, the CARC concluded that a different weighting scheme could have resulted in a different meta risk ratio. Thus, while epidemiologic literature to date does not support a direct causal association, the CARC recommends that the literature should continue to be monitored for studies related to glyphosate and risk of NHL.

Overall, the CARC concluded that there was no evidence of carcinogenicity in the eleven carcinogenicity studies conducted in Sprague Dawley or Wistar rats and CD-1 mice. There were no treatment-related increases in the occurrence of any tumor type in either sex of either species.

By contrast, the IARC concluded that there is *sufficient evidence* in experimental animals based on a positive trend in the incidence of a relatively rare tumor type, renal tubular carcinoma and renal tubule adenoma or carcinoma (combined) in CD-1 males in one feeding study. A second study reported a positive trend for hemangiosarcomas in male CD-1 mice. The CARC did not consider these tumors to be treatment-related since the observed tumors did not exhibit a clear dose-response relationship, were not supported non-neoplastic changes, were not statistically significant on pairwise analysis with concurrent control groups, and/or were within the range of the historical control data. If the kidney tumors and the hemangiosarcomas are really treatment-related, it is unlikely that the same tumors would not have been detected at higher incidences in the studies in the other studies of CD-1 mice when tested at similar or higher doses (1000–4000 mg/kg/day). Moreover, in 4 of the 11 studies (3 rat and 1 mouse) evaluated by CARC, there was no biologically or statistically significant increases in the occurrence of any tumor type in either species. The other observed differences in incidence did not show a dose response relationship, and were within the range of the background/historical control range. The four studies which were negative for carcinogenicity were reported in the review article by Greim *et al.* (2015) but were not included in the IARC evaluation. This omission of the negative findings from reliable studies may have had a significant bearing on the conclusion drawn for evidence of carcinogenicity in animals.

The CARC evaluated a total of 54 mutagenicity/genotoxicity studies which included studies submitted to the agency, as well as studies reported in the two review articles (Williams *et al.*, 2000, and Kier and Kirkland, 2013). A number of studies reported in the review article by Kier and Kirkland (2013) were not considered by IARC. The CARC, based on a weight-of-evidence of the *in vitro* and *in vivo* studies, concluded that there is no concern for genotoxicity or mutagenicity. Glyphosate was no mutagenic in bacterial reversion (Ames) assays or *in vitro* mammalian gene mutation assays. There is no convincing evidence that glyphosate induces micronuclei formation or chromosomal aberrations *in vitro* or *in vivo*.

By contrast, IARC's conclusion that glyphosate is genotoxic based on positive results that included studies that tested glyphosate-formulated products as well as studies where the test material was not well-characterized (*i.e.*, no purity information was provided). The IARC analysis also focused on DNA damage as an endpoint (*e.g.*, comet assay). DNA damage is often reversible and can result from events that are secondary to toxicity (cytotoxicity), as opposed to permanent DNA

changes which are detected in tests for mutations and chromosomal damage (*e.g.* chromosomal aberrations or micronuclei induction). The studies that IARC cited as positive findings for chromosomal damage had deficiencies in the design and/or conduct of the studies confounding the interpretation of the results. In addition these positive findings were not reproduced in other guideline or guideline-like studies evaluating the same endpoints. Furthermore, IARC's evaluation did not include a number of negative results from studies that were reported in the review article by Kier and Kirkland (2013). The inclusion of the positive findings from studies with known limitations, the lack of reproducible positive findings and the omission of the negative findings from reliable studies may have had a significant bearing on IARC's conclusion on the genotoxic potential of glyphosate.

In accordance with the 2005 Guidelines for Carcinogen Risk Assessment, based on the weight-of-evidence, glyphosate is classified as "Not Likely to be Carcinogenic to Humans". This classification is based on the following weight-of-evidence considerations:

- The epidemiological evidence at this time does not support a causal relationship between glyphosate exposure and solid tumors. There is also no evidence to support a causal relationship between glyphosate exposure and the following non-solid tumors: leukemia, multiple myeloma, or Hodgkin lymphoma. The epidemiological evidence at this time is inconclusive for a causal or clear associative relationship between glyphosate and NHL. Multiple case-control studies and one prospective cohort study found no association; whereas, results from a small number of case-control studies (mostly in Sweden) did suggest an association. Limitations for most of these studies include small sample size, limited power, risk/odd ratios with large confidence intervals, and recall bias as well as missing data. The literature will continue to be monitored for studies related to glyphosate and risk of NHL.

- In experimental animals, there is no evidence for carcinogenicity. Dietary administration of glyphosate at doses ranging from 3.0 to 1500 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in seven separate studies with male or female Sprague-Dawley or Wistar rats. Similarly, dietary administration of glyphosate at doses ranging from 85 to 4945 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in four separate studies with male or female CD-1 mice. The CARC did not consider any of the observed tumors in 11 carcinogenicity studies in rats and mice to be treatment-related since the observed tumors did not exhibit a clear dose-response relationship, were not supported pre-neoplastic changes (*e.g.*, foci, hypertrophy, and hyperplasia), were not statistically significant on pairwise statistical analysis with concurrent control groups, and/or were within the range of the historical control data.

- Based on a weight of evidence approach from a wide range of assays both *in vitro* and *in vivo* including endpoints for gene mutation, chromosomal damage, DNA damage and repair, there is no *in vivo* genotoxic or mutagenic concern for glyphosate.

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I. INTRODUCTION

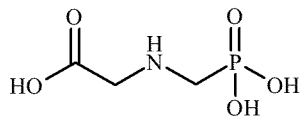
On September 16, 2015 the Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Programs met to re-evaluate the carcinogenic potential of glyphosate.

II. BACKGROUND INFORMATION

Glyphosate (*N*-(phosphonomethyl) glycine) is a nonselective herbicide that is currently registered for pre- and post-emergence application to a variety of fruit, vegetable, and field crops. Tolerances are currently established for residues of glyphosate in/on various plant commodities at 0.2–400 ppm (40 CFR §180.364 (a)) (1). Registered uses range from tree nuts, citrus, and grapes to corn, soybeans, cotton, and rice. Glyphosate is also registered for use on transgenic crop varieties such as canola, corn, cotton, soybeans, sugar beets, and wheat. Aquatic and terrestrial registered uses of glyphosate include non-selective control of nuisance aquatic weeds, ornamentals, greenhouses, residential areas, ornamental lawns and turf, fallow land, pastures, and nonagricultural rights-of-way.

The chemical structure and nomenclature for glyphosate is presented in Table 1.

Table 1. Chemical Nomenclature of Glyphosate

Compound	
Common name	Glyphosate
Company experimental name	DPX-B2856
IUPAC/CAS name	*N*-(phosphonomethyl)glycine
CAS registry number	1071-83-6

Glyphosate is formulated in liquid and solid forms, and it is applied using ground and aerial equipment. Application rates of glyphosate to food crops range from <1 pound (lb) of acid equivalent (ae) per acre (A) for a variety of crops to approximately 15 lb ae/A for spray and spot treatments of crops including tree nuts, apples, citrus, and peaches. Residential lawn and turf application rates range from <1 lb ae/A to approximately 10.5 lb ae/A. The application timing of glyphosate is varied. Glyphosate can be applied early and late in the season, at pre-plant, planting, pre-emergence, pre-bloom, bud stage, pre-transplant, pre-harvest, post-plant, post-transplant, post-bloom, and post-harvest. It can also be applied during dormant stages and to fallow land, established plantings, stubble, and when needed. In September 1993, the agency issued the glyphosate Reregistration Eligibility Decision (RED) document (D362745), available from http://www.epa.gov/pesticides/reregistration/REDs/old_reds/glyphosate.pdf.

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In 1985, the agency, in accordance with the Proposed Guidelines for Carcinogen Risk Assessment, classified glyphosate as a Group C chemical (Possible Human Carcinogen) based on the presence of kidney tumors in male mice. There was no evidence for carcinogenicity in male or female rats. Furthermore, there were no mutagenicity concerns (TXR No. 0052067).

In 1986, the agency requested the FIFRA Scientific Advisory Panel (SAP) to evaluate the carcinogenic potential of glyphosate. On February 24, 1986, the SAP recommended that glyphosate should be categorized as a Group D chemical: Not Classifiable as to Human Carcinogenicity. The panel determined that the data on renal tumors in male mice were equivocal: they were only adenomas, and the increase did not reach statistical significance. The panel also advised the agency to issue a data call-in notice for further studies in rats and/or mice to clarify unresolved questions (SAP Report, 02/24/1986). This review is available at http://www.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-103601_24-Feb-86_209.pdf

In 1991, the Carcinogenicity Peer Review Committee (CPRC) of the Health Effects Division, Office of Pesticide Programs, in accordance with the agency's 1986 *Draft Guidelines for Carcinogen Risk Assessment,* classified glyphosate as a Group E Chemical: Evidence of Non-Carcinogenicity for Humans. This classification was based upon lack of evidence for carcinogenicity in mice and rats and the lack of concern for mutagenicity (TXR No. 0008897).

In 2002, the European Union (EU) concluded that there was no evidence of carcinogenicity for glyphosate in long-term studies with mice and rats (EU, 2002).

In 2004, the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) concluded that there was no evidence of carcinogenicity for glyphosate in long term studies in mice and rats and there was no evidence for genotoxic potential (JMPR, 2004).

In 2015, the International Agency for Research on Cancer (IARC) classified glyphosate as a Group 2A chemical (Probable Human Carcinogen) based on *limited evidence* of carcinogenicity in humans and sufficient evidence in experimental animals. The limited evidence in humans was based on a positive association between non-Hodgkin lymphoma (NHL) and glyphosate exposure from published epidemiology studies. The *sufficient evidence* in experimental animals was based on a positive trend in the incidence of renal tubular carcinoma and renal tubule adenoma/ carcinoma combined in male CD-1 mice in one study and on a positive trend in the incidence of hemangiosarcomas in male CD-1 mice in another study. There is strong evidence that glyphosate causes genotoxicity (IARC, 2015).

In 2015, two chronic toxicity/carcinogenicity studies in rats (MRID Nos. 49631701; 4970460) and one carcinogenicity study in mice (MRID No. 49631702) that were reviewed by IARC, but not previously available to OPP, were submitted and reviewed. This assessment by the CARC includes all of the studies (epidemiology and animals) reviewed by IARC as well as a subset of animal studies reported in a review article by Greim *et al.* (2015) but not reviewed by IARC.

III. EPIDEMIOLOGY

This section includes a review of epidemiologic cohort and case-control studies of glyphosate to evaluate whether exposure to glyphosate is associated causally with the risk of developing cancer in humans.

The Agricultural Health Study (AHS) is a large prospective study conducted in Iowa and North Carolina. Participants (private and commercial applicators) were asked to complete a 21-page questionnaire that included data on personally mixing and/or applying pesticides (including glyphosate), and frequency (days of use per year) and duration (years of use) of pesticide use. Data on the use of personal protective equipment, other farming practices, dietary and lifestyle information, demographic data, and medical information were also collected via the questionnaire (Alavanja *et al.,* 1996). The role of pesticide use and lymph hematopoietic cancers, and in particular NHL, has been studied in several investigations. For most of the cancer endpoints studied in relation to pesticide use, only one epidemiology study is available (De Roos *et al.*, 2005); however, for NHL and other non-solid tumors, several investigations are published.

A. Cohort Study

There are multiple published studies which use data from the same cohort, the AHS (Alavanja *et al.,* 2003; Flower *et al.*, 2004; De Roos *et al.*, 2005; Engel *et al.*, 2005; Lee *et al.*, 2007; Landgren *et al.*, 2009; Andreotti *et al.*, 2009; and Dennis *et al.*, 2010). It should be noted that there is some overlap between the cases and person-time reported findings in the AHS.

B. Case-Control Studies

Three case-control studies conducted by the National Cancer Institute in Iowa and Minnesota during the 1980s were reported by Brown *et al.* (1990), Cantor *et al.* (1992) and Brown *et al.* (1993).

De Roos *et al.* (2003) and Lee *et al.* (2004a) reported the results of case-control studies conducted in Iowa, Minnesota, Nebraska and/or Kansas in the U.S.A.

The Canadian population based case-control studies were reported by McDuffie *et al.*, 2001; Hohenadel *et al.*, 2011; Karunanayke *et al.*, 2012; and Kachuri *et al.*, 2013.

Results of the Swedish case-control studies were reported by Nordstrom *et al.*, 1998; Hardell and Erikson, 1999 and Hardell *et al.*, 2002; and Eriksson *et al.*, 2008.

A single case-control study conducted in France was reported by Orsi *et al.* (2009).

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Coco *et al.*, (2013) reported the results of a pooled analyses of case-control studies conducted in six European countries between 1998 and 2004.

Case-control studies on the cancer of the brain (mainly gliomas) were reported by Ruder *et al.* 2004; Carreon *et al.*, 2005; Lee *et al.*, 2005; and Yiin *et al.*, 2012.

Case-control studies on other cancer sites were reported by Alavanja *et al.*, 2004 (lung); Bank *et al.*, 2011 and Koutros *et al.*, 2013 (prostate); Pahwa *et al.*, 2012 (soft tissue sarcoma) and Lee *et al.,* 2004b (stomach and esophagus).

Schinasi and Leon (2014) conducted a meta-analysis of the six studies that evaluated NHL and glyphosate exposure (McDuffie *et al.*, 2001; Hardell *et al.*, 2002; DeRoos *et al.*, 2003; 2005; Eriksson *et al.*, 2008; and Orsi *et al.*, 2009). Sorahan (2015) conducted a re-analysis of the multiple myeloma in the U.S. AHS.

C. Results

A summary of the studies evaluating the association between glyphosate exposure and cancer are discussed below.

- Results of the studies reporting data on solid tumors (non-lymphohematopoietic) at various anatomical sites are presented in Table 2.

- Results of the studies reporting data on glyphosate exposure and non-solid tumors (lymphohematopoietic) are presented in Table 3.

1. Solid Tumor Cancer Studies

Within the AHS study cohort, a number of authors evaluated several anatomical cancer sites in relation to pesticide use. A discussion of studies outside of the AHS cohort that addressed pesticide use in relation to non-solid tumors including multiple myeloma and NHL is presented below in Section C.2. (Non-Solid Tumor Sites).

(i) Cancer at Multiple Sites

De Roos *et al.*, (2005) evaluated associations between glyphosate exposure and cancer incidence in the AHS cohort study of 57,311 licensed pesticide applicators in Iowa and North Carolina. The authors used Poisson regression to estimate exposure-response relationships between glyphosate and incidence of all cancers combined and 12 relatively common cancer subtypes. Exposure to glyphosate was not associated with all cancers combined [Rate Ratio (RR) =1.0 with 95% Confidence Interval (CI) of 0.90–1.2)] or any cancer at a specific anatomical site.

Several AHS nested case-control analyses as well as the cohort analysis from De Roos *et al.*, 2005, also provide information concerning the carcinogenic potential of glyphosate. As presented in Table 2, there is no statistical evidence of an association with glyphosate presented across these studies. Specifically, AHS researchers reported no statistical evidence of an association between glyphosate use and cancers of the oral cavity (De Roos *et al.*, 2005), colon (De Roos *et al.*, 2005; Lee *et al.*, 2007), rectum (De Roos *et al.*, 2005; Lee *et al.*, 2007), lung (De Roos *et al.*, 2005), kidney (De Roos *et al.*, 2005), bladder (De Roos *et al.*, 2005), pancreas (De Roos *et al.*, 2005; Andreotti *et al.*, 2009), breast (Engel *et al.*, 2005), prostate (Alavanja *et al.*, 2003; Koutros *et al.*, 2013) or melanoma (De Roos *et al.*, 2005; Dennis *et al.*, 2010). The risk ratios (OR) or rate ratios (RR) and 95% confidence interval (CI) for these studies are provided in Table 2.

In a population-based study (Band *et al.*, 2011) outside of the AHS, Canadian researchers reported non-significantly elevated odds of prostate cancer in relation to glyphosate use (OR=1.36; 95% CI=0.83–2.25). This study included prostate cancer cases from 1983-1990, prior to the prostate-specific antigen (PSA) era. Consequently, the study included more advanced tumors before diagnosis. Additionally, these data are in conflict with the results of Alavanja *et al.* (2003), which reflects the PSA-era cases (*i.e.*, cases which are typically identified at an earlier stage in the progression of the disease). Koutros *et al.* (2013) did not identify an association with advanced prostate cancer (OR=0.93; 95% CI=0.73–1.18) in a prostate cancer follow-up study within the AHS.

A Canadian case-control study (Pahwa *et al.*, 2011) examined exposure to pesticides and soft tissue sarcoma and found no relation with the use of glyphosate (OR=0.90; 95% CI= 0.58–1.40).

Flower *et al.* (2004) examined the relation between parental pesticide use and all pediatric cancers reported to state registries among children of AHS participants and did not observe a significant association with maternal use exposure to glyphosate (OR=0.61; 95% CI= 0.32–1.16) or paternal (prenatal) exposure to glyphosate: (OR=0.84; 95% CI= 0.35– 2.54).

(ii) Brain (Glioma) Cancer

Lee *et al.* (2005) investigated the association between brain cancer with farming and agricultural pesticide use. The authors conducted telephone interviews of men and women diagnosed with gliomas (n=251) between 1988 and 1993 in Nebraska and in controls (n=498) identified from the same regions. Matching for age and vital status, study authors reported a non-significant elevated odds of glioma (OR=1.5; 95% CI=0.7–3.1) in relation to glyphosate use; however, the results were significantly different between those who self-reported pesticide use (OR=0.4; 95% CI=0.1–1.6), and for those for whom a proxy respondent was used (OR=3.1; 95% CI=1.2–8.2), indicating recall bias was likely a characteristic of this study.

Three population-based case-control studies evaluated the risk of brain cancer, specifically, glioma risk, among men and women participating in the Upper Midwest Health Study (Carreon *et al.*, 2005; Ruder *et al.*, 2004; Yiin *et al.*, 2012). Ruder *et al.* (2004) reported no association between brain cancer and glyphosate use, but did not present any specific results (*i.e.* quantitative data). Among glioma cases identified 1995–1997 by Carreon *et al.* (2005), the authors found little evidence of a role for glyphosate in the etiology of this tumor. Herbicide use, including glyphosate was not associated with glioma in women by proxy respondents (OR=0.75; 95% CI=0.4–1.3) or excluding proxy respondents (OR=0.6; 95% CI=0.3–1.2). In the study by Carreon *et al.* (2005), there was no difference in risk estimate by vital status (use of self-report or proxy respondent), suggesting recall bias was more limited in this study in contrast to Lee *et al.* (2005). Using a quantitative measure of pesticide exposure (in contrast to an ever-use metric), the authors similarly observed no statistical evidence of an association with glyphosate; risk estimates were roughly equal to the null value (home and garden use: OR=0.98; 95% CI=0.67–1.43; non-farm jobs: OR=0.83; 95% CI=0.39–1.73) (Yiin *et al.*, 2012).

(iii) Stomach and Esophageal Cancers

In a population-based case control study in eastern Nebraska, Lee *et al.* (2004) investigated pesticide use and stomach and esophageal adenocarcinomas. Cancer cases (stomach=170 and esophagus=137) were identified through the state cancer registry, and confirmed by a pathologist. The exposure assessment was based on self-reported pesticide use, with follow-up telephone interview to verify the reported information. There was no association between glyphosate exposure and either stomach cancer (OR=0.8; 95% CI=0.4–1.5) or esophageal cancer (OR=0.7; 95% CI=0.3–1.4).

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Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Cancer at Multiple Sites					
De Roos *et al*. (2005) AHS: Iowa and North Carolina, U.S.A.	Cohort 1993-2001 54,315 licensed pesticide applicators	Self-report questionnaire; validated, reliability tested; adjusted for other pesticides	All cancers RR =1.0 (0.9-1.2)	No association between glyphosate exposure and all cancer including NHL	Age at enrollment (continuous), education, cigarette smoking, alcohol consumption, family history of cancer in first degree relatives, and state of residence (dichotomous: Iowa/NC)
Site-Specific Cancers: Lung; Oral cavity; Colon; Rectum; Kidney; Bladder; Prostate and Melanoma					
De Roos *et al*. (2005) AHS: Iowa and North Carolina, U.S.A.	Cohort 1993-2001 54,315 licensed pesticide applicators	Self-report questionnaire; validated, reliability tested; adjusted for other pesticides	Lung RR= 0.9 (0.6-1.3) Oral Cavity RR=1.0 (0.5-1.8) Colon RR=1.4 (0.8-2.2) Rectum RR=1.3 (0.7-2.3) Pancreas RR=0.7 (0.3-2.0) Kidney RR=1.6 (0.7-3.8) Bladder RR=1.5 (0.7-3.2) Prostate RR=1.1 (0.9-1.3) Melanoma RR=1.6 (0.8-3.0)	No significant association between glyphosate exposure and cancer of the lung, oral cavity, colon, rectum, pancreas, kidney, bladder, prostate or melanomas	Age at enrollment (continuous), education, cigarette smoking, alcohol consumption, family history of cancer in first degree relatives, and state of residence (dichotomous: Iowa/NC)

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Site-Specific Cancers: Breast Cancer					
Engel *et al*. (2005) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-1997 30,454 wives of licensed pesticide applicators with no history of breast cancer at enrollment	Self-report questionnaire	Direct exposure (wives who applied) OR=0.9 (0.7-1.1) (Exposed: 82 cases, 10,016 controls) Indirect exposure (wives whose husbands applied) OR=1.3 (0.8-1.9) (Exposed: 109 cases, 9,304 controls)	No association between glyphosate exposure and breast cancer	Age, race and state of residence (Iowa and North Carolina). Limited to licensed applicators. Potential exposure to multiple pesticides
Site-Specific Cancers: Pancreatic Cancer					
Andreotti *et al.* (2009) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-1997; follow-up to 2004 93 cases 82,503 controls	Self-report questionnaire; validated, reliability tested	Ever-use OR=1.1 (0.6, 1.7) (Exposed: 55 cases)	No association between glyphosate exposure and pancreatic cancer	Age, smoke, diabetes, applicator type. Limited to licensed applicators. Potential exposure to multiple pesticides

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Site-Specific Cancers: Prostate Cancer					
Alavanja *et al.* (2003) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-1997; cancer thru 1999 55,332 male applicators	Self-report questionnaire; validated, reliability tested	No quantitative risk estimate reported	No quantitative estimate due to lack of significant exposure-response association with prostate cancer.	Age, family history. Limited to licensed applicators. Potential exposure to multiple pesticides
Band *et al.* (2011) British Columbia, Canada	Case-Control 1983- 1990 1,516 prostate cancer patients 4,994 age-matched controls	Job exposure matrix for agriculture; detailed occupational history; exposure aggregated over all jobs reported. 60 exposed cases	OR=1.36 (0.83-2.25) (Exposed: 25 cases 60 controls)	No association between glyphosate exposure and prostate cancer	Alcohol consumption, cigarette years, education level, pipe smoking years and respondent
Koutros *et al.* (2013) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-2003 1,962 incident cases, including 919 aggressive prostate cancers among 54,412 applicators	Self-report questionnaire, validated	OR=0.93 (0.73-1.18)	No association between glyphosate exposure and prostate cancer	Age, state, race, family history of prostate cancer, smoking, fruit servings, and leisure-time physical activity in the winter

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Site-Specific Cancers: Colorectal Cancer					
Lee *et al*. (2007) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-97; follow-up to 2002 56,813 licensed pesticide applicators	Self-report questionnaire	Colon OR=1.0 (0.7-1.5) (Exposed: 151 cases 49 controls) Rectum OR=1.6 (0.9-2.9) (Exposed: 74 cases 18, controls) Colorectal OR=1.2 (0.9-1.6) (Exposed: 225 cases 67 controls)	No significant association between glyphosate exposure and colon, rectum or colorectal cancer	Age, smoking, state, total days use pesticides. Limited to licensed applicators. Potential exposure to multiple pesticides
Site-Specific Cancers: Cutaneous Melanoma					
Dennis *et al.* (2010) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-1997 150 cases, 24,554 non-cases	AHS self-report questionnaire	No quantitative risk estimate reported	No quantitative estimate due to lack of an association with cutaneous melanoma	Age, sex, tendency to burn, red hair, sun exposure time, BMI at 20 years

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Site-Specific Cancers: Soft Tissue Sarcoma					
Pahwa *et al*. (2011) Canada	Case-Control 1991-1994 342 cases, 1506 age/resident matched controls	Self-reported use, structured interview/ questionnaire; cumulative exposure (+/-10 days/yr)	OR=0.90 (0.58-1.40)	No association between glyphosate exposure and soft tissue sarcoma	Significant medical history variables and with strata for the variables of age group and province of residence
Total Childhood Cancer					
Flower *et al*. (2004) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control; hybrid prospective/ retrospective 1993-1998 21, 375 children of licensed pesticide applicators In Iowa (n=17,357) North Carolina (n=4018)	Self-report questionnaire; duration and frequency of pesticide use; Female Family questionnaire (child name)	Maternal use OR=0.61 (0.32-1.16) 32 cases Paternal use (prenatal) OR=0.84 (0.35-2.34);	No association was detected between frequency of parental pesticide application of glyphosate and childhood cancer risk.	Potential exposure to other pesticides. Child age in multiple logistic [standardized incidence ratio (SIR)] was unadjusted

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Brain Cancer (Glioma)					
Lee *et al.* (2005a) Nebraska	Population based Case-Control study 1988-1993; 251 glioma cases 498 controls	Self-reported questionnaire information, telephone follow-up for unclear responses; men and women assessed separately	Self-Report OR=0.4 (0.1- 1.6) (Exposed: 4 cases 17 controls) Overall OR=1.5 (0.7-3.1) (Exposed: 17 cases 32 controls) Proxy report OR=3.1 (1.2- 8.2) (Exposed:13 cases 15 controls)	Non-significant excess risk for the overall group, but inconsistent for self-report and proxy indicating recall bias	Age, proxy, respond type
Ruder *et al.* (2004) Upper Midwest Health Study (Iowa, Michigan, Minnesota and Wisconsin, U.S.A.)	Population-based Case-Control 1995-1997 457 glioma cases 648 population controls	Self-report questionnaire, with telephone based follow-up	No quantitative risk estimate reported for glyphosate.	No association with glyphosate exposure and brain cancer	Farm residence, age, use of other pesticides

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Carreon *et al*. (2005) Upper Midwest Health Study (Iowa, Michigan, Minnesota and Wisconsin)	Population-based Case-Control 1995-1997 341 glioma cases, 528 controls	Self-report questionnaire	Proxy respondents OR=0.75 (0.4-1.3) (Exposed: 18 cases 41 Controls) Excluding proxy OR=0.6 (0.3-1.2) (Exposed:10 cases)	No association with glyphosate exposure and brain cancer	Age, education and use of other pesticide
Yin et al. (2012) Upper Midwest Health Study (Iowa, Michigan, Minnesota and Wisconsin)	Population-based Case-Control 1995-1997 798 glioma cases 1,175 controls	Self-report questionnaire	Home/garden use OR=0.98; 95% CI=0.67 - 1.43; Non-farm jobs: OR=0.83; 95% CI=0.39-1.73)	No significant positive association with glyphosate exposure and brain cancer	Age, sex, education and use of other pesticide

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Esophagus and Stomach Cancer					
Lee *et al.* (2004b) Nebraska, U.S.A.	Population based Case-Control 1988-1993 137 esophageal cases; 170 stomach cases; 502 controls	Self-report pesticide use, telephone structured interview	Esophagus OR=0.7 (0.3-1.4) (Exposed:12 cases 46 controls) Stomach OR=0.8 (0.4-1.5) (Exposed: 12 cases 46 controls)	No association with glyphosate exposure and esophagus or stomach cancer	Age, sex

2. Non-Solid Tumor Cancer Sites

A number of studies evaluating the possible link between pesticide use and lymphohematopoietic cancers such as leukemia, multiple myeloma and NHL are presented in Table 3.

(i) Leukemia

In a population-based case-control study in Iowa and Minnesota, Brown *et al.* (1990) investigated leukemia risk and pesticide use; authors did not observe an association with the ever-use of glyphosate in this study (OR=0.9; 95% CI=0.5–1.6). The study population (578 cases; 340 living and 238 deceased and 1245 controls) was identified from cancers reported to state registry or authorities in 1981–1984, and the pesticide exposure assessment was performed through in-person interviews which the authors state likely reduced the exposure misclassification (*i.e.* incorrect exposure information). Although the large sample size is a strength of this study, the limitations include not controlling for exposure to other pesticides, limited power for studying the effects of glyphosate use, and the potential for recall bias.

In a Swedish population-based case-control study, 121 cases in men and 484 controls matched for age and sex were identified in 1987–1992 through the Swedish cancer registry. The authors reported a non-statistically significant elevated risk of hairy cell leukemia in relation to glyphosate use (OR=3.1; 95% CI=0.8–12.0), controlling for age, sex, and residential location. However, because these results are based on only 4 glyphosate-exposed cases and 5 exposed controls as noted by the authors, this risk should be interpreted with caution. Also, there was limited power to detect an effect and there was no adjustment for other exposures. At this time, there is limited available literature concerning glyphosate use and leukemia (Nordstrom *et al.*, 1998).

(ii) Multiple Myeloma

In a follow-up analyses using the same study population from Iowa and Minnesota Brown *et al.* (1993) investigated whether pesticide use is also related to multiple myeloma. Among men in Iowa (173 cases, 605 controls), the authors observed a statistically non-significant elevated association with glyphosate use (OR=1.7; 95% CI=0.8–3.6). However, the authors caution that while the study may lend support to the role of pesticides in general, the study limitations preclude use of the evidence as a definitive finding for any one compound.

De Roos *et al.* (2005) reported a suggestive association between multiple myeloma and glyphosate-exposed pesticide applicators based on a small number (32) of cases. For applicators with the full data set (54,315) and without adjustment for other variables the OR was 1.1; 95% CI=0.5–2.4. In the fully adjusted model, there was a non-statistically significantly elevated risk (OR=2.6; 95% CI=0.7–9.4), however, the number of participants included in this analysis was lower (n=40,716) due to missing data for the covariates. The authors postulated that the increased myeloma risk could be due to bias resulting from a selection of subjects in adjusted analyses that differed from subjects included in unadjusted analyses.

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Sorahan (2015), using Poisson regression, re-analyzed the AHS data reported by De Roos *et al.* (2005) to examine the reason for the disparate findings in relation to the use of a full data set versus the restricted data set. Risk ratios were calculated for exposed and non-exposed subjects. When adjusted for age and sex, the OR was 1.12 with the 95% CI of 0.5–2.49 for ever-use of glyphosate. Additional adjustment for lifestyle factors and use of other pesticides did not have any effect (OR=1.24; 95% CI=0.52–2.94).

In a population-based case-control study among men in six Canadian provinces between 1991 and 1994, researchers reported non-statistically significantly elevated odds of multiple myeloma in relation to glyphosate use (OR=1.22; 95% CI=0.77–1.93), based upon 32 glyphosate exposed multiple myeloma case and 133 controls (Pahwa *et al.*, 2012).

Kachuri *et al.* (2013), using the same Canadian study population as above, further explored multiple myeloma in relation to days per year glyphosate used in 342 cases of multiple myeloma and 1357 controls. For ever use, the OR=1.19 and 95% CI=0.76–1.87. For light users (≤2 days/year) there was no association (OR=0.72; 95% CI=0.39–1.32; 15 exposed cases); whereas, for heavy users (>2 days/ year), there was a non-significant increased odds ratio (OR=2.04; 95% CI=0.98–4.23; 12 exposed cases). The limitation in this study was the same as the previous study (*i.e.*, the number of cases and controls exposed to glyphosate were very low).

Landgren *et al.* (2009), within the AHS study population, investigated the association between pesticide use and prevalence of monoclonal gammopathy of undetermined significance (or MGUS). The MGUS is considered a pre-clinical marker of multiple myeloma progression. The authors did not observe a link with glyphosate use in the AHS cohort (OR=0.50; 95% CI=0.20–1.0).

(iii) Lymphoma

The National Cancer Institute (NCI) performed a series of population-based case-control studies in the Midwestern U.S. in the early to mid-1980s. These studies include several hundred non-Hodgkin lymphoma (NHL) cases and controls, the identified cases were through disease registries which in many cases, were histopathologically confirmed. The investigators ascertained pesticide exposure through use of a structured interview with follow-up concerning pesticide use over time.

Cantor *et al.* (1992), in a case-control study of NHL interviewed a total of 622 white men and 1245 population based-controls in Iowa and Minnesota. Only 26 cases and 49 controls ever handled glyphosate yielding an OR of 1.1 with the 95% CI of 0.7–1.9. The study, however, did not adjust for exposure to other pesticides.

De Roos *et al.* (2003) used pooled analysis (n=3,417) of three case-control studies of NHL conducted in white men in Nebraska, Kansas and in Iowa and Minnesota. Based on 36 exposed cases and 61 exposed controls, the risk estimates for the association between glyphosate exposure and NHL was significant (OR=2.1; 95% CI=1.1–4.0) in the logistic regression analyses. However,

utilizing hierarchical regression techniques to adjust for exposure to other pesticide exposures, there was an increase risk, but the increase was not statistically significant (OR=1.6; 95% CI=0.90–2.8). Overall, the data showed a suggestive association.

Based on the above findings, Lee *et al*., (2004) examined the relationship between asthma and pesticide exposure, and NHL. Pooling data from several midwestern states (IA, MN, and NE) increased the study sample size, and additional pesticide use information was incorporated to adjust the risk estimate (duration and frequency of use, telephone follow-up interview). The study included 872 men with NHL and 2381 frequency-matched controls. The authors reported that the OR associated with glyphosate was not statistically significantly different among those with asthma (OR=1.2; 95% CI=0.4–3.3; 6 exposed cases) and among those without asthma (OR=1.4; 95% CI=0.98–2.1; 53 exposed cases), adjusting for age, state and vital status.

The three studies discussed above (Cantor *et al*., 1992; De Roos *et al*., 2003 and Lee *et al*., 2004) reflect the same population in the AHS and used different levels of information (duration and frequency of exposure) and different analytic techniques [hierarchical regression and stratified analysis (by atopy)]. While studies with increasing levels of refinement to methodology report a stronger risk estimates in relation to glyphosate, additional studies are needed to exclude the role of chance and other limitations that may explain positive (non-statistically significant) associations.

A population-based case–control study (Hardell and Erickson, 1999) investigated the exposure to pesticides as a risk factor for NHL in Sweden during 1987–1990. Exposure data were ascertained by comprehensive questionnaires and supplemented by telephone interviews. Of the 404 cases and 741 controls, only 4 glyphosate-exposed cases and 3 controls were included in the study. In a univariate analysis, the risk estimate was elevated, but precision was low (OR=2.3; 95% CI=0.40–13.0).

Hardell *et al*. (2002) analyzed pooled data from two case-control studies from Sweden that examined NHL (Hardell and Erickson, 1999) and another on hairy cell leukemia, a subtype of NHL (Nordstrom *et al*., 1998). In the univariate analysis glyphosate exposure was found to be significantly increased (OR=3.04; 95% CI=1.08–8.52) but, when study site, and vital status were considered in a multivariate analyses, there was a non-statistically elevated risk among glyphosate users (OR=1.85; 95% CI=0.55–6.20). However, the wide range of the CI suggest that the study is under powered and, therefore the findings do not allow definitive conclusion on the association of NHL and glyphosate exposure.

In another case-control study in Sweden (1999–2003), Eriksson *et al*. (2008) examined the effects of exposure to different agents and NHL among 910 NHL cases and 1016 non-NHL controls. Glyphosate exposure which was reported in 29 cases and 18 controls produced an OR of 2.02 (95% CI=1.10–3.71) in a univariate analysis and an OR of 1.51 (95% CI=0.77–2.94) in a multivariate analysis conducted to clarify the relative importance of exposure to different pesticides. When exposure was for more than 10 days/year, the OR was 2.36 (95% CI=1.16–4.40)

and for exposure less than 10 days/year, the OR was 1.69 (95% CI=0.7–4.07). The risk estimate was elevated also for B-cell lymphoma and glyphosate exposure (OR=1.87; 95% CI=0.998–3.51).

McDuffie *et al.* (2001) in a multicenter-population based study among men of six Canadian provinces estimated the association between glyphosate and NHL. The study included 517 cases and 1506 controls identified betwen1991and 1994 through provincial cancer registries. In this study, authors histopathologically confirmed 84% of cases, implemented a two-tiered exposure questionnaire; and assessed the validity of the questionnaire through quality control studies both of which increased the accuracy of the test results. There was a non-statistically significant increased risk of NHL from glyphosate exposure. The OR was 1.26 and the 95% CI was 0.87–1.80 for 51 exposed cases, adjusted for age and province and the OR was 1.20 with a 95% CI of 0.83–1.74 when adjusted for age, province and high-risk exposure (adjusted for statistically significant medical variables such as history of measles, mumps, cancer, allergy desensitization shots, and a positive family history of cancer in a first-degree relative).

In a follow-up study which controlled for exposure to other pesticides, the risk to NHL from glyphosate exposure was attenuated. Glyphosate exposure which was reported in 19 cases and 78 controls produced an OR of 0.92 with 95% CI of 0.54–1.55 (Hohenadel *et al.*, 2011). Within this series of studies, the authors also evaluated Hodgkin lymphoma (HL), and observed little statistical evidence of an association, using similar study design and methods. Among the 38 cases exposed to glyphosate the OR was 0.99 with a 95% CI of 0.62–1.56 (Karunanayake *et al.,* 2012).

In a hospital-based case control study conducted between 2000 and 2004 in France, authors identified 491 NHL cases and 456 age-and sex-matched controls, and performed telephone-based questionnaire to assess pesticide and other confounding variables. There was no association between NHL and glyphosate use; for the 12 exposed cases, the OR was 1.0 and the 95% CI was 0.5–2.2). For Hodgkin lymphoma, for the 6 exposed cases, the OR was 1.7 and the 95% CI was 0.6–5.0 (Orsi *et al.*, 2009).

The EPILYMPH case-control study was conducted across six countries in Europe (Czech Republic, France, Germany, Ireland, Italy, and Spain) to explore the role of occupational exposure to specific chemicals and risk of lymphoma overall, B-cell lymphoma and other subtypes. Although the study recruited 2348 cases and 2462 controls, only a very small number of cases were exposed to glyphosate (n=4) and controls (n=2). A non-significant increase in OR was observed for B-cell lymphoma (OR=3.1; 95% CI=0.6–17.1), but the estimate is unstable due to the small number of exposed cases and controls (Cocco *et al.,* 2013)

Schinasi and Leon (2014) conducted a meta-analysis exploring occupational glyphosate exposure and NHL using data from six of the above mentioned studies (McDuffie *et al.*, 2001; Hardell *et al.*, 2002; DeRoos *et al.*, 2003 and 2005; Eriksson *et al.*, 2008; and Orsi *et al.*, 2009). Since the authors identified a variety of sources of heterogeneity between publications, they calculated meta-risk ratio (RR) estimates and 95% CIs using random effect models, allowing between study heterogeneity to contribute to the variance. They reported I^2 values, which represented the

percentage of the total variance explained by study heterogeneity and measure inconsistency in results. Larger I^2 values indicate greater inconsistency. For glyphosate, the meta-risk ratio was 1.5 with a 95% CI of 1.0–2.0 and the I^2 value was 32.7% indicating greater inconsistency in these data sets. This study combined multiple smaller studies that on their own were very limited in statistical power to detect differences.

The 2015 IARC evaluation noted that fully adjusted risk estimates in two of the Swedish studies (Hardell *et al.*, 2002 and Eriksson *et al.*, 2008) were not used in the analysis conducted by Schinasi and Leon (2014). Consequently, IARC conducted a reexamination of the results of these studies. For an association between glyphosate exposure and NHL, the IARC estimated a meta-risk ratio of 1.3 (95% CI=1.03–1.65), I^2=0%; p=0.589 for heterogeneity) (IARC 2015).

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Leukemia					
Brown *et al*. (1990) Iowa and Minnesota, U.S.A.	Population-based Case-Control 1981-1984 578 cases 1245 controls	In person interview; surrogates used.	OR=0.9 (0.5-1.6) (Exposed:15 cases 49 controls)	No association between glyphosate exposure and leukemia	Vital status (alive, dead), residency (IA or MN), tobacco use, parent, sibling, or child with a lymphopoietic cancer, high risk occupation and exposure to substances (benzene, hair dyes etc) related to risk of leukemia
Nordstrom *et al*. (1998) Sweden	Population-based Case-Control 1987-1992 121 cases 484 controls	Self-reported pesticide questionnaire and follow-up telephone interview	OR=3.1 (0.8-12) (Exposed: 4 cases 5 controls)	A non-statistically significant elevated risk of hairy cell leukemia	Age, sex, country of residence (selected using matching, dissolved matching analyses) No adjustment for exposure from other pesticides
Multiple Myeloma					
Brown *et al*. (1993) Iowa, U.S.A.	Population based Case-Control 1981-1984 173cases 650 controls	Interview based questionnaire with follow-up	OR=1.7 (0.8-3.6) (Exposed: 11 cases 40 controls)	Limited power to assess association of glyphosate exposure and multiple myeloma	Age and vital status

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies

Study	Study Design	Exposure Assessment	Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)	Conclusions	Potential Confounders Considered
De Roos *et al*. (2005) Iowa and North Carolina, U.S.A.	Prospective Cohort 1993-2001 54,315 licensed pesticide applicators	Self-administered questionnaire	Full data set RR =1.1 (0.5-2.4) (Exposed: 32 cases) Adjusted for age etc RR=2.6 (0.7-9.4)	No risk for full data set. Excess risk only with no missing information of 22 cases in the restricted data set (Sorahan, 2015)	Missing data on covariates when multiple adjustments were made, limiting interpretation
Orsi *et al*. (2009) France	Hospital based Case-Control 2000-2004 491 cases 456 controls	Self-report questionnaire, with follow-up telephone based questionnaire, expert review; two stage exposure collection process	OR=2.4 (0.8-7.3) (Exposed: 5 cases 18 controls)	No significant association with glyphosate exposure and multiple myeloma	Age, center, socioeconomic category
Pahwa *et al*. (2012) Canada	Population based Case-Control 1991-1994 342 cases 1506 controls	Self-reported pesticide use, structured interview with questionnaire; cumulative exposure (+/-10 days/yr)	OR=1.22 (0.77-1.93) (Exposed: 32 cases 133 controls)	No significant association with glyphosate exposure and multiple myeloma	Significant medical history variables (history of measles, history of mumps, history of allergies, history of arthritis, history of shingles, and a positive family history of cancer in a first-degree relative), and with strata for the variables of age group and province of residence

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Kachuri *et al*. (2013) Canadian Provinces	Population based Case-Control 1991-1994 342 cases 1357 controls	Self-administered questionnaire	For ever use OR=1.19 (0.76-1.87) Exposed: 32 cases 121controls Light (<2 d/yr) use OR=0.72 (0.39 -1.32) Exposed: 15 cases 88 controls Heavy (>2 d/yr) use OR=2.04 (0.98-4.23) Exposed: 12 cases 29 controls	No association with glyphosate exposure and multiple myeloma for ever or light users Increase for heavy users is non-significant	Relatively low response rate
Monoclonal Gammopathy of Undetermined Significance (MGUS)					
Landgren *et al*. (2009) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-1997 678 participants	Self-administered questionnaire	OR=0.5 (0.2-1.0)	No association with glyphosate exposure and MGUS, a premalignant disorder that often precedes multiple myeloma	Age and education

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Non-Hodgkin Lymphoma (NHL)					
Cantor *et al.* (1992) Iowa and Minnesota, U.S.A.	Population based Case-Control 1980-1983 622 cases 1245 controls	Structured interview, questionnaire response; farm activities and specific pesticide use	OR=1.1 (0.7-1.9) Exposed: 26 cases 49 controls	No association with glyphosate exposure and NHL	Vital status, age, state, smoking, family history, high risk occupation, high risk exposure. Not controlled for exposure to other pesticides.
De Roos *et al.* (2003) Iowa, Nebraska, Minnesota, Kansas, U.S.A.	Case-Control 1983-1986\Nebraska 1979-1981\Kansas 1979-1986 870 white male cases 2569 white male controls	Interview-based questionnaire, demographic	Logistic regression OR=2.1 (1.1-4.0) Exposed: 36 cases 61 controls Hierarchical regression OR=1.6; (0.9-2.8)	Significant increased OR in logistic model but in the hierarchical model, the OR attenuated and no significant association with glyphosate exposure and NHL	Age, study site, use of all other pesticides (group); hierarchal regression informed priors based on chemical-specific information
Lee *et al.* (2004a) Iowa, Nebraska, Minnesota, U.S.A	Population based Case-Control 1980-1986 872 white male cases	In person, structured interview (pesticide use, duration, frequency, first and last year used); 5-yr follow-up interview, 10-min telephone on pesticide use	Non-asthmatic OR=1.4 (0.98-2.1) (Exposed: 53 cases 91 controls) Asthmatic OR=1.2 (0.4-3.3) (Exposed: 6 cases 12 controls)	No significant association with glyphosate exposure and NHL either for asthmatics or non-asthmatics	Adjusted for age, vital status, state

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies

Study	Study Design	Exposure Assessment	Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)	Conclusions	Potential Confounders Considered
De Roos *et al.* (2005) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-2001 54,315 licensed pesticide applicators	Self-administered questionnaire	OR=1.1 (0.7-1.9 (Exposed: 92 cases)	No significant association with glyphosate exposure and NHL	Age, smoking, other pesticides, alcohol consumption, family history of cancer, education
Hardell and Erickson (1999) Sweden	Population based Case-Control 1987-1990 404 male cases 741 male controls	Questionnaire and follow-up interview	Univariate OR=2.3 (0.4-13.0) (Exposed: 4 cases 3 controls) Multivariate OR=5.8 (0.6-54)	Some evidence of a link with glyphosate, matching variables; cannot conclude regarding causal role for any specific pesticide	Age, region, vital status (matching). Few subjects exposed. Variables used in multivariate were no specified. Study has limited power to detect an effect
Hardell *et al.* (2002) Sweden	Population based Case-Control Combined Hardell 1999 with another case-control study examining hairy cell leukemia (one of 61 types of NHL) 1987-1990 515 cases 1141 controls	Questionnaire and follow-up interview	Univariate OR=3.04 (1.08-8.52) (Exposed: 8 cases 8 controls) Multivariate OR=1.85 (0.55-6.20)	Risk attenuates when adjusted for other variables in the multivariate analysis	Age, country, study site, vital status, other pesticide exposure in the multivariate analysis

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies

Study	Study Design	Exposure Assessment	Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)	Conclusions	Potential Confounders Considered
Eriksson *et al*. (2008) Sweden	Population based Case-Control 1999-2002 910 cases 1016 controls	Questionnaire and follow-up interview	Univariate OR=2.02 (1.10-3.71) (Exposed: 29 cases 18 controls) Multivariate OR=1.55 (0.77-2.94) With <10 days/ year OR=1.69 (0.7-4.07) (Exposed: 12 cases 9 controls) With > 10 days/year OR=2.36 (1.04-5.37) (Exposed: 17 cases 9 controls) B-cell lymphoma OR=1.87 (0.998-3.51)	Suggestive association for NHL with glyphosate exposure	Age, sex, year of diagnosis. Multivariate analysis adjusted for exposure to other pesticides
McDuffie *et al.* (2001) Canada	Population based Case-Control 1991-1994 517 cases 1506 controls	Two-tiered self-report questionnaire; cumulative exposure (≥ 10 days/yr)	Univariate OR=1.26 (0.87-1.8) (Exposed: 51 cases 133 controls) Multivariate OR=1.20 (0.83-1.74)	No significant association with glyphosate exposure and NHL	Adjusted for statistically significantly medical variables (history of measles, mumps, cancer, allergy shots, and a positive family history of cancer) males only

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Hohenadel *et al.* (2011) Canada	Case-Control 1991-1994 513 cases 1506 controls	Two-tiered self-report questionnaire; cumulative exposure (≥ 10 days/yr)	OR=0.92 (0.54-1.55) (Exposed: 19 cases 78 controls)	No significant association with glyphosate exposure and NHL	Age, province and proxy respondent, males only
Orsi *et al*. (2009) France	Hospital based Case-Control 2000-2004 491 cases 456 controls	Self-report questionnaire, with follow-up telephone based questionnaire, expert review; two stage exposure collection process	OR=1.0 (0.5-2.2) (Exposed: 12 cases 24 controls)	No association with glyphosate exposure and NHL	Age, center, socioeconomic category
Cocco *et al.* (2013) Czech Republic, France, Germany, Italy, Ireland and Spain	EPICLYMPH Case-Control 1998–2003 2348 cases 2462 controls	Occupational exposure; trained interviewers conducted in person interviews with cases and controls	OR=3.1 (0.6-17.1) (Exposed: 4 cases 2 controls)	No significant association with glyphosate exposure and B-cell	Age, center, socioeconomic category
Hodgkin Lymphoma					
Orsi *et al*. (2009) France	Hospital based Case-Control 2000-2004 491 cases 456 controls	Self-report questionnaire, with follow-up telephone based questionnaire, expert review; two stage exposure collection process	OR=1.7 (0.6-5.0) (Exposed: 6 cases 15 controls)	No significant association with glyphosate exposure and HL	Age, center, socioeconomic category

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Karunanayake *et al.,* (2012). Canada	Case-Control 1991-1994 361 cases 1,506 controls	Questionnaire and follow-up interview	Univariate OR=1.14(0.74-1.76) (Exposed :38 133 controls) Multivariate OR=0.99 (0.62-1.56)	No association with glyphosate exposure and HL	History of measles, acne, hay fever, shingles and positive family history of cancer in a first-degree relative

D. Discussion

In epidemiologic studies, the quality of the exposure assessment is a major concern since the validity of the evaluations depends in large part on the ability to correctly quantify and classify an individual's exposure. During their life-time, farmers are typically exposed to multiple pesticides and several of them are used together posing a challenge for identifying specific risk factors. Moreover, there is no direct information on pesticide exposure or absorbed dose because analyses are based on self-reported pesticide use. The studies included in this epidemiology assessment relied primarily on questionnaires and interviews to describe participants' past and/or current exposure to glyphosate. Since the questionnaires are commonly used to account for exposure and capture self-reporting, it can be subject to misclassification and recall bias. For example, case-control studies are at risk of recall bias in the reporting of pesticide use in the past because cases may have spent more time thinking about past exposures than controls. This could lead to differential misclassification and bias relative risk from null. The possible effect of confounding factors, which are related to both the exposure of interest and the risk of disease, may make it difficult to interpret the results. Therefore, the ability of epidemiologic studies to provide convincing evidence of causation under such circumstances may be limited. Causation is suspected if several studies are consistent in their findings and; if the association between the agent and the risk of disease is strong (*i.e.*, high risk ratio). Support from animal data will help to make the case for causation, particularly by establishing biological plausibility and the existence of a potential mechanism. Another important consideration in assessing epidemiologic studies is that commercially formulated products (not the active ingredient) are used by farmers. For example, glyphosate is sold as Roundup®, which is a combination of the active ingredient and other chemicals that often include a surfactant (polyethyleneamine) used to enhance the spreading of spray droplets when they contact the foliage. Thus, it is possible that different glyphosate-containing formulations were used across the different studies.

Most of the studies discussed here were hypothesis-generating in nature, consisted of small sample sizes with limited power to detect associations and evaluated use of glyphosate in addition to several other pesticides and often evaluated risk of multiple different types of cancer. Therefore, the role of chance given the many different statistical tests performed and the lack of a pre-specified hypothesis, limit epidemiologic inference. This hypothesis-generating evidence observed in the studies requires further prospective follow-up studies to determine whether a true association with glyphosate is indeed null. The case-control studies are retrospective studies and are susceptible to recall bias for exposure reporting which could account for discrepancies in the study findings. Variation in the quality of exposure assessment, study design and methods, as well as available information concerning potential confounding variables could also explain these inconsistencies in the data. In contrast, a prospective cohort study evaluates a number of diseases simultaneously and facilitates performance of periodic assessments of agricultural and other exposures. Periodic assessment of recent exposures enhances recall and reduces non-differential misclassification. The ability to determine exposure prior to the onset of a disease eliminates the case-recall bias, which was an issue identified as a weakness in case-control studies.

IV. EVALUATION OF CARCINOGENICITY IN ANIMALS

A total of 11 chronic toxicity/carcinogenicity studies (7 rat and 4 mouse) were included in this weight of evidence review. Of these, six studies were submitted for review to EPA under the registration/reregistration programs including two studies in rats (MRID No. 496311701 and 49704601) and one in mouse (MRID No. 49631702) not previously reviewed. Data for review of the other five studies were obtained from a published review article by Greim *et al.*, 2015 and were available online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423. The IARC acknowledged the Greim *et al.,* (2015) review article, but did not evaluate the studies cited in the review because the information provided in the review and its supplement was insufficient.

For this assessment, each study reported in the Greim *et al.,* (2015) review article was evaluated in accordance with the agency's 2012 Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment (http://www.epa.gov/pesticides/science/lit-studies.pdf). In accordance with this guidance, the following four studies were not included in this weight of evidence assessment since there is low confidence were determined to be unreliable for carcinogenicity evaluation.

- A two year feeding study in Sprague-Dawley rats (Excel, 1997) was not included due to the lack of test article characterization (no purity of test material).

- The two-year drinking water study in Wistar rats reported by Chruscielska *et al.*, (2000) was not included since the tested material was a formulated product (13.6% ammonium salt) and there were a number of deficiencies (lack of purity, water consumption and body weight data) in the conduct and reporting of the study.

- An initiation-promotion study (George *et al.*, 2010) in male Swiss mice that tested a commercial formulation of glyphosate (41%) with study deficiencies (*e.g.* small number (20) of animals, tested only males, and lack of histopathological examination).

- A carcinogenicity study in Swiss mice (Feinchemie Schwebda, 2001) was not included due to the presence of viral infection within the colony, which confounded the interpretation of the study findings. Malignant lymphomas were reported in this study in all groups. However, lymphomas are one of the most common types of spontaneous neoplastic lesions in aging mice (Brayton *et al.*, 2012). Murine leukemia viruses (MuLVs) are a common cause of lymphoma in many different strains of mice (Ward 2006). Tadesse-Heath *et al.* (2000) reported 50% lymphoma (mostly B-cell origin) incidence in a colony of Swiss mice. Although the incidences in this study were within or near the normal variation of background occurrence, it is not clear whether or not the viral component may have contributed to incidence value reported or the lower survival seen at the high dose in the study. Raw data are not available to perform appropriate statistical analyses of the lymphomas correcting for the intercurrent mortality.

A. Carcinogenicity Studies in Rats

1. Lankas, G, P. A Lifetime Study of Glyphosate in Rats. December 23, 1981. Unpublished report No. 77-2062 prepared by Bio Dynamics, Inc. EPA Accession. No. 247617 – 247621. MRID No. 00093879.

a. Experimental Design

Groups of Sprague-Dawley rats (50/sex/dose) were fed diets containing glyphosate (98.7%, pure) at concentrations of 0, 30, 100 or 300 ppm for 26 months. These concentrations were adjusted during the course of the study so that actual doses of 0, 3, 10, and 31 mg/kg/day in males and 0, 3, 11, and 34 mg/kg/day in females were maintained.

b. Survival Analysis

There were no treatment-related effects on survival at any dose level.

c. Discussion of Tumor Data

There was an increase in the incidences of interstitial cell tumors in the testes of male rats at the low (3/5; 6%), mid (1/50; 2%) and the high dose (6/50; 12%; P=0.013 pairwise comparison) when compared to controls (0/50; 0%). In 1991, HED's Cancer Peer Review Committee (CPRC) did not consider the increases to be treatment-related based on the following weight of evidence considerations: 1) lack of dose-response; 2) absence of pre-neoplastic lesions (*i.e.*, interstitial cell hyperplasia); 3) the incidences were within the normal biological variation seen for this tumor type in this strain of rats; 4) the incidences in the concurrent controls (0%) was not representative of the normal background incidences noted in the historical control animals (mean, 4.5%; range, 3.4% to 6.7%) and 5) no interstitial cell tumors were seen when tested at much higher doses in the same strain of rats in an another study (discussed below). The CARC agreed with the CPRC conclusion and rationale and noted additional rat studies which also showed no effect on interstitial cell tumors.

Although there was no evidence of a treatment-related increase in the incidences of pancreatic islet cell tumors in male rats, the data are presented in Table 4 since this tumor also seen in the second study discussed below.

Table 4. Pancreatic Islet Cell Tumors in Male Sprague-Dawley Rats (MRID 00093879)				
Tumor Type	0 ppm	30 ppm	100 ppm	300 ppm
Adenomas (%)	0/50 (0)	5/49 (10)	2/50 (4)	2/50 (4)
Carcinomas (%)	0/50 (0)	0/49 (0)	0/50 (0)	1/50 (2)
Combined (%)	0/50 (0)	5/49 (10)	2/50 (4)	3/50 (6)

d. Non-Neoplastic Lesions

No treatment-related non-neoplastic lesions were seen.

e. Adequacy of the Dosing for Assessment of Carcinogenicity

The CPRC concluded that the highest dose tested was not adequate to assess the carcinogenic potential of glyphosate. Consequently, a second study was conducted (discussed below).

2. Stout, L. D. and Rueckerf, P.A. (1990). Chronic Study of Glyphosate Administered in Feed to Albino Rats. Laboratory Project No. MSL-10495; September, 26, 1990, MRID No. 41643801; Historical Controls; MRID No. 41728701.

a. Experimental Design

Groups of Sprague-Dawley rats (60/sex/dose) were fed diets containing glyphosate (96.5%, pure) at dietary concentrations of 0, 2000, 8000 or 20,000 ppm 24 months. These levels were equivalent to 0, 89, 362 or 940 mg/kg/day, respectively, for the males and 0, 113, 457 or 1183 mg/kg/day, respectively, for the females. An interim sacrifice was conducted on 10 rats/sex/dose at 12 months.

b. Discussion of Tumor Data

The most frequently seen tumors were pancreatic cell adenomas, hepatocellular adenomas and thyroid C-cell adenomas in males. Data for these tumors and the respective historical control data are presented in Tables 5 thru 11.

Pancreatic cell adenomas are presented in Table 5 and the historical control data are presented in Table 6. Hepatocellular adenomas seen in males are presented in Table 7 and the historical control data are presented in Table 8. The thyroid C-cell adenomas and/or carcinomas observed in males and females are presented in Tables 9 and 10, respectively, and the historical control data are presented in Table 11.

(i) Pancreas

There was no statistically significant trend test by dose for pancreatic islet cell tumors. Increased incidences of adenomas only were observed at the low- and high-dose groups but not at the mid-dose group.

Table 5. Pancreatic Islet Cell Tumors in Male Sprague-Dawley Rats Cochran-Armitage Trend & Fisher's Exact Test (MRID No. 41643801)

Tumor Type	0 ppm	2000 ppm	8000 ppm	20000 ppm
Adenomas (%) P =	1/43[a] (2) 0.170	8/45 (18) 0.018*	5/49 (10) 0.135	7/48[b] (15) 0.042*
Carcinomas (%) P=	1/43[c] (2) 0.159	0/45 (0) 0.409	0/49 (0) 0.467	0/48 (0) 0.472
Combined (%) P=	2/43 (2) 0.241	8/45 (18) 0.052	5/49 (10) 0.275	7/48 (15) 0.108

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55.
b. First adenoma observed at week 81 in the 20,000 ppm group
c. First carcinoma observed at week 105 in the controls (0 ppm)
* Significant in a pair-wise comparison (P<0.05)

Historical control data on the incidence of pancreatic islet cell adenomas in male Sprague-Dawley rats in 2-year studies (1983–1989) conducted at the testing facility (Monsanto Environmental Health Laboratory; MRID No. 41728701) are presented in Table 6.

Table 6. Historical Control Data — Pancreatic Islet Cell Adenomas in Male Sprague-Dawley Rats (MRID No. 41728701)

Study No.	1	2	3	4	5	6	7
Study Year	07/83	02/85	10/85	6/85	9/88	1/89	3/89
Tumor Incidence	2/68	5/59	4/69	1/57	5/60	3/60	3/59
%	2.9%	8.5%	5.8%	1.8%	8.3%	5.0%	5.1%

The CPRC concluded that the pancreatic islet cell adenomas are not treatment-related based on the following weight of evidence considerations: 1) although the incidences at the low (18%) and high (15%) dose groups exceeded the historical control range (1.8–8.5%), there was lack of statistical significance in Cochran-Armitage trend test; 2) the tumor incidence in the concurrent control was at the low end of the historical control range; 3) considerable inter-group variability in the numbers of males with tumors (*i.e.*, no dose-response); 4) there were no preneoplastic changes; 5) there was no progression from adenomas to carcinomas; and 6) the apparent statistical significance of the pairwise comparisons of the treated groups with the concurrent control may be due to the low incidences in the controls and not to an actual carcinogenic response. Furthermore, the incidences of pancreatic cell tumors for the two studies did not show dose-response and the incidences were within the historical control range (0 to 17%) reported in the open literature (Arnold *et al.,* 1985; Borelli *et al.*, 1990; Borzelleca *et al.*, 1986, 1989, 1990; Burnett *et al.*, 1988; Trochimowicz *et al.*, 1988). The CARC agreed with the CPRC conclusion and rationale and noted subsequent rat studies which also showed no effect on islet cell tumors.

(ii) Liver

There was a dose trend for adenomas only. There were no statistically significant increases in the occurrence of benign or malignant hepatocellular tumor types (Table 7). The observed variations in incidence were within the range of the historical control data.

Table 7. Glyphosate: Hepatocellular Tumors in Male Sprague-Dawley Rats Cochran-Armitage Trend & Fisher's Exact Test (MRID No. 41643801)

Tumor Type	0 ppm	2000 ppm	8000 ppm	20000 ppm
Adenomas (%) P =	2/44[a] (5) 0.016*	2/45 (4) 0.683	3/49 (6) 0.551	7/48[b] (15) 0.101
Carcinomas (%) P =	3/44 (7) 0.324	2/45 (4) 0.489	1/49 (2) 0.269	2/48[c] (4) 0.458
Adenoma/Carcinoma (%) P =	5/44 (11) 0.073	4/45 (9) 0.486	4/49 (8) 0.431	9/48 (19) 0.245

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55.
b. First adenoma observed at week 88 in the 20000 ppm group
c. First carcinoma observed at week 85 in the 20000 ppm group

Historical control data on the incidence of hepatocellular adenomas and carcinomas in male Sprague-Dawley rats in 2-year studies (1983–1989) conducted at the testing facility (Monsanto Environmental Health Laboratory; MRID No. 41728701) are presented in Table 8.

Table 8. Historical Control Data : Hepatocellular Adenomas in Male Sprague-Dawley Rats (MRID No. 41728701)							
Study No.	1	2	3	4	5	6	7
Study Year	07/83	02/85	10/85	6/85	9/88	1/89	3/89
Adenomas	5/60 (8.3%)	11/68 16.2%)	1/70 (1.4%)	3/59 (5.1%)	11/60 (18.3%)	5/60 8.3%)	4/60 (6.7%)
Carcinomas	4/60 (6.7%)	0/68 (0%)	1/70 (1.4%)	2/59 (3.4%)	3/60 (5%)	1/60 (1.7%)	0/60 (0%)

The CPRC concluded that the slightly increased incidence of adenomas in male rats are not treatment-related since: 1) the increase was not statistically significant in pairwise comparison with the controls; 2) the incidences were within the historical control range; 3) except for a single animal at the mid-dose late in the study (89 weeks), no hyperplasia, preneoplastic foci or other non-neoplastic lesions were seen; and 4) there was no evidence of progression from adenomas to carcinomas. The CARC agreed with the CPRC conclusion and rationale.

(iii) Thyroid

The increased incidences in C-cell adenomas observed at the mid and high-dose groups of rats of both sexes did not show a statistically significant difference in pairwise comparisons with the controls (Table 9 and 10, respectively). There was a dose trend observed for adenomas and adenomas/carcinomas in females (P=0.03). Historical control data are presented in Table 11.

Table 9. Glyphosate: Thyroid C-Cell Tumors in Male Sprague-Dawley Rats Cochran-Armitage Trend & Fisher's Exact Test (MRID No. 41643801)				
Tumor Type	0 ppm	2000 ppm	8000 ppm	20000 ppm
Adenomas (%) P =	2/54[a, b] (4) 0.069	4/55 (7) 0.348	8/58 (14) 0.060	7/58 (12) 0.099
Carcinomas (%) p =	0/54 (0) 0.452	2/55[c] (4) 0.252	0/58 (0) 1.000	1/58 (4) 0.518
Adenoma/Carcinoma (%) p =	2/54 (11) 0.077	6/55 (11) 0.141	8/58 (14) 0.060	8/58 (14) 0.060

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55.
b. First adenoma observed at week 54 in the controls
c. First carcinoma observed at week 93 in the 20,000 ppm

Table 10. Glyphosate: Thyroid C-Cell Tumors in Female Sprague Dawley Rats Cochran-Armitage Trend & Fisher's Exact Test (MRID No. 41643801)				
Tumor Type	0 ppm	2000 ppm	8000 ppm	20000 ppm
Adenomas (%) P=	2/57[a] (4) 0.031*	2/60 (7) 0.671	6/59[b] (10) 0.147	6/55 (11) 0.124
Carcinomas (%) P=	0/57 (0) 0.445	0/60 (0) 1.000	1/59[c] (2) 0.509	0/55 (0) 1.000
Adenoma/Carcinoma (%) p=	2/57 (4) 0.033*	2/60 (3) 0.671	7/59 (12) 0.090	6/55 (11) 0.124

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55.
b. First adenoma observed at week 72 in the controls
c. First carcinoma observed at week 93 in the 8000 ppm group.

Table 11. Historical Control Data – Thyroid C-cell Tumors in Sprague-Dawley Rats (MRID No. 41728701)		
Tumor Type	Males	Females
Adenomas	1.8 – 10.6%	3.3 – 10.0%
Carcinomas	0.0 – 5.2%	0.0 – 2.9%

The CPRC concluded that the thyroid tumors in either sex are not treatment-related since: 1) the increased incidences exhibited no statistically significant trend or pairwise comparisons with the controls in males; 2) in females, there was a trend but no pairwise significance; 3) there was no progression from adenomas to carcinomas; and 4) there was no dose-related increase in severity of grade or incidence of hyperplasia in males or females. The CARC agreed with the CPRC conclusion and rationale and noted other rat studies which showed no effect on thyroid C-cell tumors.

c. Non-Neoplastic Lesions

There were no treatment-related precursor lesions at any dose level.

d. Adequacy of the Dosing for Assessment of Carcinogenicity

Dosing was considered to be adequate to assess carcinogenicity since the highest dose tested was near or beyond the limit dose (1000 mg/kg/day).

3. **Atkinson, C., Strutt, A., Henderson, W., et al. (1993). 104-Week chronic feeding/ oncogenicity study in rats with 52-week interim kill. Inveresk Research International (IRI), Tranent, Scotland. Study No. 438623; IRI Report No. 7867. April 7, 1993. MRID No. 49631701. Unpublished.**

a. Experimental Design

In a combined chronic toxicity/carcinogenicity study, glyphosate (98.9% pure) was administered to 50 male and female Sprague-Dawley rats/sex/dose in the diet at 0, 10, 100, 300, and 1000 mg/kg/day for 104 weeks. An interim sacrifice was conducted on 15 rats/sex/dose after 52 weeks of treatment.

b. Survival Analysis

No adverse effects on survival were seen in either sex across the doses tested

c. Discussion of Tumor Data

There were no treatment-related increases in the occurrence of any tumor type in this study.

d. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in this study.

e. Adequacy of the Dosing for Assessment of Carcinogenicity

Dosing was considered to be adequate to assess carcinogenicity since the highest dose tested was the limit dose (1000 mg/kg/day) and at this dose increased salivary gland weight accompanied by cellular alterations in the mandibular and/or parotid glands occurred in both males and females.

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4. **Brammer. (2001). Glyphosate Acid: Two Year Dietary Toxicity and Oncogenicity Study in Rats. Central Toxicology Laboratory, Alderley Park Macclesfield, Cheshire, UK: Syngenta. (MRID No. 49704601).**

a. Experimental Design

In a combined chronic toxicity study, glyphosate acid (97.6% pure) was administered to groups of Wistar rats in the diet. Groups of 52 male and 52 female rats received diets containing 0, 2,000, 6,000, and 20,000 ppm glyphosate for 24 months. The achieved doses were 0, 121, 361 or 1214 mg/kg/day in males and 0, 145, 437 or 1498 mg/kg/day in females, respectively. Three satellite groups of 12 rats/sex/group were also included for

interim sacrifice at 12 months of treatment. Parameters evaluated included clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, as well as organ weights, necropsy and histopathological examination.

b. Survival Analysis

No adverse effects on survival were seen in either sex across the doses tested

c. Discussion of Tumor Data

As shown in Table 12, there was an increase in the incidence of hepatocellular adenomas in male rats at the high dose when compared to controls. This increase was not considered to be treatment-related due to 1) absence of dose-response relationship; 2) lack of progression to malignancy; 3) no evidence of pre-neoplastic lesions; 4) the incidences were within the range (0–11.5%) of historical controls for this strain (Wistar) of rats in 26 studies conducted during the relevant time period (1984–2003) at the testing laboratory; and 5) the 0% incidence in concurrent controls is lower than the average background incidence for liver adenomas in male Wistar rats.

Table 12. Liver Adenomas in Male Wistar Rats Fisher's Exact Test and Exact Trend Test Results

	0	2000	6000	20000
Adenomas (%) P =	0/52[a] (0) 0.00804**	2/52 (4) 0.24757	0/52 (0) 1.00000	5/52 (10) 0.02826*

a =Number of tumor-bearing animals/Number of animals examined.

In addition, statistically higher survival (P=0.02) was observed in males at 20,000 ppm at the end of 104 weeks relative to controls, and an overall trend for improved survival was observed in treated males (P=0.03). The inter-current (early) deaths were 37/52, 36/52, 35/52, and 26/52 for the control, low, mid and high dose groups, respectively. The terminal deaths were 16/52, 17/52, 18/52, and 26/52 for the control, low, mid and high dose groups, respectively. This survival bias in the high dose group could easily explain a modestly higher incidence of an age-related background tumor like liver adenoma (and fits with lack of associated lesions). In the 1990 study in Sprague-Dawley rats (MRID No. 41643801) there was also a weak but significant trend test for liver adenomas in males (P=0.02, no pairwise); however, in that study adenomas in all treatment groups were still within the historical control and the CPRC concluded that this effect was not treatment-related, as discussed above. The lack of increased liver tumor incidence in the other rat studies provide additional evidence for lack of an actual carcinogenic response in the liver.

d. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in any organs of either sex at any dose level tested.

e. Adequacy of Dosing for Assessment of Carcinogenicity

The highest dose tested in both sexes (1214 mg/kg/day in males and 1498 mg/kg/day in females) exceeded the limit dose (1000 mg/kg/day). Treatment-related findings at these doses were observed in the liver and kidney, notably renal papillary necrosis, prostatitis, periodontal inflammation, urinary acidosis, hematuria and slight increases in the incidence of proliferative cholangitis and hepatitis.

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5. Feinchemie Schwebda. (1996). Combined Chronic Toxicity and Carcinogenicity Study with Glyphosate Technical in Wistar Rats. Bangalore, India: Rallis India, Ltd. (Cited in Greim *et al.*, 2015).

a. Experimental Design

In a combined chronic/carcinogenicity study, glyphosate (96.0-96.8% pure) was administered to groups of Wistar rats in the diet. Groups of 50 rats/sex/group received diets containing 0, 100, 1000, and 10000 ppm glyphosate for 24 months. The average achieved doses were 0, 7.4, 73.9, and 740.6 mg/kg/day. Parameters evaluated included clinical signs, body weights, food consumption, hematology, clinical chemistry, and urinalysis, organ weights, gross necropsy, and histopathological examination.

b. Survival Analysis

No adverse effects on survival were observed in either sex across the doses tested.

c. Discussion of Tumor Data

There were no statistically significant increases in any tumor type in this study. Details are provide by Greim *et al.,* 2015 can be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

d. Non-Neoplastic Lesions

There were no non-neoplastic lesions at any dose level in either sex.

e. Adequacy of Dosing for Assessment of Carcinogenicity

The doses tested were determined to be adequate in both sexes since the highest dose tested (741 mg/kg/day) approached the limit dose (1000 mg/kg/day).

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6. Arysta Life Sciences. (1997a). HR-001: 24-Month Oral Chronic Toxicity and Oncogenicity Study in Rats. Kodaira-shi, Tokyo, Japan: The Institute of Environmental Toxicology (Cited in Greim *et al.*, 2015).

a. Experimental Design

In a combined chronic/carcinogenicity study, glyphosate (94.6–97.6% pure) was administered to groups of Sprague-Dawley rats in the diet. Groups of 50 rats/sex/group received diets containing 0, 3000, 10000, or 30000 ppm glyphosate for 24 months. The achieved doses were 0, 104, 354 or 1127 mg/kg/day in males and 0, 115, 393, or 1247 mg/kg/day in females, respectively. Parameters evaluated included clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, organ weights, gross necropsy and histopathological examination.

b. Survival Analysis

No adverse effects on survival were observed in either sex across the doses tested.

c. Discussion of Tumor Data

There were no statistically significant increases in any tumor type in this study. Details are provide by Greim *et al.,* 2015 can be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

d. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in this study.

e. Adequacy of Dosing for Assessment of Carcinogenicity

The highest dose 10,000 ppm (1127 mg/kg/day in males and 1247 mg/kg/day in females) exceed the limit dose (1000 mg/kg/day) and there were increased cecum weights, distension of the cecum, loose stool, follicular hyperkeratosis and/or folliculitis/follicular abscess of the skin, and decreased body weights.

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7. **Nufarm. (2009a). Glyphosate Technical: Dietary Combined Chronic Toxicity/ Carcinogenicity in the Rat. Shardlow, Derbyshire, UK: Harlan Laboratories Ltd. (Cited in Greim *et al.*, 2015)**.

a. Experimental Design

In a combined chronic toxicity study, glyphosate (95.7% pure) was administered to groups of Wistar rats in the diet. Groups of 51 rats/sex/group received diets containing 0, 1500, 5000, and 15,000 ppm glyphosate for 24 months. To ensure that a received limit dose of 1000 mg/kg/day was achieved, the highest dose level was progressively increased to 24000 ppm. The achieved doses were 0, 86, 285 or 1077 mg/kg/day in males and 0, 105, 349 or 1382 mg/kg/day, in females. Parameters evaluated included clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, as well as organ weights, necropsy and histopathological examination.

b. Survival Analysis

No adverse effects on survival were seen in either sex across the doses tested.

c. Discussion of Tumor Data

There were no statistically significant increases in any tumor type in this study. Details are provide by Greim *et al.,* 2015 can be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

d. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in either sex at any dose level.

e. Adequacy of Dosing for Assessment of Carcinogenicity

The highest doses 1077 mg/kg/day in males and 1382 mg/kg/day in females exceed the limit dose (1000 mg/kg/day).

B. Carcinogenicity Studies in Mice

1. Knezevich, A.L and Hogan, G. K. (1983). A chronic feeding study of glyphosate in mice. Unpublished report prepared by Bio/Dynamic Inc., dated July 21, 1983. Report No. 77-2011. EPA Accession No. 251007 – 251009, and 251014.

a. Experimental Design

In a carcinogenicity study, groups of 50 male and female CD-1 mice received glyphosate (99.78%, pure) at dietary levels of 0, 1000, 5000, or 30,000 ppm for two years. These doses were equivalent to 0, 161, 835, 4945 mg/kg bw/day for males and 0, 195, 968, and 6069 mg/kg bw/day for females) for 24 months. Parameters evaluated included clinical signs, body weight, food consumption, organ weights, and histopathological examination.

b. Discussion of Tumor Data

The incidences of renal tubule adenomas were as follows: 0/49 in the controls; 0/49 at the low-dose; 1/50 at the mid-dose; and 3/50 at the high dose (TXR No. 0004370).

In 1985, the Registrant directed a re-evaluation of the original renal section by a consulting pathologist (Dr. Marvin Kuschner). This evaluation identified a small renal tubule adenoma in one control male mouse (animal number 1028) which was not diagnosed as such in the original pathology report (TXR No. 0004855).

In 1986, at the request of the agency, additional renal sections (3 sections/kidney/mouse spaced at 150 micron intervals) were evaluated in all control and all glyphosate-treated male mice in order to determine if additional tumors were present. The additional pathological and statistical evaluations concluded that the renal tumors in male mice were not compound-related (TXR No. 0005590).

At the request of the agency, the Pathology Work Group (PWG) examined all sections of the kidneys including the additional renal sections. The renal tubular-cell lesions diagnosed by the PWG are presented below in Table 13. The PWG noted that because differentiation between tubular-cell adenoma and tubular-cell carcinoma is not always clearly apparent and because both lesions are derived from the same cell type, it appropriate to combine the incidences for purposes of evaluation of statistical analysis. Statistical analyses are presented in Table 14. The PWG unanimously concluded that these lesions are not compound-related based on the following considerations: 1) renal tubular cell tumors are spontaneous lesions for which there is a paucity of historical control data for this mouse stock; 2) there was no statistical significance in a pairwise comparison of treated groups with the controls and there was no evidence of a significant linear trend; 3) multiple renal tumors were not found in any animal; and 4) compound-related nephrotoxic lesions,

including pre-neoplastic changes, were not present in male mice in this study (TXR No. 0005590).

Table 13. Glyphosate: Kidney Tumor in Male CD-1 Mice — PWG				
Dose/Tumor Type	Control	1000 ppm	5000 ppm	30,000 ppm
	0 mg/kg/day	161 mg/kg/day	835 mg/kg/day	4945 mg/kg/day
Tubular-cell adenoma	1/49	0/50	0/50	1/50
Tubular-cell carcinoma	0	0/50	1/50	2/50
Combined incidence	1/49 (2%)	0/50 (0%)	1/50 (2%)	3/50 (6%)

Statistical analysis of the male mouse renal tumors diagnosed by the PWG are presented below in Table 14.

Table 14. Kidney Tumors in Male CD-1 Mice — PWG Cochran-Armitage Trend & Fisher's Exact Test (MRID 00130406)				
Tumor Type	0 mg/kg/day	161 mg/kg/day	835 mg/kg/day	4945 mg/kg/day
Adenomas (%) P =	1/49 (2) 0.4422	0/49 (0) 1.0000	0/50 (0) 1.00000	1/45 (2) 0.7576
Carcinomas (%) P =	0/49 (0) 0.0635	0/49 (0) 1.0000	1/50 (2) 0.5051	2/50 (4) 0.2525
Combined (%) P =	1/49 (2) 0.0648	0/49 (0) 1.0000	1/50 (2) 0.7576	3/50 (6) 0.3163

Historical control data from the testing laboratory (Bio-dynamics) during the glyphosate-study period (1976-1982) are presented in Table 15.

Table 15. Historical Control Data- Kidney tumors in CD-1 Mice — Bi/dynamics Inc.														
Study I.D	A		B		C		D		E		F		G	
Study Period	6/78 - 7/80		12/77-4/80		12/77-3/80		10/78-4/81		11/78-4/81		11/77-4/80		10/77-4/80	
No. Examined	57	54	61	51	53	59	60	60	60	60	60	60	60	60
Tubular Adenoma		1	0	0	0	0	0	0	0	2	0	0	0	0

Historical control data from 14 studies conducted between 1977 and 1981 at the testing laboratory indicated that the mouse renal tumors ranged from 0 to 3.3% and the incidence in the current study (3/50; 6%) exceeded the upper limit of the historical control range (TXR No. 0007252).

The CPRC determined that glyphosate produced an equivocal carcinogenic response in male mice characterized by an increased incidence of renal tubular neoplasms. The biological significance of the findings was questionable because of: a) lack of significance in pairwise comparison with concurrent controls for adenomas, carcinomas and the combined tumors; b) there was no concurrent increase in non-neoplastic renal tubular lesions in male mice (*e.g.* tubular necrosis/regeneration, hyperplasia, hypertrophy, etc.), c) the examination of multiple sections of kidneys from all groups resulted in no additional neoplasms; this fact is particularly important since not only were the original sections closely scrutinized by more than one pathologist, but additional sections as well, d) increased incidence in high dose group was very small compared to control considering the very high concentration which produced highly significant reduction in body weight gain in males; e) although the incidences exceeded the historical control, this finding did not override the lack of statistical significance of comparison to the concurrent controls. Furthermore, the increased incidence of chronic interstitial nephritis in males is not relevant to the tubular neoplasms. There was actually a decrease in renal tubular epithelial changes (basophilia and hyperplasia) in males, and although there was a dose-related increase in these changes in female mice, no tubular neoplasms were observed in females. Overall, the Peer Review Committee did not consider the renal tumors to be treatment-related. The CARC reaffirmed the CPRC conclusion and rationale. Also, the lack of increased renal tumors in the other mouse studies in the same strain provides additional evidence for lack of an actual carcinogenic response in the kidneys.

c. Non-Neoplastic Lesions

The incidence of centrilobular hepatocyte hypertrophy was slightly but not significantly increased in high-dose male mice at terminal sacrifice if all mice were included in the analyses. Centrilobular hepatocyte necrosis was significantly ($P \leq 0.01$) increased in high-dose male mice (10/50; 20%) compared to controls (2/49; 4%). No significant increases in centrilobular hepatocyte hypertrophy or necrosis were observed in treated female mice. There was a dose-dependent increase in the proximal tubular epithelial basophilia in female mice; the incidences were: 0/50 (0%) in the controls, 2/50 (4%) at the low dose, 4/50 (8%) at the mid dose, and 9/50 (18%) at the high dose ($P \leq 0.01$). All other tissue alterations occurred sporadically and were found with approximately equal frequency and severity in contro1 and treated animals. These were considered unrelated to glyphosate treatment.

d. Adequacy of the Dosing for Assessment of Carcinogenicity

The high dose tested in males (4945 mg/kg/day) and females (6069 mg/kg/day) was approximately 4 to 6-fold higher than the limit dose (1000 mg/kg/day), which produced highly significant reduction in body weights in both sexes. Therefore, the doses tested were determined to be adequate to assess the carcinogenic potential of glyphosate in this study.

2. Atkinson, C., Martin, T., Hudson, P., and Robb, D. (1993). Glyphosate: 104 week dietary carcinogenicity study in mice. Inveresk Research International, Tranent, EH33 2NE, Scotland. IRI Project No. 438618. April 7, 1993. MRID 49631702.

a. Experimental Design

In a carcinogenicity study, glyphosate (97.5 – 100.2% pure) was administered to groups of 50 CD-1 mice/sex/dose in the diet at doses of 0, 100, 300, or 1000 mg/kg/day for 104 weeks. No interim sacrifices were performed. Parameters evaluated included clinical signs, body weight, food consumption, organ weights, necropsy and histopathological examination.

b. Discussion of Tumor Data

As shown in Table 16, hemangiosarcomas were found in 4/45 (9%) high-dose male mice compared to none in the controls. In the treated mice at the high dose, one had the tumors present in the liver and spleen, one had the tumor present in the liver only, one had the tumors present in the liver, spleen, and prostate, and one had the tumor present in the spleen only. No hemangiosarcomas were found in the control or low- and mid-dose mice.

Table 16. Hemangiosarcomas in Male CD-1 Mice Fisher's Exact Test and Exact Trend Test Results

Dose (mg/kg/day)	0	100	300	1000
Hemangiosarcomas (%) P =	0/47[a] (0) 0.00296**	0/46 (0) 1.00000	0/50 (0) 1.00000	4/45 (9) 0.05332

a= Number of tumor bearing animals/Number of animals examined, excluding those that died before week 52.
Note: ** Significance of trend (P<0.01) denoted at control.

The increase in hemangiosarcomas in male mice was not considered to be treatment-related due to 1) tumors seen only at the limit dose; 2) absence of statistical significance in the pairwise analysis; 3) the incidences was near or the same as the upper limit (0–8%) for the performing laboratory; 4) hemangiosarcomas were not seen in male mice in the other three studies when tested at comparable doses (946–1467 mg/kg/day) or at considerably higher doses (4348–5874 mg/kg/day) in this strain of mouse; 6) the considerable inter-group variability in the number of female mice with this tumor (0, 2 , 0 and 1 in the control, low-, mid- and high-dose groups, respectively); 7) Hemangiosarcomas are commonly observed in mice as both spontaneous and treatment-related tumors arising from endothelial cells; 8) hemangiosarcomas appear in both sexes but are generally more common in males (CD-1); 9) As vascular tumors, they can occur at different sites but liver and spleen tend to be the most common sites in male mice.

c. Non-Neoplastic Lesions

No treatment-related non-neoplastic lesions were seen.

d. Adequacy of the Dosing for Assessment of Carcinogenicity

The highest dose tested was the limit dose (1000 mg/kg/day).

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3. Arysta Life Sciences. (1997b). HR-001: 18-Month Oncogenicity Study in Mice. Kodaira-shi, Tokyo, Japan: The Institute of Environmental Toxicology (Cited in Greim *et al.*, 2015).

a. Experimental Design

In a carcinogenicity study, groups of ICR-CD-1 mice (50/sex/group received diets containing glyphosate (94.6–97.6% pure) at 0, 1600, 8000 or 40,000 ppm for 18 months. The achieved doses were 0, 165, 838 or 4348 mg/kg/day in males and 0, 153, 787 or 4116 mg/kg/day in females, respectively. Parameters evaluated included clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, organ weights, gross necropsy and histopathological examination.

b. Survival Analysis

No adverse effects on survival were observed in either sex across the doses tested.

c. Discussion of Tumor Data

There were no statistically significant increases in any tumor type in this study. Details provided by Greim *et al.* (2015) can be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

d. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in this study.

e. Adequacy of Dosing for Assessment of Carcinogenicity

The highest dose tested in both sexes exceeded (4-fold) the limit dose (1000 mg/kg/day).

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4. Nufarm. (2009b). Glyphosate Technical: Dietary Carcinogenicity Study in the Mouse. Derbyshire, UK: Harlan Laboratories Ltd. (Cited in Greim *et al.*, 2015).

a. Experimental Design

In another feeding study, CD-1 mice (50/sex/dose) received glyphosate (94.6–97.6%, pure) at 0, 500, 1500, or 5000 ppm for 18 months. The calculated test substance intake was 0, 85, 267 or 946 mg/kg/day. Parameters evaluated included clinical signs, body weight, food consumption, organ weights, gross necropsy and histopathological examination.

b. Discussion of Tumor Data

In male mice at the high dose (5000 ppm) there were increases in the incidences of adenocarcinomas of the lung and malignant lymphomas as shown in Tables 17. For the lung adenocarcinomas, the increases did not reach statistically significant pairwise differences, although the trend was significant. For the malignant lymphomas there was a trend and pairwise significance. Details provided by Greim *et al.* (2015) can be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

Table 17. Lung Adenocarcinomas and Malignant Lymphomas in Male CD-1 Mice (Greim *et al.*, 2015)
Fisher's Exact Test and Exact Trend Test Results

Dose (ppm)	0	500	1500	5000
Lung Adenocarcinoma (%) P =	5/51[a] (10) 0.02906**	5/51 (10) 0.62953	7/51 (14) 0.37996	11/51 (22) 0.08609
Malignant Lymphoma (%) P =	0/51 (0) 0.006633**	1/51 (2) 0.50000	2/51 (4) 0.24752	5/51 (10) 0.02820*

a= Number of tumor bearing animals/Number of animals examined.
Note: ** Significance of trend (P<0.01) denoted at control.

The increase in lung adenocarcinomas was not considered to be treatment-related due to: 1) absence of statistical significance in the pairwise analysis; 2) the incidences in all treatment groups including the controls were within the historical control range (1.43–26%) for the performing laboratory; and 3) lung tumors were not seen in the other three studies when tested at doses ranging from 814 to 4945 mg/kg/day for up to two years.

Historical control data and results from the 5 studies can be used to put this finding into perspective. The malignant lymphomas were not considered to be treatment-related since the 0% incidence of this lesion in the concurrent control for male mice was lower than the historical control mean (4.5%) and range (1.5–21.7%) in this strain and age of mice (Gikins and Clifford, 2005; Son and Gopinath, 2004). Therefore, the apparent statistical significance of the pairwise comparisons of the high dose male groups with the concurrent control might have been attributable to this factor and not to actual carcinogenic response. In addition, malignant lymphomas were not seen in the other three studies in this strain of mice when tested at doses ranging from 814 to 4945 mg/kg/day for up to two years.

c. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in this study.

d. Adequacy of the Dosing for Assessment of Carcinogenicity

The highest dose (947 mg/kg/day) tested approached the limit dose (1000 mg/kg/day).

IV. TOXICOLOGY

A. Metabolism

Single or repeated doses of radiolabeled ^{14}C-glyphosate were administered orally to male and female Sprague-Dawley rats. Following a single oral dose of, ^{14}C-glyphosate, 30 to 36% of the dose was absorbed and less than 0.27% of the dose was eliminated as CO_2. 97.5% of the administered dose was excreted in the urine and feces as the parent compound, glyphosate. Amino methyl phosphonic acid (AMPA) was the only metabolite found in urine (0.2–0.3% of the administered dose) and feces (0.2–0.4% of the administered dose). Less than 1.0% of the absorbed dose remained in tissues and organs, primarily in bone tissue. Repeated dosing at 10 mg/kg did not significantly change the metabolism, distribution or excretion of glyphosate.

In a second study, male and female Sprague-Dawley rats received single intraperitoneal injections of radiolabeled ^{14}C-glyphosate at 1150 mg/kg. Blood samples were collected 0.25, 0.50, 1, 2, 4, 6 and 10 hours after injection. Femoral bone marrow samples were collected from one third of the male and female rats sacrificed at 0.5, 4, or 10 hours after injection. Thirty minutes after injection of glyphosate, the concentration of radioactivity in the bone marrow of male and female rats was equivalent to 0.0044% and 0.0072%, respectively, of the administered dose. Assuming first order kinetics, the decrease in radioactivity in bone marrow occurred with a half-life of 7.6 and 4.2 hours for males and females, respectively. Similarly, the half-lives of the radioactivity in plasma were approximately 1 hour for both sexes. These findings indicate that very little glyphosate reaches bone marrow, that it is rapidly eliminated from bone marrow, and that it is even more rapidly eliminated from plasma.

B. Mutagenicity

In 1991, the Carcinogenicity Peer Review Committee concluded that there was no evidence of genotoxicity for glyphosate based on negative findings in submitted guideline studies for the bacterial reverse mutation test (MRID 00078620), *in vitro* mammalian cell gene mutation test in CHO cells (MRID 00132681), *in vivo* mammalian bone marrow chromosomal aberration test (MRID 00132683) and a "rec assay" used to detect DNA-damaging agents in *Bacillus subtilis* (MRID 00078619) (TXR 0008898).

Glyphosate has also been evaluated for its genotoxic potential in other regulatory and published literature studies. Extensive reviews of the available genotoxicity studies for glyphosate and glyphosate products were conducted by Williams *et al.* (2000) and by Kier and Kirkland (2013). IARC also conducted a review of the publically available genetic toxicity data for glyphosate and glyphosate-based formulations (IARC, 2015).

Williams *et al.*, (2000) concluded that "glyphosate is neither mutagenic nor clastogenic." Similarly, Kier and Kirkland (2013) concluded a "lack of genotoxic potential for both glyphosate and glyphosate based formulations (GBFs) in core gene mutation and chromosomal effect endpoints." Kier and Kirkland (2013) also stated that "the observations of DNA-damage effects seems likely to be secondary to cytotoxic effects." However, IARC (2015) concluded that "there is strong evidence that glyphosate causes genotoxicity." It should be noted that the IARC's conclusion was based not only on studies conducted with the active ingredient but also on studies conducted with the formulation products such as Roundup. Roundup is a combination of the active ingredient and other chemicals, including a surfactant (polyoxyethyleneamine) which enhances the spreading of spray droplets when contact foliage. Of note, the review article by Kier and Kirkland (2013) and supplemental information provided on the publisher's website were not considered in the IARC evaluation.

In this assessment, the CARC considered a total of 54 studies including those submitted to the agency under 40 CFR Part 158 as well as the studies presented in the review articles by Williams *et al.* (2000), Kier and Kirkland (2013), and the IARC monograph (2015). Consistent with OPP's Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment (http://www.epa.gov/pesticides/science/lit-studies.pdf), literature studies discussed in the reviews such as IARC that did not meet the Klimisch criteria for reliability (*e.g.* lack of adequate glyphosate purity information for the test material) were not considered by the CARC. The CARC determined the mutagenic potential of glyphosate in humans by conducting a weight-of-evidence evaluation of the results from the cited bacterial reversion (Ames) assays, *in vitro* mammalian gene mutation assays, *in vitro* and *in vivo* chromosomal aberration and micronucleus assays as well as other relevant assays evaluating DNA damage.

1. Bacterial reverse mutation assays

As shown in Table 18, glyphosate was not mutagenic in any of the *in vitro* bacterial mutation assays using *S. typhimurium* or *E. coli* tester strains with or without microsomal S9 metabolic activation. These results are consistent with the negative findings in the previously reviewed EPA guideline (870.5100) bacterial reverse gene mutation study (MRID 00078620).

Table 18. Results from Bacterial Reverse Gene Mutation Assays[1]

Author	Cell/Strain[2]	Purity	Highest test concentration	Results –S9	Results +S9
Akanuma,M. (1995)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	95.7%[3]	5000 µg/plate	Negative	Negative
Callander, R.D. (1996)	TA98, TA100, TA1535, TA1537; WP2P and WP2*uvr*A	95.6%[3]	5000 µg/plate	Negative	Negative
Flügge, C. (2010)	TA98, TA100, TA102, TA1535, TA1537	76.1%[4]	100 µg/plate	Negative	Negative
Flügge, C. (2010)	TA98, TA100, TA102, TA1535, TA1537	96.4%	3160 µg/plate	Negative	Negative
Flügge, C. (2009)	TA98, TA100, TA102, TA1535, TA1537	98.8%	3160 µg/plate	Negative	Negative
Jensen, J.C. (1991)	TA98, TA100, TA1535, TA1537	98.6%	2500 µg /plate w/o S9; 5000 µg /plate w/ S9	Negative	Negative
Li and Long (1988)	TA98, TA100, TA1535, TA1537, TA1538;	98%	5000 µg/plate	Negative	Negative
NTP (1992)	TA97, TA100, TA1535	98%	10,000 µg /plate	Negative	Negative
Schreib, G. (2010)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	96%	5000 µg/plate	Negative	Negative
Shirasu et al. (1978)	TA98, TA100, TA1535, TA1537, TA1538 and WP2*uvr*A	98.4%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2007c)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	95.0%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2007a)	TA98, TA100, TA1535, TA1537; WP2uvrA	95.1%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2009b)	TA98, TA100, TA1535, TA1537;WP2P and WP2*uvr*A	96.3%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2009a)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	96.66%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2007b)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	97.7%	5000 µg/plate	Negative	Negative
Suresh, T.P. (1993)	TA98, TA100, TA1535, TA1537, TA1538	96.0%	1000 µg/plate	Negative	Negative
Thompson, P.W. (1996)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	95.3%	5000 µg/plate	Negative	Negative

1. Studies cited in Williams *et al*. (2000), Kier and Kirkland (2013), or IARC monograph.
2. *S. typhimurium* strains (TA97, TA98, TA100, TA102, TA1535, TA1537, and/or TA1538) or *E. coli* strains (WP2P and WP2*uvr*A)
3. Glyphosate acid
4. Monoammonium glyphosate salt

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2. *In vitro* mammalian cell gene mutation assays

Glyphosate did not induce forward mutations in mouse lymphomas cells or Chinese hamster ovary (CHO) cells in the presence or absence of metabolic (S9) activation (Table 19).

Table 19. Results from mammalian gene mutation assays[1].

Author	Assay Type	Cell type	Purity	Highest conc.	Result -S9	Result +S9
Clay (1996)	*In vitro* mammalian gene mutation	L5178Y mouse lymphoma cells/ tk locus	95.6%	1.0 mg/mL	Negative	Negative
Jensen, J.C. (1991)	*In vitro* mammalian gene mutation	L5178Y mouse lymphoma cells/ tk locus	98.6%	5.0 mg/mL	Negative	Negative
Li and Long (1988)	*In vitro* mammalian gene mutation	CHO cells/ HGPRT locus	98%	22.5 mg/mL	Negative	Negative

1. Studies cited in Williams's *et al*. (2000), Kier and Kirkland (2013), or IARC monograph.

3. *In vitro* chromosomal aberration assays

Lioi *et al*. (1998a, 1998b) reported positive findings for chromosomal aberrations in human and bovine lymphocytes treated with glyphosate *in vitro* in the absence of S9 activity. As discussed in the Williams review, there is less confidence in the Lioi *et al*. results based on the use of an unusual 72-hour treatment protocol and the observation of reduced cell growth in glyphosate-exposed cells (an indication of a toxic effect) which can affect the evaluation of the study. Lioi *et al.* also reported chromosomal damage in lymphocytes treated with other known non-genotoxic pesticides in this study at concentration ranges similar to where they reported effects for glyphosate. By contrast, when the tests were performed according to the OECD guideline, Van de Waart (1995) reported no significant increase in chromosomal aberrations in human lymphocytes treated with up to 0.56 mg/mL (-S9) and 0.33 mg/mL (+S9) glyphosate, which are concentrations 3 orders of magnitude higher than those at which Lioi *et al*. reported aberrations. Glyphosate was negative in two other *in vitro* chromosomal aberrations studies using human lymphocytes (Fox, 1998; Manas *et al*. 2009) and did not induce chromosomal aberrations in Chinese hamster lung cells (Matsumoto, 1995; Wright, 1996). A summary of the findings is presented in Table 20.

Table 20. Results from *in vitro* chromosomal aberration assays[1].

Authors	Assay	Cell type	Purity	Highest test concentration	Result -S9	Result +S9
Van de Waart (1995)	Chromosomal Aberration	Human peripheral lymphocytes	>98%	0.56 mg/mL with S9; 0.33 mg/mL w/o S9	Negative	Negative
Fox, V. (1998)	Chromosome Aberration	Human peripheral lymphocytes	95.6%[2]	1250 ug/mL	Negative	Negative
Lioi et al. (1998a)	Chromosomal Aberration	Human peripheral lymphocytes	>98%	1.4 mg/L	Positive	Not Tested
Manas et al. (2009)	Chromosomal Aberration	Human peripheral lymphocytes	96%	6 mM	Negative	Not Tested
Lioi et al. (1998b)	Chromosomal Aberration	Bovine peripheral lymphocytes	>98%	2.9 mg/L	Positive	Not Tested
Matsumoto, K. (1995)	Chromosomal Aberration	Chinese Hamster Lung (CHL) cells	95.68%[2]	1000 ug/mL	Negative	Negative
Wright, N.P. (1996)	Chromosomal Aberration	Chinese Hamster Lung (CHL) cells	95.3%	1250 ug/mL	Negative	Negative

1. Studies cited in Williams *et al*., (2000), Kier and Kirkland (2013), or IARC monograph.
2. Glyphosate acid

4. *In vivo* micronucleus and chromosomal aberration assays

Numerous studies were evaluated to determine the potential for glyphosate to induce micronuclei in rodent bone marrow cells. Studies included both intraperitoneal (IP) and oral routes of glyphosate administration. In a literature study by Bolognesi *et al*. (1997), the authors reported an induction of micronuclei in male mice treated with up to 300 mg/kg (injected as two ½ doses). It is noted that this study included only 3 animals/dose, rather than the 5 animals/dose recommended in the agency's test guideline (870.5395). In another literature study, Manas *et al*. (2009) reported an induction of micronuclei in BALB/C mice when tested up to 200 mg/kg glyphosate. However, there is some concern regarding how the micronuclei were scored in this study. As stated in the Kier and Kirkland review, Manas *et al.* (2009) reported their findings as an increase in micronucleated erythrocytes rather than polychromatic erythrocytes. Scoring all erythrocytes rather than immature polychromatic erythrocytes can impact the interpretation of the study as the effects cannot be solely attributed to treatment by the test article. Suresh *et al*. (1993) reported an increase in micronuclei in females only in Swiss albino mice treated with 5 mg/kg glyphosate; however, this occurred at a dose that is more than twice the limit dose for the agency's guideline study. Although the above authors reported positive findings, a vast majority of the *in vivo* genotoxicity studies (including the previously reviewed guideline mammalian bone marrow chromosomal aberration test) were negative at doses similar to or higher than the studies discussed above, regardless of the dosing regimen or route of administration. Furthermore, glyphosate was also negative in two rodent dominant lethal tests. A summary of the findings are reported in Table 21.

Table 21. Results from *in vivo* genotoxicity assays[1].

Author	Assay Type	Species/strain	Purity	Highest conc.	Results	Comments
Bolognesi *et al.* (1997)	Micronucleus test	Male mice (strain not provided)	99.9%	300 mg/kg	Positive	Two IP injections of ½ dose; 3 mice/dose
Durward, R. (2006)	Micronucleus test	Young adult male and female albino Crl:CD-1TM(ICR)BR mice	95.7%	600 mg/kg	Negative	Single IP injection; Significant increase in % PCEs per 1000 erythrocytes was observed in the 24-hour; however not 48-hour at 600 mg/kg
Flügge, C. (2009)	Micronucleus test	Male and female CD rats	98.8%	2000 mg/kg	Negative	Single dose; oral gavage
Fox and Mackay (1996)	Micronucleus test	Male and female CD-1 BR mice	95.6%[2]	5000 mg/kg	Negative	Single dose; oral gavage
Honavar, N. (2005)	Micronucleus test	Male and female NMRI mice	97.73%	2000 mg/kg	Negative	Single dose; oral gavage
Honavar, N. (2008)	Micronucleus test	NMRI male mice	99.1%	2000 mg/kg	Negative	Single dose; oral gavage
Jensen, J.C. (1991)	Micronucleus test	Young adult male and female NMRI SPF mice	98.6%	5000 mg/kg	Negative	Single dose; oral gavage
Manas *et al.* (2009)	Micronucleus	BALB/C mice	96%	200 mg/kg	Positive	Two IP doses, 1 day apart
NTP (1992)	Micronucleus test	Male and female B6C3F1 mice	99%	11,379 mg/kg/day	Negative	Dietary admin., 13 weeks
Suresh, T.P. (1993)	Micronucleus test	Young Swiss albino male and female mice	98.6%	5000 mg/kg	Males: Negative Females: Positive	Two doses 1 day apart; oral gavage
Suresh, T.P. (1994)	Mouse Bone Marrow Chromosome Aberration	Male and female Swiss albino mice	96.8%	5000 mg/kg	Negative	Two doses, 24 hours apart; oral gavage
Suresh, T.P. (1992)	Rodent dominant lethal test	Male and female Wistar rats	96.8%	500 mg/kg (single dose); 100 mg/kg (5 daily doses)	Negative	
Wrenn (1980)	Rodent dominant lethal test	Mouse; gavage	98.7%	2000 mg/kg	Negative	

1. Studies cited in Williams *et al.*, (2000), Kier and Kirkland (2013), or IARC monograph.
2. Glyphosate acid
3. IP= intraperitoneal injection

5. Other genotoxicity assays

Inconsistent responses were reported in a number of assays designed to detect DNA damage, including sister chromatid exchange (SCE) assay, unscheduled DNA synthesis assay, and the comet assay (also known as the single cell electrophoresis assay). Positive responses in these assays do not necessarily indicate a chemical is DNA-reactive (*i.e.* mutagenic), but rather that DNA damage occurred under conditions of the assay. Glyphosate was also negative in two Rec-DNA repair tests in *B. subtilis*. The results of these genotoxicity studies are presented in Table 22.

Table 22. Additional genotoxicity assays of glyphosate

Authors	Assay Type	Cell Type	Purity	Highest test conc.	Results
Bolognesi *et al.* (1997)	Sister chromatid exchange (SCE)	Human peripheral blood (*in vitro*)	99.9%	1000 ug/mL	Positive
Lioi *et al.* (1998a)	SCE	Human peripheral blood (*in vitro*)	>98%	1.4 mg/L	Equivocal
Lioi *et al.* (1998b)	SCE	Bovine peripheral blood (*in vitro*)	>98%	2.9 mg/L	Equivocal
Li and Long (1988)	Unscheduled DNA synthesis (UDS)	Rat hepatocytes (*in vitro* exposure)	98%	0.125 mg/mL	Negative
Rossberger,(1994)	UDS	Primary rat hepatocytes	98%	111.69 mM	Negative
Bolognesi *et al.* (1997)	DNA Damage /reactivity/UDS	Mouse; IP administration	99.9%	300 mg/kg	Equivocal
Bolognesi *et al.* (1997)	DNA Damage/reactivity/UDS	Mouse; IP; alkaline solution of extracted DNA	99.9%	300 mg/kg	Positive
Alvarez-Moya et al. (2014)	Comet assay	Human lymphocytes	96%[2]	700 µM	Positive
Lueken *et al.* (2004)	Comet assay	Human fibroblasts GM 5757	98.4%	75 mM	Negative
Manas *et al.*(2009)	Comet assay	Liver Hep-2 cells	96%	7.5 mM	Positive
Mladinic et al. (2009)	Comet assay	Human lymphocytes	98%	580 ug/mL (toxic); approximately 3.43 mM	Positive
Rossberger, S. (1994)	DNA repair test	Male SD rat primary hepatocytes	>98%	111.69 mM	Negative
Akanuma, M. (1995)	DNA repair test (Rec- assay)	*Bacillus subtilis* M45 rec-/ H17 rec+	95.68%[2]	240 ug/disk	Negative
Li and Long (1988)	DNA repair test (Rec assay)	*B. subtilis* H17, rec+; M45, rec-	98%	2 mg/disk	Negative

1. Studies cited in Williams *et al.*, (2000), Kier and Kirkland (2013), or IARC monograph.
2. Glyphosate acid

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6. Conclusions

In summary, glyphosate was not mutagenic in bacteria or mammalian cells *in vitro*. Additionally, glyphosate did not induce chromosomal aberrations *in vitro*. Although some studies in the open literature reported positive findings for micronuclei induction in rodents, these findings were not replicated in the majority of the rodent micronuclei or chromosomal aberration studies considered in this assessment by the CARC. Some positive results were reported in SCE and comet assays in the open literature; however, there is no convincing evidence that the DNA damage is a direct effect of glyphosate exposure, but rather may be secondary to cytotoxicity or oxidative damage.

C. Structure-Activity Relationship

At present there are no structurally related pesticides registered by the agency which resemble glyphosate. Sulfosate, the trimethylsulfonium salt of glyphosate (also known as glyphosate-trimesium) is a 1:1 molar salt of N-(phosphonomethyl) glycine anion (PMG) and the trimethylsulfonium cation (TMS). Sulfosate was evaluated for its carcinogenic potential following dietary administration to male and female mice at 0, 10, 1000 or 8000 ppm (equivalent to 0, 16, 159 or 1341 mg/kg/day, respectively) for 18 months, and in male and female Sprague-Dawley rats at 0, 100, 500, or 1000 ppm (equivalent to 0, 5.4, 27 or 557 mg/kg/day, respectively) for two years. There was no evidence of carcinogenicity in either species. Sulfosate is classified as a Group E Chemical: "Not Likely to be Carcinogenic to Humans" based on the absence of carcinogenicity in mice and rats in two acceptable studies. Based on the available mutagenicity studies, there is no concern for mutagenicity (TXR Nos. 0006452 and 0011156).

D. Subchronic and Chronic Toxicity Studies

1. Subchronic Toxicity

In a 90-day feeding study (MRID No. 00036803) CD-1 mice were fed diets containing 0, 250, 500 or 2500 mg/kg/day of glyphosate for three months. Body weight gains of the high-dose males and females were about 24% and 18% lower, respectively, than those of the controls. Body weight gains of the low-dose and mid-dose groups were comparable to those of the controls. For systemic toxicity, the NOAEL is 500 mg/kg/day and the LOAEL is 2500 mg/kg/day, based on decreased body weight gain in both sexes.

In a 90-day feeding study (MRID No. 40559401), Sprague-Dawley rats were fed diets containing 0, 63, 317, and 1267 mg/kg/day of glyphosate, respectively in males and 0, 84, 404 and 1623 mg/kg/day of glyphosate, respectively, in females. Treatment-related findings were: (1) increased serum phosphorus and potassium in all treated groups, males and females; (2) increased serum glucose in the mid-dose and high-dose males; (3) increased blood urea nitrogen (BUN) and serum alkaline phosphatase in the high-dose males; and (4) occurrence of pancreatic lesions in the high-dose males (pancreas was not examined at the low-dose and mid-dose groups). Based on these findings, the systemic NOAEL is <1000 ppm (not determined definitively) for both sexes.

2. Chronic Toxicity

(i) Rats

A chronic feeding/carcinogenicity study (MRID No. 00093879) was conducted using male and female Sprague-Dawley rats which were fed diets containing 0, 30, 100, or 300 ppm of glyphosate for 26 months. These levels were equivalent to 0, 3, 10, and 34 mg of glyphosate/kg/day, respectively. There were no effects based on any of the parameters examined (toxic signs, mortality, body weights, food consumption, hematology, clinical chemistry, urinalysis, organ weights and organ/tissue pathology). Therefore, the NOAEL for systemic toxicity is 300 ppm (males: 31 mg/kg/day and females: 34 mg/kg/day).

A second chronic feeding/carcinogenicity study (MRID No. 41643801) was conducted using male and female Sprague-Dawley rats which were fed diets containing 0, 2000, 8000, or 20,000 ppm of glyphosate for two years. These levels were equivalent to 0, 89, 362, or 940 mg/kg/day, respectively, for the males and 0, 113, 457, or 1183 mg/kg/day, respectively, for the females. Treatment-related effects observed only in the high-dose group included: (1) decreased body weight gain in females; and (2) increased incidence of cataracts and lens abnormalities, decreased urinary pH, increased absolute liver weight, and increased liver weight/brain weight ratio (relative liver weight) in males. No significant systemic effects were observed in the low-dose and mid-dose male and female groups. Therefore, the NOAEL for systemic toxicity is 8000 ppm (males: 362 mg/kg/day and females: 457 mg/kg/day) and the LOAEL is 20,000.

In a combined chronic toxicity/carcinogenicity study (MRID No. 49631701), glyphosate (98.9% a.i.) was administered to 85 Sprague-Dawley rats/sex/dose in the diet for 104 weeks ater 0, 10, 100, 300, and 1000 mg/kg/day to both sexes over the course on the study. Designated for the toxicity portion of the study were 35 rats/sex/dose with the remainder designated for the oncogenicity portion of the study. There were no statistical differences between treated and control groups in survival rates. Pale feces were observed during weeks 16–104 in both sexes at the high dose and in females from the low-mid and high-mid dose levels. No treatment-related effect was observed in food consumption, hematology, ophthalmology, and gross pathology data. Males from the high-dose group had statistically lower mean body weight ($P \leq 0.01$) by 5% to 11% beginning Week 2 of the study until Week 104, and at termination was 10% lower (-14% weight gain). Females at the high dose had statistically lower body weight ($P \leq 0.05$) by 5% to 12% beginning Week 20 through Week 80 (with several exceptions), and at termination was 8% lower (-11% weight gain). Statistically increased ALP activities (+46% to +72%) were observed in males at the high dose throughout the study except for the 51 week interval when the mean value was 31% higher than control. Elevated ALP activities were observed in females at the high dose (+34% to +53%) throughout the study, and through most of the study at the high-mid dose by +20% to +67%, though not always statistically significant. Urinalysis data showed reduced pH (5.5–6) in males at the high dose throughout the study.

The absolute liver weight was decreased significantly in females at the high dose after 52 weeks, but after correcting for final body weight the difference was statistically significant at the three highest doses. The parotid salivary gland weight was increased significantly in males at the three highest doses (56–111%) after 52 weeks, but not after 104 weeks. The combined weight of the sublingual and submaxillary salivary glands was significantly increased by 13% (22% after correcting for body weight) at the high dose after 52 weeks. In females, the parotid gland was not affected but the sublingual and submaxillary combined weight was significantly higher by about 15%. The changes in salivary gland weights were accompanied by increased incidence of mild to severe parotid salivary gland cell alterations and slight to moderate mandibular salivary gland cell alterations were observed in both sexes at the 52-week and 104-week intervals. The lesions were described as cells and/or acini that appeared larger and stained in a weakly basophilic manner without showing a tendency toward proliferative or degenerative changes over time. In males, the increased incidence and severity of lesions in the parotid gland were significant ($P \leq 0.01$) at 100, 300, and 1000 mg/kg bw/day at 52 weeks, and significant at 300 and 1000 mg/kg bw/day at 104 weeks. The increased incidence of lesions in the mandibular gland were significant at 300 and 1000 mg/kg bw/day at 52 weeks and significant ($P \leq 0.001$) at 100, 300, and 1000 mg/kg bw/day at 104 weeks. In females, the increased incidence of parotid lesions was significant at 300 and 1000 mg/kg bw/day at 52 weeks, and significant at 100, 300, and 1000 mg/kg bw/day at 104 weeks. The increased incidence in the mandibular gland lesions was significant at the high dose at both 52 and 104 weeks. The incidence and/or severity of kidney nephropathy decreased in males at 100, 300, and 1000 mg/kg bw/day at 52 weeks and at the high dose at 104 weeks. Urothelial hyperplasia significantly decreased in females from the high dose group at both the 52-week and 104-week intervals. The LOAEL in male and female Sprague-Dawley rats administered glyphosate for 104 weeks in the diet was 100 mg/kg bw/day based on microscopic lesions in the parotid and mandibular salivary glands. The NOAEL was 10 mg/kg bw/day (MRID No. 49631701).

In another chronic toxicity/carcinogenicity study (MRID No. 49704601), groups of 52 male and 52 female Alpk:APSD (Wistar-derived) rats were fed diets containing glyphosate at 0, 2000, 6000, or 20,000 ppm for two years. These doses were equivalent to 0, 121, 361 or 1214 mg/kg/day in males and 0, 145, 437, or 1498 mg/kg/day in females, respectively. Treatment-related findings were confined to the liver and kidneys at the highest dose (20,000 ppm). In both sexes, treatment-related changes manifested as papillary necrosis, prostatitis, periodontal inflammation, urinary acidosis, and hematuria. The LOAEL was 20,000 ppm (1214 mg/kg/day in males and 1498 mg/kg/day in females) and the NOAEL was 6000 ppm (361 mg/kg/day in males and 437 mg/kg/day in females)

(ii) <u>Mice</u>

In a carcinogenicity study (MRID No. 00251007), glyphosate (Technical, 99.7% a.i.) was administered to groups of 50 male and 50 female CD-1 mice/sex/dose in the diet at dose levels of 0, 1000, 5000, or 30,000 ppm (approximately equivalent to 0, 161, 835, 4945 mg/kg bw/day for males and 0, 195, 968, and 6069 mg/kg bw/day for females) for 24 months. Cage-side and detailed clinical observations were done. Body weight and food intake were monitored throughout the study. Water consumption was measured during months 12 and 24. Erythrocyte, as well as total

white cell counts and differentials, were done at months 12, 18, and 24. Tissues and organs were collected from all mice whether dying during the study or at terminal sacrifice. Microscopic analyses were done on all collected tissues.

No treatment-related effects were found on survival, body weight, food or water consumption, or hematology parameters of treated male or female mice. The terminal body weight of high-dose males was significantly decreased 9% while the absolute liver weight of high-dose males was significantly decreased 16%; however, no significant treatment-related effects were found on the liver-to-body-weight ratio. The absolute testes weight of high-dose male mice was increased 7%, while the relative to body testes weight was increased 17. Neither were statistically significant, and no microscopic histological correlates were found. The incidences of centrilobular hepatocyte hypertrophy were slightly, but not significantly increased in high-dose male mice. Centrilobular hepatocyte necrosis was significantly higher in high-dose males (10/50** (20%) vs. control 2/49 (4%), P≤0.01). No significant increases in centrilobular hepatocyte hypertrophy or necrosis were observed in treated female mice; however, proximal tubular epithelial basophilia was significantly increased in high-dose females (9/50 (18%) vs control 0/50 (0%), P≤0.01). No other microscopic treatment-related effects were found. Based on increased centrilobular hepatocellular necrosis in high-dose males and proximal tubular epithelial basophilia in high-dose females, the systemic LOAEL for male and female CD-1 mice was 30,000 ppm (approximately 4945 mg/kg bw/day for males and 6069 mg/kg bw/day for females). The NOAEL for the study was 835 mg/kg bw/day for males and 968 mg/kg bw/day for females) (MRID No. 00251007).

In another carcinogenicity study (MRID No. 49631702), glyphosate (97.5–100.2% a.i.) was administered to groups of 50 CD-1 mice/sex/dose in the diet at doses of 0, 100, 300, or 1000 mg/kg/day for 104 weeks. Mortality, body weight, body weight gain, and food consumption were monitored throughout the study. WBC differential counts were done during Weeks 52, 77, and 102 of the study. Organ weights were measured and tissues collected for microscopic analyses. Treatment of male and female mice for 104 weeks did not increase mortality and did not decrease body weight, body weight gain or food consumption. No treatment-related clinical signs of toxicity were observed and no effects were found on WBC differential counts. Treatment did increase the absolute and relative thymus weights of male and female mice treated with 300 or 1000 mg/kg bw/day approximately 2–3-fold, but only the results of male mice were statistically increased. However, no treatment-related effects were found microscopically. At necropsy, the incidence of lung masses was slightly increased in high-dose male mice, but were considered coincidental. Microscopically, there was a slight, but statistically significant increase in mineral deposition in the brains of mid- and high-dose male mice. A non-significant increase was observed in female mice. Kidney cysts were also slightly but statistically increased in low- and mid-dose males, but no increase of cortical tubular eosinophilic droplets was found in female mice. The significance of these findings is questionable since they did not follow a dose-response. The systemic NOAEL for glyphosate in male and female CD-1 mice treated up to 104 weeks was 1000 mg/kg bw/day. A LOAEL was not identified (MRID No. 49631702).

V. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE-EVIDENCE

A. Evidence for Carcinogenicity in Humans

The CARC evaluated one cohort study and seven nested case-control studies based on the cohort study population and twenty-five case-control studies that examined the association between glyphosate exposure and one or more cancer outcomes.

1. Cancer at Multiple Sites

Several case-control studies reported no association for cancer of the oral cavity, colon, rectum, colorectum, lung, pancreas, kidney, bladder, prostate, breast or melanoma from exposure to glyphosate (De Roos *et al.*, 2005; Engle *et al.*, 2005; Lee *et al.*, 2007; Andreotti *et al.*, 2009; and Dennis *et al.*, 2010).

In single case-control studies, no associations were found for cancers of the esophagus, stomach, prostate or soft-tissue sarcoma from exposure to glyphosate (Alavanja *et al.*, 2003; Lee *et al.*, 2004; Band *et al.*, 2011; Pahwa, *et al.*, 2011; Koutros *et al.,* 2013). No association for childhood cancer was found from maternal or paternal exposure to glyphosate (Flower *et al.*, 2004).

2. Brain Cancer

A case-control study in Nebraska and the Upper Midwest Health case-control study in Iowa, Michigan, Minnesota and Wisconsin did not find any no association of glyphosate with adult brain cancer, specifically for gliomas (Ruder *et al.*, 2004; Carreon *et al.*, 2005; and Lee *et al.*, 2005).

3. Leukemia

No significant association with leukemia was reported in a case-control study in Iowa and Minnesota (Brown *et al.*, 1990) or in the AHS cohort (De Roos *et al.*, 2005). A Swedish case-control study reported a non-statistically significant elevated risk for hairy cell leukemia. However, the authors stipulated that this risk should be interpreted with caution since it was based on only 4 glyphosate-exposed cases (Nordstrom *et al.*, 1998).

4. Multiple Myeloma

No significant association for multiple myeloma from exposure to glyphosate was found in three separate population-based case-control studies: one in Iowa and Minnesota (Brown *et al.*, 1993) and the other in Iowa and North Carolina, USA (De Roos *et al.*, 2005; Sorhan 2015); and the third study in Canada (Pahwa *et al.*, 2012; Kachuri *et al.*, 2013), and in a hospital-based case-control study in France (Orsi *et al.*, 2009). A cohort study found no association with glyphosate exposure and monoclonal gammopathy of undetermined significance, a pre-clinical marker of multiple myeloma progression (Landgren *et al.*, 2009).

5. Non-Hodgkin Lymphoma

There is conflicting evidence for an association between glyphosate exposure and NHL; seven case-control studies reported no association in the U.S, Canada, and France, while two case-control studies from Sweden reported positive association.

No association between glyphosate exposure and NHL was found in four population-based case-control studies in the United States: in Iowa and Minnesota (Cantor *et al.*, 1992); in Iowa, Nebraska and Minnesota (Lee *et al.*, 2004a); in Iowa, Nebraska, Minnesota and Kansas (De Roos *et al.*, 2003) and in the AHS cohort with 57,311 licensed pesticide applicators in Iowa and North Carolina (De Roos *et al.*, 2005).

Similarly, no association between glyphosate exposure and NHL was seen in two population-based case-control studies conducted in various Canadian provinces (McDuffie *et al.*, 2001; Hohenadel *et al.,* 2011).

A hospital based case-control study from France did not find an association between glyphosate exposure and NHL (Orsi *et al.*, 2009).

The first report of an association between glyphosate exposure and NHL was in a population-based case-control study from Sweden (OR=23.3; 95% CI=0.40–13.0); however, this finding was based on only 4 glyphosate-exposed cases and 3 controls (Hardell and Erickson, 1999).

In a 2002 follow-up study, data from two case-control studies in Sweden, one on NHL and the other on hairy cell leukemia, were pooled and analyzed. A univariate analysis showed an increased risk (OR=3.04; 1.08–8.52); however, when study site, vital status, and exposure to other pesticides were taken into account in a multivariate analysis, risk declined (OR=1.85; 95% CI=0.55–6.20) (Hardell *et al.*, 2002).

In another case-control study in Sweden, among the 29 glyphosate-exposed cases, a multivariate analyses showed a statistically significantly increased risk for NHL (OR=1.51; 95% CI=0.77–2.94) and B-cell lymphoma (OR=1.87; 95% CI=0.998–3.51) (Erickson *et al.*, 2008).

A meta-analysis of the six studies (De Roos *et al.,* 2003; 2005; McDuffie *et al.*, 2001; Hardell *et al.*, 2002; Erickson *et al.*, 2008; and Orsi *et al.*, 2009) that showed an association between glyphosate exposure and NHL, resulted in a meta-risk ratio of 1.5 (95% CI=1.1–2.0) (Schinasi and Leon, 2014).

In an attempt to address the noted power/sample size issues and after considering the adjusted estimates of the two Swedish studies, IARC performed a meta-analysis of the data and estimated a meta-risk ratio of 1.3 (95% CI=1.03–1.65) (IARC, 2015).

In summary, the epidemiological evidence at this time does not support a causal relationship between glyphosate exposure and solid tumors. There is also no evidence to support a causal relationship between glyphosate exposure and non-solid tumors: leukemia, multiple myeloma or Hodgkin lymphoma. The epidemiological evidence at this time is inconclusive for a causal or clear associative relationship between glyphosate exposure and NHL. Multiple case-control studies and one prospective cohort study found no association with NHL; whereas, results from a small number of case-control studies (mostly in Sweden) did suggest an association. Most of the studies in the database were underpowered, suffered from small sample size of cancer cases with glyphosate exposure, and risk/odds ratios with large confidence intervals. Additionally, some of the studies had biases associated with recall and missing data. The CARC recognizes the meta-analysis conducted by IARC to try to address the power/sample size issues. However, given the limitations of the studies used, a different weighting scheme could easily change the meta-risk ratio. Thus, while the epidemiologic literature to date does not support causal association, the CARC recommends that the literature continue to be monitored for studies related to glyphosate and risk of NHL.

B. Evidence for Carcinogenicity in Experimental Animals

1. Evidence for Carcinogenicity in Rats

A total of seven chronic toxicity/carcinogenicity studies in Wistar or Sprague-Dawley strain rats were available for review. In these studies, glyphosate was administered in the diet to both sexes at doses ranging from 3.0 mg/kg/day to 1500 mg/kg/day for 2-years.

(i) Testes

In Sprague-Dawley rats (MRID No. 00093879), there was a non-dose-related increase in the incidences of interstitial cell tumors in the testes of males at 3 mg/kg/day (6%), 10 mg/kg/day (2%) and 30 mg/kg/day (12%; P=0.013) when compared to controls (0%). The CARC reaffirmed the previous conclusion that these tumors are not treatment related based on the following considerations: 1) lack of dose-response; 2) absence of pre-neoplastic lesions (*i.e.*, interstitial cell hyperplasia); 3) the incidences were within the normal biological variation seen for this tumor type in this strain of rats; 4) the incidences in the concurrent controls (0%) was not representative of the normal background incidences noted in the historical control animals (mean, 4.5; range, 3.4% to 6.7%;) and 5) this finding is not replicated in the other studies in the same strain of rats (*i.e.*, no interstitial cell tumors were seen when tested up to 1100 mg/kg/day). The CARC concluded that the interstitial cell tumors are not treatment-related.

(ii) Pancreas

Benign pancreatic islet cell tumors were seen in male Sprague-Dawley rats in two studies. In the first study (MRID No. 00093879), there was no dose response or statistical significance; the incidences for adenomas were: 0%, 10%, 4% and 4% at the control, low, mid, and high dose groups. Carcinomas were seen in one rat at the high dose. In the second study (MRID No. 41643801), there was a statistically significant increase in adenomas at the lowest (100 mg/kg/day) and the highest (1000 mg/kg/day) doses compared to controls: lowest dose, 8/45 (18%; P=0.018); intermediate dose, 5/49 (10%); and highest dose, 7/48 (15%; P=0.042) versus controls, 1/43 (2%). The CARC reaffirmed the previous conclusion that the benign pancreatic islet cell tumors are not treatment-related due to lack of dose-response, absence of pre-neoplastic lesions, lack of progression to malignancy, and incidences within the historical control range (0–17%) reported for this tumor in this strain of rats. This neoplasm was not seen in the other five studies. The CARC concluded that the pancreatic islet tumors are not treatment-related.

(iii) Liver

In male Sprague-Dawley rats (MRID No. 41643801), there was a statistically significant positive trend in the incidence of hepatocellular adenomas (P=0.016). The CARC concluded that the minimal increase in adenomas is not treatment-related due lack of statistical significance in pairwise comparison, absence of pre-neoplastic lesions, no progression to malignancy, and the incidences were within the historical control range (1.4–18.3%) of the testing laboratory.

In male Wistar rats (MRID No. 49704601), there was a statistically significant trend (P=0.00804) and pairwise significance for the increase in hepatocellular adenomas at the highest (1214 mg/kg/day) dose compared to controls: lowest dose, 2/52 (4%); intermediate dose, 0/52 (0%); and highest dose, 5/52 (10%; P=0.02826) versus controls, 0/52 (0%). The CARC concluded that this increase is not attributable to treatment based on the following considerations: 1) absence of dose-response relationship; 2) lack of progression to malignancy; 3) no evidence of pre-neoplastic lesions; 4) the incidences were within the historical control range (0–11.5%).

The CARC noted that survival was better at the high dose (25/52; 13%) compared to the controls (16/52; 8.3%) which could be reason for the slightly higher incidence (5/52) of age-related background tumors like liver adenomas in the absence of any associated lesions. Furthermore, with a weak genotoxic effect one would expect to see an effect on carcinomas (or at least adenomas/ carcinomas, combined) and shorter latency period, which were not observed in this study. With a weak cytotoxic or mitogenic effect one would expect to see an increase in foci and other non-neoplastic lesions. In addition, as discussed above, only a linear trend (no pairwise) was seen for this tumor type in another strain (Sprague-Dawley) for rats where the incidences were still within the historical control range. Also, liver tumors were not seen in the other four studies. This provides additional evidence for lack of an actual carcinogenic response in the liver. The CARC concluded that the liver tumors are not treatment-related.

(iv) Thyroid

In Sprague-Dawley rats (MRID No. 41643801), there was a statistically significant positive trend in the incidence of thyroid C-cell tumors in females (P=0.031). The CARC concluded that the minimal increase is not treatment-related due to lack of statistical significance in pairwise comparison, no progression to carcinomas, no increase in severity of grade or incidence of hyperplasia, and the incidences were within the historical control range (3.3–10%). The CARC concluded that the thyroid tumors in female rats are not treatment-related.

In summary, dietary administration of glyphosate at doses ranging from 3.0 to 1500 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in male or female Sprague-Dawley or Wistar rats.

2. Evidence for Carcinogenicity in Mice

Four carcinogenicity studies in CD-1 mice were available for review. In these studies, glyphosate was administered in the diet to both sexes at doses ranging from 85 mg/kg/day to 4800 mg/kg/day for 18–24 months. In one study there were no statistically significant or otherwise notable increases in the occurrence of any tumor types. Tumors observed in the other three studies are discussed below.

(i) Kidney

Kidney (renal tubular) tumors were seen in male CD-1 mice in one study (MRID No. 00251007). The incidences of adenomas was 1/49 (2%), 0/49 (0%), 0/50 (0%), and 1/50 (2%) in the control (0 mg/k/day), low- (157 mg/kg/day), mid- (814 mg/kg/day) and high-dose (4945 mg/kg/day) groups, respectively. The incidence of carcinomas was 0/49 (0%), 0/49 (0%), 1/50 (2%) and 2/50 (4%) in the control, low-, mid- and high-dose groups, respectively. The incidence of adenomas or carcinoma (combined) was 1/49 (2%), 0/50 (0%), 1/50 (2%), and 3/50 (6%) in the control, low-, mid-, and high-dose groups, respectively. None of these differences showed statistical significance.

The CARC reaffirmed the previous conclusion that the kidney tumors are not treatment-related based on the following weight-of-evidence considerations: a) lack of dose-related trend or statistical significance in pairwise comparisons; b) lack of non-neoplastic renal tubular lesions (*e.g.* tubular necrosis/regeneration, hyperplasia, or basophilia); c) the examination of multiple sections of kidneys from all groups resulted in no additional neoplasms; this fact is particularly important since not only were the original sections closely scrutinized by more than one pathologist, but additional sections as well; and d) the difference in incidence between high-dose group (3/50) and the control group (1/49) was minimal, especially considering the very high concentration given (4 x time the limit dose).

Furthermore, the Pathology Work Group concluded that the renal tumors were not treatment-related since none of the treatment groups differed from the controls for a linear trend or pairwise statistical significance, there was no treatment-related nephrotoxic lesions including pre-neoplastic changes, and multiple renal tumors were not seen in any animal.

In addition, the CARC noted that renal tumors were not observed when tested at a similar dose (4348 mg/kg/day) in this strain of mice in another study(Arysta, 1997b) or in two other studies at the limit dose (MRID No. 49631702, Nufarm, 2009b). If really treatment-related, it is unlikely that the same tumor would not have been detected at higher incidences in CD-1 mice with top doses >1000 – 4000 mg/kg/day.

(ii) Lung adenocarcinoma

There was a dose-dependent increase in the incidence of bronchiolar-alveolar adenocarcinoma of the lung in male CD-1 mice (Nufarm, 2009b). There was a positive trend (P=0.02906) in the incidence of lung adenocarcinomas: 5/51 (10%), 5/51 (10%), 7/51 (14%) and 11/51 (22%) at the 0, 85, 267 or 946 mg/kg/day groups, respectively. The CARC determined that this increase is not treatment-related due to lack of statistical significance in pairwise comparison, absence of pre-neoplastic lesions in the lung (*e.g.*, bronchiolar-alveolar hyperplasia), and incidences in all treated groups within the background range (1.42–26%) for this tumor in this strain and age of mice. Also, lung tumors were not seen when tested at a comparable dose (1000 mg/kg/day) or at considerably higher doses (4116–4945 mg/kg/day) in this strain of mice in the other three studies (MRID Nos. 00251007; 49631702; Arysta, 1997b).

(iii) Lymphoma/Lymphosarcomas

There was a dose-dependent and statistically significant increase in the incidence of malignant lymphomas in male mice (Nufarm, 2009b). The incidence was: 0/51 (0%; trend P=0.006633), 1/51 (2%), 2/51 (4%) and 5/51 (10%; P=0.02820) at the 0, 85, 267 or 946 mg/kg/day groups, respectively. The CARC determined that this increase is not treatment-related since the incidences in the concurrent controls (0%) were not representative of the normal background incidences noted in the historical controls (mean, 4.5%; range, 1.5% to 21.7%), and the apparent statistical significance of the pairwise comparison of the high dose group with the concurrent control might have been attributable to this factor rather than an actual carcinogenic response. Also, this neoplasm was not seen in other studies in this strain of mice. For example, in the study by Knezevich and Hogan 1983 (MRID No. 00251007), there was no significant difference in the incidence of lymphomas between control and high-dose groups (P=1.00 for males, P=0.12 for females). In the study by Atkinson *et al.* (1993) (MRID No. 496317), the incidence values in "lymphoreticular/ hematopoietic tissue" were not significantly different between control and high-dose groups (males: 4 in controls, 6 in high-dose group; females: 14 in controls, 13 in high-dose group). In the Arysta 1997 study (Greim *et al.*, 2015), the incidence of lymphoma in males was 2/50, 2/50, 0/51, 6/50 in the control, low, mid and high dose groups, respectively. There were no statistically significant pairwise differences observed in any of these studies.

(iv) Hemangioscarcomas

Hemangiosarcomas were seen in multiple organs including, liver, spleen, and prostate in males and liver and uterus in female CD-1 mice (MRID No. 49631702). There was a positive trend (P=0.00296) in the incidence of hemangiosarcomas in male mice: 0/47 (0%), 0/46 (0%), 0/50 (0%) and 4/45 (9%) at the 0, 100, 300 and 1000 mg/kg/day groups, respectively. The hemangiosarcomas were present in the liver, spleen or prostate in the high dose males. In females, this neoplasm was seen in one female at the low dose (uterus) and in one high dose (spleen). The CARC did not consider the hemangiosarcomas in males to be treatment-related based on the following considerations: 1) there was no pairwise significance; 2) lack of dose-response; 3) the incidence was near the upper limit (0–8%) of the background rate at the performing laboratory; 4) hemangiosarcomas are commonly observed in mice as spontaneous tumors and are generally more common in males in CD-1 strain mice; 5) there was not a significant increase in hemangiosarcomas seen in the other three mouse studies; and 6) if really treatment-related, it is unlikely that the same tumor would not have been detected at higher incidences in CD-1 mice with top doses >1000-4000 mg/kg/day.

In summary, dietary administration of glyphosate at doses ranging from 85 to 4945 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in male or female CD-1 mice.

C. Discussion

When determining the carcinogenic potential of chemicals, the IARC identifies a cancer "hazard" if an agent (*e.g.*, chemical) is capable of causing cancer under some circumstance and the agent is termed "carcinogenic" if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The IARC also considers that there is "*sufficient evidence of carcinogenicity"* based on the occurrence of increased tumors (benign, malignant, or combination) in: 1) two or more species of animals; 2) two or more independent studies in one species; and/or 3) an increased incidence of tumors in both sexes of a single species. Furthermore, a single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumor or age at onset, or when there are strong findings of tumors at multiple sites (IARC Preamble, 2006).

In March 2015, the IARC evaluated the carcinogenic potential of glyphosate. The IARC determined that there was a positive trend in the incidence of a rare tumor type, renal tubular carcinoma and renal tubule adenoma or carcinoma (combined) in males in one feeding study in CD-1 mice. A second study reported a positive trend for hemangiosarcomas in male CD-1 mice. Thus, in accordance with one of the preamble criteria, "the occurrence of tumors in two studies in one species," IARC determined that there is "sufficient evidence" in experimental animals for the carcinogenicity of glyphosate (IARC, 2015).

In contrast, the USEPA's carcinogenicity classification is based on weight-of-evidence considerations in accordance with the agency's 2005 Guidelines for Carcinogen Risk Assessment. The cancer guideline emphasizes the importance of weighing all of the evidence in reaching conclusions about the human carcinogenic potential of agents. This evaluation is accomplished in a single integrative step after assessing all of the individual lines of evidence. Evidence considered includes tumor findings, or lack thereof, in humans and laboratory animals; an agent's chemical and physical properties; its structure-activity relationships (SARs) as compared with other carcinogenic agents; and studies addressing potential carcinogenic processes and mode(s) of action, either *in vivo* or *in vitro*. Data from epidemiological studies are generally preferred for characterizing human cancer hazard and risk. However, all of the information discussed above could provide valuable insight into the possible mode(s) of action and likelihood of human cancer hazard and risk (USEPA, 2005).

Conclusions for evidence of carcinogenicity are based on the combined strength and coherence of inferences appropriately drawn from all of the available information. The following observations add significance to the tumor findings: tumors in multiple species, strains, or both sexes; dose-related increases; progression of lesions from pre-neoplastic to benign to malignant; proportion of malignant tumors; reduced latency of neoplastic lesions; and both biological and statistical significance of the findings (USEPA, 2005).

The IARC attributed the kidney tumors observed in male CD-1 mice at the high dose in the feeding study (MRID No. 00251007) to treatment since they are rare and there was borderline significance in trend test (P=0.034 for carcinoma and P=0.037 for combined adenoma or carcinoma) in a Cochran-Armitage trend test. However, as shown in Table 14, the agency's statistical analyses did not show a significant trend for either carcinoma (P=0.06345) or the combined adenoma or carcinoma (P=0.06483). In a Fisher's exact test, when compared to the concurrent control, there was no pairwise significance for any tumor type (adenoma, carcinoma, or combined). There were no pre-neoplastic renal tubular lesions such as tubular necrosis/ regeneration, hyperplasia or hypertrophy, despite a high dose level (4945 mg/kg/day) that was approximately 5-fold higher than the limit dose (1000 mg/kg/day) recommended by the agency's guidelines. Examination of multiple sections of kidneys from all animals by more than one pathologist did not result in any additional neoplasms. Although the highest dose tested (4945 mg/kg/day) was approximately 5-fold higher than the limit dose (1000 mg/kg/day) recommended by the agency's guideline, the incidence of the kidney tumors was minimal (1/50 adenomas and 2/50 carcinomas) compared to controls (1/49 adenomas). An evaluation by the PWG concluded that the renal tumors are not treatment-related since there were no compound related nephrotoxic lesions, including pre-neoplastic changes, multiple tumors were not found in any animals, and there was no evidence of a significant linear trend at the 0.5 level in a one-tailed Cochran-Armitage test or pairwise significance in a Fisher's exact test. Furthermore, kidney tumors were not seen when tested at lower (85 to 1000 mg/kg/day) doses or at a comparable (4116 mg/kg/day) dose in this strain of mice in the other three studies. Thus, the totality of data available from 4 carcinogenicity studies provides a strong support for the conclusion that the kidney tumors seen in one study is not the result of a carcinogenic response to glyphosate.

The IARC attributed the hemangiosarcomas observed in male CD-1 mice at the high dose in separate feeding study (MRID No. 49631702) to treatment due to the positive trend (P<0.001) in a Cochran-Armitage trend test. As shown in Table 16, the agency's statistical analyses also showed a positive trend (P=0.00296) in the trend test. In the Fisher's exact test, there was no pairwise significance when compared to controls. In contrast with the IARC, the CARC did not consider the hemangiosarcomas to be treatment-related based on the following weight-of-evidence considerations: 1) there was no pairwise significance; 2) lack of dose-response; 3) the incidence was near the upper limit (0–8%) of the background rate at the performing laboratory; 4) hemangiosarcomas are commonly observed as spontaneous tumors in male CD-1 strain mice; and 5) hemangiosarcomas were not seen when tested at comparable doses (946–1467 mg/kg/day) or at considerably higher doses (4116–4945 mg/kg/day) in this strain of mice in the other studies (MRID No.00251007, Arysta, 1997b, Nufarm, 2009b). It is noted that JMPR in their evaluation also concluded that the hemangiosarcomas are not treatment-related owing to lack of dose-response relationship, lack of statistical significance and incidences within the historical control range (JMPR, 2004).

Hemangiosarcomas have similar histopathological features in rodents and humans but differ in both incidence and tissue site. In human populations, hemangiosarcomas have an incidence rate of approximately 0.2 new cases/100,000 people (0.0002%) (1996–2000, US National Cancer Institute–SEER Database) and account for <1% of all human sarcomas. The historical background incidence of hemangiosarcomas in B6C3F1 and CD-1 mice relative to the incidence rate in humans has thus been estimated to be approximately 10,000-fold higher than in people (Pegg *et al.,* 2012). The most common sites for spontaneous hemangiosarcomas in rodents are liver, spleen, bone marrow, and to a lesser extent in lymph nodes and skin (see references in Pegg *et al.* (2012). In male mice, liver and spleen tend to be the most common sites. Human hemangiosarcoma is most commonly reported in skin (Weiss *et al.*, 2001). Primary liver hemangiosarcoma in humans has been linked to chemical exposure, notably thorotrast and vinyl chloride, which are both considered genotoxic carcinogens. There are several examples of induction of hemangiosarcomas by non-genotoxic agents in mice, but no clear examples of hemangiosarcoma induction by non-genotoxic agents in human populations (Cohen *et al.,* 2009). Several studies have looked at potential mode of action (MOA) for these tumors in mice in response to various drugs or chemicals. These MOAs generally relate to hypoxia or vascular toxicity as early key events.

1. Mutagenicity

Glyphosate was not mutagenic in bacteria or mammalian cells *in vitro*. Additionally, glyphosate did not induce chromosomal aberrations *in vitro*. Although some studies in the open literature reported positive findings for micronuclei induction in rodents, these findings were not replicated in the majority of the rodent micronucleus assay studies. There is no convincing evidence that the DNA damage is a direct effect of glyphosate, but under some conditions may be secondary to cytotoxicity or oxidative damage. Furthermore, the chemical structure of glyphosate, with its absence of alkyl groups also provides SAR support for the lack of mutagenic/genotoxic potential.

IARC concluded that "there is strong evidence that exposure to glyphosate or glyphosate-based formulations is genotoxic"; however, the IARC analysis included studies that tested glyphosate-formulated products as well as studies where the test material was not well-characterized (*i.e.*, no purity information was provided). The CARC did not include such studies in their evaluation. The IARC analysis also focused on DNA damage as an endpoint (*e.g.*, comet assay); however, DNA damage is often reversible and can result from events that are secondary to toxicity (cytotoxicity), as opposed to permanent DNA changes which are detected in tests for mutations and chromosomal damage (*e.g.* chromosomal aberrations or micronuclei induction). The studies that IARC cited, where positive findings were reported for chromosomal damage, had study limitations confounding the interpretation of the results. In addition, these positive findings were not reproduced in other guideline or guideline-like studies evaluating the same endpoints. This includes many negative studies cited by Kier and Kirkland (2013) that were considered by CARC, but were not included in the IARC decision.

2. Structure Activity Relationship

Sulfosate (the trimethylsulfonium salt of glyphosate) is classified as a Group E Chemical: "Not Likely to be Carcinogenic to Humans," based on the lack of evidence of carcinogenicity in mice and rats in two acceptable studies, and absence of mutagenicity concern.

VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the 2005 Guidelines for Carcinogen Risk Assessment, glyphosate is classified as "Not Likely to be Carcinogenic to Humans." This classification is based on the following weight-of-evidence considerations:

- The epidemiological evidence at this time does not support a causal relationship between glyphosate exposure and solid tumors. There is also no evidence to support a causal relationship between glyphosate exposure and the following non-solid tumors: leukemia, multiple myeloma, or Hodgkin lymphoma. The epidemiological evidence at this time is inconclusive for a causal or clear associative relationship between glyphosate and NHL. Multiple case-control studies and one prospective cohort study found no association; whereas, results from a small number of case-control studies (mostly in Sweden) did suggest an association. Limitations for most of these studies include small sample size, limited power, risk ratios with large confidence intervals, and recall bias as well as missing data. The literature will continue to be monitored for studies related to glyphosate and risk of NHL.

- In experimental animals, there is no evidence for carcinogenicity. Dietary administration of glyphosate at doses ranging from 3.0 to 1500 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in seven separate studies with male or female Sprague-Dawley or Wistar rats. Similarly, dietary administration of glyphosate at

doses ranging from 85 to 4945 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in four separate studies with male or female CD-1 mice. The CARC did not consider any of the observed tumors in 11 carcinogenicity studies in rats and mice to be treatment-related since the observed tumors did not exhibit a clear dose-response relationship, were not supported pre-neoplastic changes (*e.g.*, foci, hypertrophy, and hyperplasia), were not statistically significant on pairwise statistical analysis, and/or were within the range of the historical control data.

- Based on a weight of evidence approach from a wide range of assays both *in vitro* and *in vivo* including endpoints for gene mutation, chromosomal damage, DNA damage and repair, there is no *in vivo* genotoxic or mutagenic concern for glyphosate.

VII. QUANTIFICATION OF CARCINOGENIC POTENTIAL

Not required.

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