Message

**From:** HEYDENS, WILLIAM F [AG/1000] [/o=Monsanto/ou=NA-1000-01/cn=Recipients/cn=230737]
on behalf of HEYDENS, WILLIAM F [AG/1000]
**Sent:** 1/13/2016 11:26:42 PM
**To:** 'Ashley Roberts Intertek' [REDACTED]@intertek.com]
**Subject:** RE: Summary report
**Attachments:** Combined Manuscript DRAFT JAN 11 2016 (3) wfh review.docx

Hi Ashley,

Here are my suggested edits to the Draft Combined Manuscript. Most of my edits were made in Section 3.1 (Exposures to Glyphosate), as it read like a repeat of the entire Results section from Keith's Exposure paper/chapter, including table/graph replication as also noted in John Acquavella's email.

One thing I noted right off the bat was the order of tackling the 4 areas – 1) Exposure, 2) Animal, 3) Genetox/MOA, 4) Epid. This is different than IARC and different than what I thought we discussed, but I'm not opposed if you/others think this is the best overall flow.

Also, just FYI, it appears that your writer did not have the latest version of Keith's paper, as I found some differences which I confirmed with Marian Bleeke – I think I caught all the differences and made the changes in the Combined Manuscript as part of my editing. And I am going to thoroughly read the latest version of Keith's paper tomorrow; but now I am not inclined to suggest substantial re-writing (adding of text) because I don't want to slow progress down any more than necessary (my management would love to get all this off to CRT/Roger by very early February).

As an aside, I was struck by how similar the criticism of IARC in today's EFSA response to Portier was to points made by the expert panel – I think they are very closely meshed and complement each other nicely.

Anyway, let me know if you have any questions or concerns regarding my suggested edits.

Thanks much,

Bill

**From:** Ashley Roberts Intertek [mailto:a[REDACTED]@intertek.com]
**Sent:** Monday, January 11, 2016 12:35 PM
**To:** HEYDENS, WILLIAM F [AG/1000]
**Subject:** Summary report

Hi Bill,

Please find attached the summary report for your review.

If okay we will add in the references and have wordpro format properly.

Thanks

Ashley

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**From:** HEYDENS, WILLIAM F [AG/1000] [mailto:[REDACTED]@monsanto.com]
**Sent:** January-11-16 8:35 AM
**To:** Ashley Roberts Intertek
**Subject:** FW: Publication Plans

Ashley, this is the quick response I sent back to Larry Saturday. So far, I have not heard back from him.

**From:** HEYDENS, WILLIAM F [AG/1000]
**Sent:** Saturday, January 09, 2016 1:07 PM
**To:** Larry Kier
**Subject:** Re: Publication Plans

Hi Larry,

The current concept is 6 papers back to back in a single issue, possibly a stand alone supplement:
Introduction
Overall comprehensive summary
Epidemiology
Animal bioassays
Genotoxicity
Exposure

The order could change.

This is what Ashley and I thought would work best, and Roger McClellan seemed to agree in a preliminary conversation.

Do you see a problem with this?

Thanks
Bill

-------- Original Message --------
Subject: Publication Plans
From: Larry Kier <[redacted]@g.com>
Date: Jan 9, 2016, 8:15 AM
To: "HEYDENS, WILLIAM F [AG/1000]" <[redacted]@monsanto.com>

Bill,

One of our panelists inquired about the publication plans because they were told at the August meeting at Intertek that the panel report would be published as one paper with different sections and It now appears there will be separate papers.

Could you or Ashley please clarify the current publication plans?

Thanks.

Larry Kier

# Glyphosate: Carcinogenic Potential – the Conclusions of IARC (2015) – A Critical Review by an Expert Panel

Add all authors and affiliations

# 1 Introduction

Glyphosate, or N-(phosphonomethyl)glycine, is a colorless crystalline solid that is moderately soluble in water that is a widely used broad-spectrum, non-selective post-emergent herbicide. It effectively suppresses the growth of many species of trees, grasses, and weeds. Glyphosate works by interfering with the synthesis of the aromatic amino acids phenylalanine, tyrosine, and tryptophan, through the inhibition of the enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS). Inhibition of this enzyme results in accumulation of shikimate in plant tissues. This enzyme is not present in mammalian species. Glyphosate is extensively used in agriculture, especially in the post-emergent control of weeds in fields of corn, cereals, soybean, oilseed, and sugar beet. To further enhance the effectiveness of glyphosate in agriculture, a number of genetically modified crop varieties have been developed which are glyphosate tolerant (i.e., allows for application after emergence of the crops species). In addition, given its effectiveness and broad-spectrum activity, glyphosate is also used worldwide for household weed control.

The safety, including the potential carcinogenicity, of glyphosate has been extensively reviewed by many regulatory authorities worldwide, including the US EPA, the European Commission, and the Canadian Pest Management Regulatory Agency (Williams et al., 2000; Kier and Kirkland, 2013; WHO/FAO, 1994; US EPA 1993; Canadian Pest Management Regulatory Agency, [Doliner, 1991]; European Commission, 2001; US EPA, 2013). The consensus among these reviews was that proper use of glyphosate and glyphosate-based formulations (GBFs) does not pose a genotoxic or carcinogenic hazard/risk. As a result, glyphosate based herbicides have been approved for use in over 160 countries.

In 2015, IARC published the Glyphosate Monograph of Volume 112 (IARC, 2015). IARC (2015) categorized glyphosate as "*probably carcinogenic to humans*" (Group 2A) ~~on the basis~~ based on their conclusion of "*limited evidence*" of carcinogenicity in human, citing a positive association with non-Hodgkin's lymphoma, and of "*sufficient evidence*" of carcinogenicity in experimental animals. In addition, IARC (2015) stated that there was strong evidence supporting that "glyphosate can operate through two key characteristics of known human carcinogens" including genotoxicity and induction of oxidative stress. This was viewed as providing strong support for IARC classifying glyphosate as probably carcinogenic to humans, Group 2A.

The classification of glyphosate as *probably carcinogenic to humans* is controversial as it is not consistent with the views and opinions of regulatory bodies worldwide. These regulatory bodies, including the US FDA, EFSA, JECFA, and many others have reviewed all of the available scientific evidence, including the results of a plethora of epidemiology studies, numerous cancer bioassays in laboratory animal species, and an extensive array of genetic and mechanistic stud-

**Commented [wh1]:** I suggest deleting these words, as it makes the sentence a little awkward ("that is that is") and they aren't needed for the points you are making. FYI in its salt form, which it exists in formulations and use solutions, it is highly water soluble.

**Commented [wh2]:** This seems redundant given the list of agencies mentioned 2 paragraphs up. Why not say "including those mentioned above and many others"

**Commented [wh3]:** I don't think we should say that. So far, only EFSA has gone back and taken a look at all the MoA studies that IARC used.

ies, including data both reported in the published literature as well as the results of GLP- and OCED/Redbook-compliant animal studies conducted by ~~Monsan-to~~several companies as part of the normal series of studies conducted to support registration of an agricultural herbicide product.

Given that the IARC conclusion is inconsistent with the conclusions reached by worldwide regulatory authorities, as well as of other independent scientists, and noting that the IARC classification is solely based on "hazard" without acknowledgement of exposure, and hence risk, an Expert Panel was convened to assess the available data on glyphosate with respect to exposures, results of carcinogenicity studies conducted in experimental animals, the available genetic toxicity and mechanistic data, and the body of epidemiological studies conducted to date. These broad areas of research were evaluated in relation to the opinions reached by IARC (2015). The Expert Panel was composed of individuals with documented expertise in the 4 broad areas of interest with respect to the carcinogenic potential of glyphosate. Presented herein are the results of the deliberations of the Expert Panel and a summary of their conclusions. For each of the 4 areas of research (exposure, animal cancer bioassays, genetic toxicity, and epidemiology) the data evaluated, and the method of evaluation, are outlined in the Methods Section below.

**Commented [wh4]:** OECD?

**Commented [wh5]:** While this is true to a degree, we have tried to steer away from such wording because it infers that IARC found a hazard when they in fact did not. Could we say something like "and noting that the IARC classification ignores the important role exposure plays in a proper overall risk assessment "

**Commented [wh6]:** Is re a reason why this order was used here and throughout the document? – 1) Exposure, 2) Animal Studies, 3) Genetox/MOA, 4) Epidemiology. IARC orders the sections differently, and I thought Ashley and I discussed doing even a different order. But I am OK with what you have here if you think it flows better this way.

**Commented [wh7]:** Same comment as above

# 2 Methods

## 2.1 Assessment of Exposure

Unpublished reports of studies on exposure to glyphosate in applicators were provided by Monsanto Company ~~and~~ which covered uses in agriculture and forestry. Other data on exposures were obtained from the open literature as a result of searches in PubMed ®, references in reviews, and Google Scholar®. These papers and reports were grouped into sources of exposures and the data analyzed as described below.

Only one paper reported concentrations of glyphosate in air. In a study conducted in Iowa, Mississippi, and Indiana in 2007 and 2008, concentrations of glyphosate and its major environmental degradate, aminomethylphosphonic acid (AMPA), were measured in air and precipitation (Chang et al. 2011). For estimation of human exposure, it was assumed that there was total absorption of glyphosate from the air into the body of a 70 kg human breathing 8 $m^3$ air (half a day for an adult, USEPA 2009). Also, surface water measurements made for glyphosate as part of the NAWQA program (USGS 2015) since 2002 were downloaded from the NAWQA data warehouse and then sorted by concentration. All values measured across the US between 2002 and 2014 were pooled for the analysis. Where concentrations were less than the level of detection (0.02 µg glyphosate a.e./L), these values were substituted with a dummy value of "zero". The estimated concentrations are thus a worst-case.

Studies documenting exposures through food and to "bystanders" were reviewed and data extracted (Curwin et al., 2007~~; Acquavella et al. 2004~~; Mesnage et al., 2012; Hoppe et al., 2013; Honeycutt and Rowlands, 2014; Niemann et al. 2015). For those~~,~~ publications that provided actual systemic dose calculations, these values were used, rather than estimates calculated from the default of default exposure factors (*e.g.*, body weight, water consumption, breathing rate, *etc.*). Where the systemic dose was calculated, it was used. Where dietary exposures were calculated the urinary concentration was used to calculate the systemic dose on the assumption of 2 L of urine per day and a 60 kg person (Niemann et al. 2015). In addition, in 2011, the JMPR reviewed dietary exposures to glyphosate (glyphosate, N-acetyl glyphosate, aminomethylphosphonic acid (AMPA) and N-acetyl AMPA) and calculated the international estimated daily intakes (IEDI) of glyphosate for 13 regional food diets, based on estimated mean residues from supervised agricultural trials conducted under normal or good agricultural practice.

A relatively large number of studies on exposures of applicators to glyphosate have been conducted (121 dosimetry studies and 128 biomonitoring studies).

For studies using dosimetry, the normalization to systemic dose was conducted using the following assumptions: 70 kg adult, 2.1 $m^2$ surface area for a 70 kg male (USEPA 2009), 10% penetration through clothing if not actually measured, 3% dermal penetration. ~~procedure outlined in **Table 1.**~~ The estimated systemic doses were ranked from smallest to largest and a cumulative frequency distribution derived. These values were plotted on a log-probability scale ~~as above~~. The median (50$^{th}$ centile) and 90$^{th}$ centile values were calculated from the raw data using the Excel function <=percentile>.

~~**Table 1. Procedure for normalization of dosimetry data to estimate systemic dose.**~~

| ~~**Step**~~ | ~~**From**~~ | | ~~**To**~~ | ~~**Explanation**~~ |
|---|---|---|---|---|
| ~~1~~ | ~~Total residue on patches µg/cm$^2$)~~ | ~~to~~ | ~~Potential body exposure (µg)~~ | ~~2.1 m$^2$ surface area for a 70 kg male (USEPA 2000)~~ |
| ~~2~~ | ~~Potential body exposure (µg)~~ | ~~to~~ | ~~Actual body exposure (µg)~~ | ~~Measured penetration through clothing or default of 10%~~ |
| ~~3~~ | ~~Actual body exposure (µg)~~ | ~~to~~ | ~~Systemic body exposure (µg)~~ | ~~3% dermal penetration.~~ |
| ~~4~~ | ~~Systemic body exposure (µg)~~ | ~~to~~ | ~~Systemic dose (mg/kg b.w./day)~~ | ~~70 kg adult.~~ |

Where an applicator makes a single application, the systemic dose of glyphosate can be estimated from the total amount of glyphosate excreted in the urine over the four or five days following and including the day of application (Acquavella et al. 2004). If applications are conducted every day, the amount excreted each day provides a time-weighted average for daily exposures. Because glyphosate is applied infrequently in normal agricultural practice, the assumption of a single initial exposure is considered appropriate for risk assessment purposes.

**Commented [wh8]:** Note: Acquavella was dropped ina later version from Keith

**Commented [wh9]:** Is this really what you meant to say?

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**Commented [wh10]:** Log-probability scale was not mentioned above

## 2.2 Assessment of Animal Bioassays

The recommended method for evaluating the results of ~~extensive~~ an extensive database of toxicology and carcinogenicity bioassays as exist for glyphosate involves the application of a weight-of-evidence (WOE) approach. A methodology for using WOE approaches has been identified and developed by the U. S. Environmental Protection Agency (Suter and Cormier 2011) and although not universally approved the approach has widespread acceptance. Such an approach requires that all reliable information from whatever source should be evaluated in making a judgement. However, quality of the data/information must be scrutinized. It therefore follows that in reviewing data on compounds that have been tested over many years, a careful examination of the precise nature of the studies reviewed must be made lest they fail to satisfy current standards of reliability. In any review, if certain studies are to be ignored, the reasons for this should be provided. The incidences of the tumors in the various studies were assessed with respect to dose-response, rate of occurrence relative to known spontaneous rates in control animals, and on the basis of biological plausibility.

## 2.3 Assessment of Genetic Toxicity

It is expected that a chemical as extensively tested as glyphosate exhibit some positive responses in its genotoxicity database that would be considered "misleading" and therefore not predictive of its true genotoxic or carcinogenic hazard/risk potential. The universally recommended method for evaluating the databases of the type associated with glyphosate (including glyphosate-based formulations (GBFs) and AMPA), involves the application of a weight-of-evidence (WOE) approach as discussed recently for genetic toxicology testing (US FDA, 2006; Dearfield et al, 2011). One of the most important requirements is that individual test methods should be assigned a weight that is consistent with their contribution to the overall evidence, and different types of evidence or evidence categories must be weighted before they are combined into a WOE.

**Commented [wh11]:** First time used

The weight of a category of evidence used in the Expert Panel evaluation is based on four considerations: (1) Different categories of evidence (i.e., assay types) have different weights, (2) The aggregate strength (robustness of protocols and reproducibility) and quality of evidence in the category also influence the weight (Klimisch et al, 1997), (3) The number of pieces of evidence within a category influences the weight, and (4) Tests with greater ability to extrapolate results to humans carry greater weigh (*e.g.*, test with non-human/mutated cell lines vs human donor derived cells).

Publications in which glyphosate or GBF's have been tested for genotoxicity in a variety of non-mammalian species other than bacterial reverse mutation appear

to be included in the IARC review, with only a few regulatory or published studies not included. Many of these studies used non-standard species (e.g., fish) and exposure protocols (e.g., inclusion of surfactants). As a consequence, the Expert Panel did not consider data from a majority of the non-mammalian systems and non-standard tests with glyphosate, GBF and AMPA to have significant weight in the overall genotoxicity evaluation, especially given the large number of standard core studies in the gene mutation and chromosomal effects categories available in mammalian systems. Rationale supporting this consideration is the absence of internationally accepted guidelines for such non-mammalian test systems, lack of databases of acceptable negative control data or positive control responses, and no results from validation studies suggesting concordance with carcinogenicity. OECD guidelines specifically state that use of any non-standard test requires justification along with stringent validation including establishing robust historical negative and positive control databases (OECD, 2014, Guidance Document for Describing Non-Guideline in Vitro Test Methods Series on Testing and Assessment No. 211).

**Commented [wh12]:** I don't understand why this phrase is here – you wouldn't expect regulatory studies because regulations don't call for non-mammalian species

The above considerations were applied in the WOE assessment of the genotoxic potential of glyphosate.

## 2.4 Assessment of Epidemiological Data

The approach taken to evaluate the epidemiology data with respect to glyphosate exposure and non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) was consistent with the PRISMA guidelines for systematic reviews (Moher et al., 2009), standard approaches to critically evaluating epidemiologic studies (Aschengrau and Seage, 2003) and well-recognized interpretative methods—e.g. the criteria-based methods of causal inference (Hill, 1965; Hill, 1971)—sometimes referred to as "weight of evidence" methods (Weed, 2005). With this approach in mind, the following questions were addressed:

1. Does the current published epidemiologic evidence establish a causal relationship between glyphosate exposure and NHL?
2. Does the current published epidemiologic evidence establish a causal relationship between glyphosate exposure and MM?

A systematic search of the medical literature was performed to identify all analytic epidemiological studies that have examined the possible relationships between exposure to glyphosate and NHL and MM. After removal of duplicates and examining the titles and abstracts, 11 publications were identified as relevant. Reasons for exclusions include: not analytical epidemiology, glyphosate not examined, and NHL and/or MM not examined. An additional 5 relevant analytic epidemiological studies were identified after examining reference lists from the initial 11 publications. Data collected included the following: first author, year of publication, study design, number of cases and controls (for case-control studies), number of participants in cohort studies, results (typically in terms of an estimate

of the relative risk (RR), e.g. an odds ratio (OR) with accompanying 95% confidence interval (95% CI)), exposure-response (if available, variables adjusted for in the analyses, and outcome (e.g. NHL, MM).

Each study was evaluated by the Expert Panel for the following key features that relate to study validity, including: recall bias (likely/unlikely), exposure misclassification (likely/unlikely), exposure-response analyses with a trend test (yes/no), selection bias (likely/unlikely), adjustment for confounding by other (non-glyphosate) pesticides (yes/no), adjustment for confounding from other variables, pathological review of cases (yes/no), proxy respondents (%cases/%controls), bias from sparse data (possible/no), blinding of interviews (yes/no/unclear),and consideration of induction/latency (yes/no).

# 3 Results

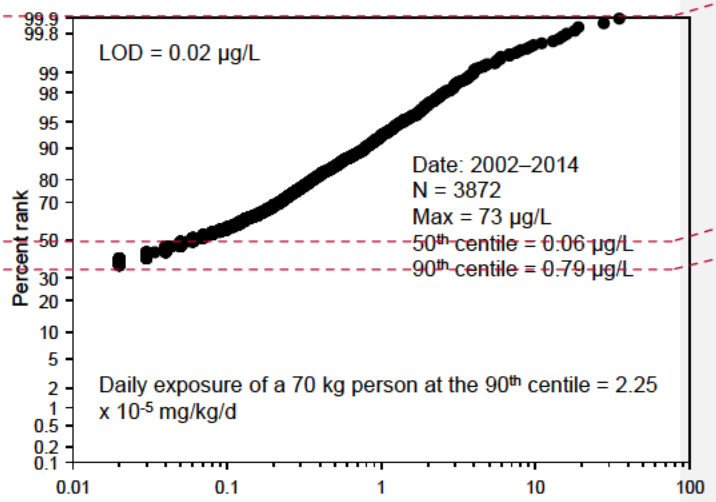
## 3.1 Exposures to Glyphosate

### 3.1.1 Air

Based on the above assumptions, inhaling glyphosate in air at the maximum measured concentration would result in an exposure of 1.04 x $10^{-6}$ mg/kg b.m./d. This is about 6-orders of magnitude less than the current USEPA's reference dose (RfD) of 1.75 mg/kg b.m./d.

### 3.1.2 Water

~~The cumulative frequency distribution of concentrations of glyphosate measured in surface waters of the US are shown in Figure 1. The 50th centile concentration was 0.06 µg/L and the 90th centile was 0.79 µg/L. The maximum concentration measured was 73 µg/L. Consumption of~~




Concentrations of glyphosate measured in surface waters of the US (µg/L) between 2002 and 2014

**Figure 1. Distribution of concentrations of glyphosate measured in surface waters across the US.**

**Commented [wh13]:** NOTE: Based on conversation with Marian Bleeke who has been working with Keith S., I believe Keith has modified his Exposure section after the version used by Intertek

**Commented [wh14]:** t looks to me like the entire Results section from Keith's Exposure paper is repeated here, minus the new Figure 3. I think we should scale back here. I suggest eliminating Figures 1 and 2 and Table 2; then just handle key points with brief text. For example, in section 3.1 2, something like: "The concentrations of glyphosate measured in US surface waters ranged from X to 73 ug/L. The 90th centile value was 0.79 ug/L, which corresponds to a systemic dose of 2.25 x 10-5 mg/kg/day (approximately 5-orders of magnitude under the US EPA's RfD)."

**Commented [wh15]:** Can we do a global change in units to "mg/kg/day" to be consistent with how they appear in other sections of the documents

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~~2 L of drinking water by a 70 kg person at the 90th centile concentration is estimated to result in a systemic dose of 2.25 x $10^{-5}$ mg/kg b.m./d. This is about 5-orders of magnitude less than the USEPA's RfD.~~ "The concentrations of glyphosate measured in US surface waters ranged from 0.02 to 73 ug/L. The 90th centile value was 0.79 ug/L, which corresponds to a systemic dose of 2.25 x 10-5 mg/kg/day (approximately 5-orders of magnitude under the US EPA's RfD).

### 3.1.3 Food and bystanders

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~~3.1.3~~ Estimates of glyphosate exposures to bystanders and the general public have been reported by various investigators (Curwin et al., 2007; Mesnage et al., 2012; Hoppe, 2013; Markard, 2014; Kruger et al., 2014; Honeycutt and Rowlands, 2014). In these studies, the range for estimates of systemic doses was 0.000022-00063 mg/kg/day. All of these estimates are at least 3 orders of magnitude less than the US EPA's RfD.

Commented [wh16]: Per my comment 14 above, text in this section could be something like this

~~Estimates of the systemic dose resulting from exposures of bystanders and the general public to glyphosate are shown in **Table 2.**~~

~~**Table 2. Summary of glyphosate exposures of bystanders and the general public.**~~

| ~~Study~~ | ~~Source of exposure~~ | ~~Systemic dose (mg/kg b.m./d)~~ | ~~Comment~~ |
|---|---|---|---|
| ~~(Acquavella et al. 2004)~~ | ~~Child bystanders and or food and water~~ | ~~Only one value >LOD in children who did not participate in application.~~ | ~~Not calculated because the body mass was not available for children.~~ |
| ~~(Curwin et al. 2007)~~ | ~~Bystanders from farm and non-farm households in Iowa, mixed sources~~ | ~~0.0001~~ | ~~Greatest mean~~ |
| ~~(Mesnage et al. 2012)~~ | ~~Farm family of five, mixed sources~~ | ~~0.00033~~ | ~~Mean~~ |
| ~~(Hoppe 2013)~~ | ~~Presumably from food and water~~ | ~~0.000066~~ | ~~Maximum estimated from urinary concentration, two L of urine and a body mass of 60 k~~ |
| ~~(Markard 2014)~~ | ~~Food and water~~ | ~~0.000022~~ | |
| ~~(Krüger et al. 2014)~~ | ~~Presumably from food and water~~ | ~~0.00016~~ | |
| ~~(Honeycutt and Rowlands 2014)~~ | ~~Presumably from food and water~~ | ~~0.00066~~ | |

~~All of these systemic doses (**Table 2**) are three or more orders of magnitude less than the USEPA's RfD. Based on the estimates of daily intake from the FAO, the mean systemic dose would be 0 to 0.02 mg/kg b.m./d. This conservative assumption is almost two orders of magnitude less than the USEPA's RfD.~~

### ~~3.1.4~~3.1.4 Applicators

~~For the applicator studies, the corrections were applied as in Table 1 and the results are presented graphically in Figure 2.~~

~~The range of values for systemic doses measured in the dosimeter studies was greater than in the biomonitoring studies. Given the corrections applied to the data, this is surprising; however, there are a number of assumptions used in the normalization of the systemic doses that might result in overestimation of exposure. These are likely related to the amount of absorption though the skin and the penetration of clothing. The assumption of 3% penetration through the skin is greater than the value of 2% estimated in (Acquavella et al. 2004) or the 0.7% suggested from observations in an in vitro model with human skin (Bo Nielsen et al. 2009).~~ The 50th and 90th centiles in the dosimetry studies were 0.0015 and 0.064 mg/kg~~/ b.m./~~day, respectively. Neither of these values is particularly large when compared to the current USEPA's RfD of 1.75 mg/kg ~~b.m./~~day.

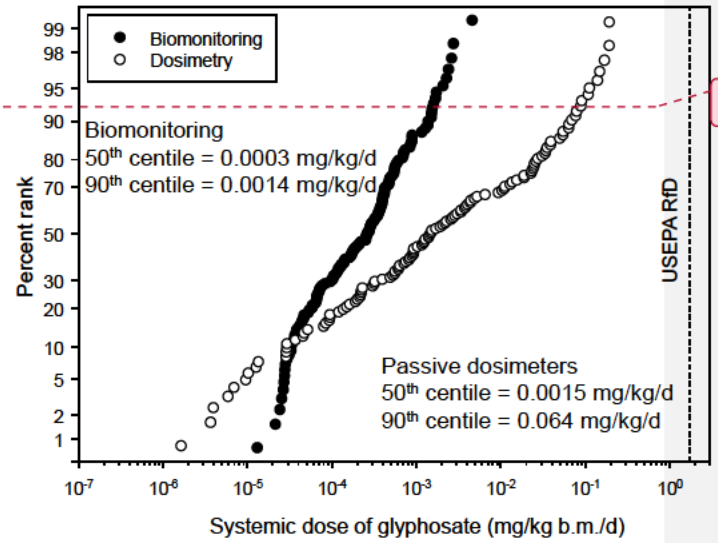


**Figure 2. Systemic doses of glyphosate measured in exposure studies conducted in applicators.**

The range of values for the systemic doses determined by biomonitoring was smaller than for the passive dosimeters and more accurately reflects the true exposures. The 50th and 90th centiles were 0.0003 and 0.0014 mg/kg~~/ b.m./~~day, respectively. These are several orders of magnitude less than the USEPA's RfD.

In summary, there is a robust dataset on glyphosate exposures to humans. Even when using various unrealistic/worst-case assumptions, systemic exposures to applicators, bystanders and the general public are very small. Based on current RfDs and measured exposures, there is no hazard from exposure to glyphosate via normal uses.

## 3.2 Cancer Bioassays

**Commented [wh17]:** Table 1, not 11

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In the Monograph, IARC concluded that there is ***sufficient evidence in experimental animals*** for the carcinogenicity of glyphosate;, IARC concluded that glyphosate induced:;

a) a positive trend in the incidence of a rare neoplasm, renal tubule carcinoma in male CD-1 mice only;

b) a significant positive trend for the incidence of haemangiosarcoma in male mice in a different study;

c) in two studies, a significantly increased incidence of pancreatic islet-cell neoplasia in male SD rats, and,

d) ~~in one of two studies,~~ a significant positive trend in the incidences of hepatocellular neoplasia in male S-D rats and of thyroid C-cell neoplasia in female SD rats.

The Expert Panel considered each of these conclusions.

In regards to the renal tubular tumors in male CD-1 mice, The Expert Panel noted that the conclusions of the IARC were based on only two 2-year oral mouse carcinogenicity studies, (Monsanto 1983 [Knezevich and Hogan 1983]; Cheminova 1993a [Atkinson et al. 1993] excluding 2 additional 18-month oral studies in CD-1 mice (Arysta Life Sciences 1997; Nufarm 2009) and one 18-month oral study in Swiss Albino mice (Feinchemie Schwebda 2001). All of the studies were considered by authoritative bodies to have met the guidelines for a carcinogenicity bioassay in mice (ICH 1997; U. S. Environmental Protection Agency 1990).

In the one ~~of two~~ studies considered by IARC (2015) to show evidence of renal tubular development associated with glyphosate treatment (Monsanto, 1983), the overall final incidence of renal neoplasms in male mice was as follows: 1/49, 0/49, 1/50, and 3/50. The important non-neoplastic renal findings of hyperplasia, were as follows: 3/49, 0/49, 4/50, and 2/50, indicating lack of a dose-response, with the highest incidence in the MD group, followed by the control group, and the HD group. The LD group had no renal findings. It is informative to apply to the study by Monsanto (1983) [Knezevich and Hogan 1983] a modified form of the Hill viewpoints, covering 8 of the 9 criteria of causation (Hill 1965; Woodside and Davis 2013) in order to determine whether an association between exposure and effect (two variables) might be deemed strong, consistent, specific, temporal, plausible, coherent, and to demonstrate a dose-response pattern. Several conclusions can be drawn, including:

1. The association is not strong, since the higher incidences of rare renal neoplasms in dosed groups are not considered to be statistically different from the control group.

**Commented [wh18]:** As written, it could be construed to mean there were kidney findings in 2 studies

2. The association is not consistent, since 4 out of 5 mouse studies did not reproduce similar renal neoplasms at comparable doses.
3. The association is not specific, since females of this pivotal study, which have been exposed to higher levels of glyphosate did not develop renal neoplasms. Also, there were no renal findings in the LD group, whereas the control group had two.
4. The time required between exposure and effect, i.e., a reduced latency time was not present; all tumors were observed only at termination.
5. The biological gradient of association or the dose-response curve was absent, since the females and the males in the LD group had no neoplasms, whereas there was one in the control group.
6. A plausible explanation for the association was absent, since the mode of action for induction of these renal neoplasms was not established.
7. Coherence of the association was also absent, as female mice and male and female rats did not display kidney effects. Also in the other 4 mouse carcinogenicity studies the mice did not develop similar neoplastic renal lesions.
8. The association does not demonstrate a dose-response pattern (see #5, 6), since the "in-study" females had neither neoplasms nor any of the other renal lesions, although they were exposed to higher levels of glyphosate. Consequently, under the conditions of this assessment, the renal neoplastic effects are not associated with glyphosate exposure. This conclusion is in agreement with that of Williams et al. (2000) and Greim et al. (2015).

With respect to haemangiosarcoma in male mice, in the CD-1 mouse study ~~in CD-1 mice~~ reported by Cheminova 1993b [Atkinson et al. 1993] (1993)], there were no statistically significant increases in the incidence of any tumors when compared with the control groups and no dose response was evident. IARC, based on their own statistical analysis (no reason was given for the choice of method) indicated/reported that there was an increase in the incidence of haemangiosarcoma in males [P < 0.001, Cochran-Armitage trend test] (**Table 3**). In addition, IARC (2015) did not comment on the lack of renal tumors in this mouse study.

**Table 3 Tumor Incidence/number of animals examined (mg/kg bw/day)***

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| | **0** | **100** | **300** | **1000** | **0** | **100** | **300** | **1000** |
| Haemangiosacromas | 0/50 | 0/50 | 0/50 | 4/50 (8%) | 0/50 | 2/50 (4%) | 0/50 | 1/50 (2%) |

* Taken from Greim, et al. 2015

If the likelihood of the occurrence of haemangiosarcoma is considered in terms of the viewpoints of Bradford Hill, it is clear that there is no strength in the association. For example, pairwise comparisons are not significant, there is no consistency (some mouse studies show no tumours of this type at all), and a

dose/response effect is not seen (some high dose groups have a lower incidence than lower doses). In terms of plausibility, recent studies emphasise both the frequency and the distinctive cellular origins of haemangiosarcomas in mice (Kakiuchi-Kiyota et al. 2013; Liu et al. 2013).

Given the foregoing analysis, the Expert Panel concludes that there is no substantive evidence, based on the data available from the entire dataset, that glyphosate exposure results in increased incidence of haemangiosarcoma in mice.

The IARC Working Group (WG) indicated that there was *"…a significant positive trend in the incidences of hepatocellular adenoma in males..."* (IARC, 2015). This opinion was based on its interpretation of the Stout and Ruecker (1990) study as presented by the U. S. Environmental Protection Agency's Peer Review of Glyphosate (U. S. Environmental Protection Agency 1991a,b). (see **Table 4**)

The Stout and Ruecker study has been reviewed twice by the US Environmental Protection Agency (U. S. Environmental Protection Agency 1991a,b). The final interpretation of the U. S. Environmental Protection Agency Review committee was appropriate: "*Despite the slight dose-related increase in hepatocellular adenomas in males, this increase was not significant in the pair-wise comparison with controls and was within the historical control range. Furthermore, there was no progression from adenoma to carcinoma and incidences of hyperplasia were not compound-related. Therefore, the slight increased occurrence of hepatocellular adenomas in males is not considered compound-related*" (U. S. Environmental Protection Agency 1991b). As noted previously, the U. S. Environmental Protection Agency ultimately concluded that glyphosate should be classified as a Group E (evidence of non-carcinogenicity for humans) chemical (U. S. Environmental Protection Agency 1991a,b).

**Commented [wh19]:** I don't see where this was 'noted previously' in this document

| Table 4 Sprague-Dawley Male Rats, Hepatocellular Tumor Rates+ and Cochran-Armitage Trend and Fisher's Exact Tests Results (p values). | | | | |
|---|---|---|---|---|
| | Dose (ppm) | | | |
| Tumors | 0 | 2,000 | 8,000 | 20,000 |
| Carcinomas | 3/34 | 2/45 | 1/49 | 2/48[a] |
| (%) | (7) | (4) | (2) | (4) |
| p | 0.324 | 0.489 | 0.269 | 0.458 |
| | | | | |
| Adenomas | 2/44 | 2/45 | 3/49 | 7/48[b] |
| (%) | (5) | (4) | (6) | (15) |
| p | 0.016* | 0.683 | 0.551 | 0.101 |
| | | | | |
| Adenoma+Carcinoma | 5/44 | 4/45 | 4/49 | 9/48 |
| (%) | (11) | (9) | (8) | (19) |
| p | 0.073 | 0.486 | 0.431 | 0.245 |
| | | | | |
| Hyperplasia only | 0/44 | 0/45 | 1/49[c] | 0/48 |
| (%) | (0) | (0) | (2) | (0) |
| p | 0.462 | 1.000 | 0.527 | 1.000 |

source: EPA (1991a,b)

There are other aspects of the Stout and Ruecker data that support the conclusions that glyphosate did not exert oncogenic effect on the liver of SD rats. For example, chemically-induced rat hepatocellular carcinogenesis is a multiple stage process characterized by progressive functional, morphological and molecular changes that indicate or precede the full establishment of neoplasia, such as enzyme induction, hepatocyte hypertrophy, degeneration and necrosis, hepatocyte proliferation, altered hepatocellullar foci, etc. (Williams 1980; Bannasch et al. 2003; Maronpot et al. 2010; Shah et al. 2011). Identification and analyses of these liver changes – that span from adaptive to irreversible toxic effects – can help support characterization of key events along the carcinogenesis process and inform the mode of action of the tested chemical (Williams and Iatropoulos 2002; Holsapple et al. 2006; Carmichael et al. 2011). These changes were not apparent in this study.

In the last 30 years the systemic carcinogenic potential of glyphosate has been assessed in at least eight studies in Sprague-Dawley or Wistar rats (Greim et al., 2015); a ninth could not be evaluated because of a high mortality and the low dose used (Chruscielska et al., 2000a). Considered jointly, the animals were exposed through the diet to 24 different doses distributed across a wide range of 3.0 to 1,290.0 mg/kg b.w./day. In exposed males, the incidences of hepatocellular adenomas across the doses showed no dose-response relationship and varied within the same range as the controls. Similar rates were also seen for hepa-

tocellular carcinomas. These observations confirm the absence of carcinogenic potential of glyphosate on the rat liver.

With respect to the pancreatic islet cell tumors, oral and dermal application of glyphosate to mice did not induce pancreatic islet tumors (Greim et al. 2015; IARC 2015). In 2 of the 9 carcinogenicity studies in rats, evaluated by IARC, tumors of islet cells of the pancreas were diagnosed in both males and females. Both studies were made available to IARC by EPA (U.S. Environmental Protection Agency 1991a,b,c).

In the first study Sprague-Dawley, rats received 0, 2000, 8000, and 20,000 ppm glyphosate (96.5% purity) in the diet, fed ad libitum for 24 months. In males, ~~in the controls and the three doses (low to high)~~ the following pancreatic islet cell tumor incidences were observed in the controls and three dose groups (low to high): adenoma: 1/58 (2%), 8/57 (14%), 5/60 (8%), 7/59 (12%); carcinoma: 1/58 (25), 0/57, 0/60, 0/59. Corresponding incidence values in females were: 5/60 (8%), 1/60 (2%), 4/60 (7%), 0/59 and 0/60, 0/60, 0/60, 0/59. The historical control rates for pancreatic islet cell tumors at the testing laboratory were in the range 1.8-8.5%. The Expert Panel agrees with the conclusion of IARC that there is no statistically positive trend in the incidence of pancreatic tumors and no apparent progression to carcinoma.

**Commented [wh20]:** Would it sound better to state something like: "Despite the apparent increased tumor incidence, IARC concluded that there is no statistically positive trend in the incidence of pancreatic tumors and no apparent progression to carcinoma; the Expert Panel grees with this conclusion."

In the second study, Sprague-Dawley rats received doses of 0, 30, 100, and 300 ppm in the diet for 26 months. No pancreatic islet carcinomas were observed. Adenomas were found but without the positive trend seen in the study with higher doses. The ~~figures~~ tumor incidences for controls, low, mid and high doses, respectively, are: males-
0/50, 5/49 (10%), 2/50 (4%), 2/50 (4%) and females 2/50 (4%), 1/50 (2%), 1/50 (2%) 0/50. As IARC noted, there was no statistically positive trend in the incidence of pancreatic tumours and, again, no apparent progression to carcinoma. Four additional studies in rats, described by Greim et al. (2015) not evaluated by IARC, similarly did not show pancreatic islet carcinoma. Based on this information, the Expert Panel concludes that there is no evidence that glyphosate induces carcinoma in the pancreas.

**Commented [wh21]:** Shouldn't it say "tumors", not "carcinomas", since an increase in adenomas was also indicated by IARC

**Commented [wh22]:** Same comment

As with the liver tumors, IARC's initial assessment (Guyton et al. 2015) did not mention a positive trend in the incidence of thyroid C-cell adenoma in females noted in the Monograph (IARC 2015). However, IARC later concluded that "there was also a statistically significant positive trend in the incidence of thyroid follicular cell adenoma in females (*P* = 0.031)." IARC based their opinion, again, on its interpretation of the Stout and Ruecker (1990) study and the U. S. Environmental Protection Agency's Second Peer Review of Glyphosate (U. S. Environmental Protection Agency 1991). In the Stout and Ruecker study (1990), no statistically significant difference (group comparison) was reported in the incidence of thyroid C-cell neoplasms, as shown in **Table 5** below. Additionally, the U.S. Environmental Protection Agency (1991) concluded that "the C-cell adeno-

mas in males and females are not considered compound-related." Although the C-cell adenomas were slightly increased in male and female mid- and high-dose groups, there was no dose related progression to carcinoma and no significant dose-related increase in severity of grade or incidence of hyperplasia in either sex.

Commented [wh23]: Shouldn't there be a conclusion sentence for the thyroid tumors like there was for all the other tumor types discussed previously

**Table 5 Tumor Incidence/number of animals examined (mg/kg bw/day)***

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| | **0** | **89** | **362** | **940** | **0** | **113** | **457** | **1183** |
| Thyroid C cell adenoma | 2/60 | 4/58 | 8/58 | 7/60 | 2/60 | 2/60 | 6/60 | 6/60 |
| Thyroid C cell carcinoma | 0/60 | 2/58 | 0/58 | 1/58 | 0/60 | 0/60 | 1/60 | 0/60 |
| *Stout and Ruecker 1990 (all deaths reported) | | | | | | | | |

In sum, the Expert Panel is of the opinion that there is no reliable evidence for carcinogenic activity of glyphosate in experimental animals. Rather, in fact, the totality of the data would argue for evidence of non-carcinogenicity of glyphosate.

## 3.3 Genetic Toxicity Data

IARC did not consider the chemical structure of glyphosate in its mechanistic section. Many guidelines recommend that the presence of structural alerts be considered in evaluation of or testing for genotoxicity (Cimino et al. 2006; Eastmond et al. 2009; EFSA 2011; ICH 2011). As reported in Kier and Kirkland (2013), analysis of the glyphosate structure by DEREK software identified no structural alerts for chromosomal damage, genotoxicity, mutagenicity or carcinogenicity. The lack of structural alerts in the glyphosate molecular structure would tend to suggest lack of genotoxicity or that genotoxic effects might be secondary to toxicity or resulting from mechanisms other than DNA-reactivity.

Genetic toxicology tests relied upon by most regulatory bodies to support decisions focus on a set of core endpoints that are known to be involved either in direct activation of genes responsible for neoplastic initiation in somatic cells or alteration of the genetic information in germ cells (Kirkland et al 2011; ICH S2(R1) 2011; EFSA, 2011). Therefore, the endpoints given the greatest weight in **Table 6** include gene mutation and chromosomal aberrations.

**Table 6. Summary of the Panel's Evaluation of Human, Non-human Mammalian and Selected Microbial Genotoxicity Studies from IARC Section 4.2.1 and Other Published Sources**

| Test Category | Source | Endpoint | Weight | Glyphosate (Pos/Neg) | GBFs (Pos/Neg) | AMPA (Pos/Neg) | Total (Pos/Neg) |
|---|---|---|---|---|---|---|---|
| Bacterial reverse mutation | Kier and Kirkland (2013) and Other Published Studies not Included in | Gene Mutation | High | 0/19 | 0/20 | 0/1 | 0/40 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | IARC | | | | | | |
| Mammalian *In Vitro* | | Gene Mutation | Moderate | 0/2 | ND | ND | 0/2 |
| | | Chromosome Aberrations | Moderate | 1/5 | 1/0 | ND | 2/5 |
| | | Micronucleus | Moderate | 2/0 | 1/0 | ND | 3/0 |
| | | UDS | Low | 0/1 | ND | 0/1 | 0/2 |
| | | SCE | None | ND | 1/0 | ND | 1/0 |
| Mammalian *In Vivo* | | Chromosome Aberrations | High | 0/1 | 2/0 | ND | 2/1 |
| | | Micronucleus | High | 0/13 | 0/17 | 0/1 | 0/31 |
| | | SCE | None | ND | 1/0 | ND | 1/0 |
| | | | | | | | |
| Bacterial reverse mutation | IARC Monograph 112 | Gene Mutation | High | 0/1 | 0/0 | ND | 0/1 |
| Mammalian *in Vitro* | | Gene Mutation | Moderate | 0/1 | ND | ND | 0/1 |
| | | Chromosome Aberrations | Moderate | 1/2 | ND | 1/0 | 2/2 |
| | | Micronucleus | Moderate | 2/0 | ND | 1/0 | 3/0 |
| | | Comet/DNA breaks | Low | 5/0 | 2/0 | 1/0 | 8/0 |
| | | UDS | Low | 0/1 | ND | ND | 0/1 |
| | | SCE | None | 3/0 | 2/0 | ND | 5/0 |
| Mammalian *in Vivo* | | Chromosome Aberrations | High | 0/1 | 1/1 | ND | 1/2 |
| | | Micronucleus | High | 2/1 | 2/3 | 1/0 | 5/4 |
| | | Comet/DNA breaks | Moderate | 1/0 | 1/0 | ND | 2/0 |
| | | Dominant Lethal | High | 0/1 | ND | ND | 0/1 |
| Human *In Vivo* | | Chromosome Aberrations | High | ND | 0/1 | ND | 0/1 |
| | | Micronucleus | High | ND | 0/3 | ND | 0/3 |
| **High Weight *Combined Totals (IARC results only)*** | | | | **2/37 (2/4)** | **5/45 (3/5)** | **1/2 (1/0)** | **8/84 (6/9)** |
| **Moderate Weight *Combined Totals (IARC results only)*** | | | | **7/10 (4/3)** | **2/0 (0/0)** | **2/0 (2/0)** | **11/10 (6/3)** |
| **Low Weight *Combined Totals (IARC results only)*** | | | | **5/2 (5/1)** | **3/0 (3/0)** | **1/1 (1/0)** | **9/3 (9/1)** |

Footnotes:
1. All responses based on study critiques and conclusions of Expert Panel members.
2. Non-mammalian responses from IARC Monograph in this table did not include 4 positive studies measuring DNA strand breaks in bacteria and 1 negative Rec assay in bacteria from Monograph Table 4 6.
3. ND = No Data.

An evaluation of the studies in **Table 6** according to their relative contributions to a WOE produced the following results:

- Test methods identified as providing low contribution to the WOE (Low Weight) produced the highest frequency of positive responses, regardless

of whether the responses were taken from the results of IARC evaluated studies alone (9 of 10) or from all studies combined (9 of 12).

- The highest frequencies of positive responses were reported for test endpoints and systems considered most likely to yield false or misleading positive results due to their susceptibility to secondary effects. This relationship was constant regardless of whether the results were taken from IARC evaluated studies alone or all studies combined.

- The numbers of studies providing strong evidence of relevant genotoxicity (High Weight) were in the minority for both the IARC and the Expert Panel's evaluations, with 6 out of 15 studies identified as High Weight being positive for the IARC evaluation, and only 8 out of 92 studies identified as High Weight being positive for all studies combined.

In summary, the WOE from *in vitro* and *in vivo* mammalian tests for genotoxicity indicates that:

- Glyphosate does not induce gene mutations *in vitro*. There are no *in vitro* mammalian cell gene mutation data for GBFs or AMPA, and no gene mutation data *in vivo*.
- Glyphosate, GBFs and AMPA are not clastogenic *in vitro*. Glyphosate is also not clastogenic *in vivo*. Some positive *in vivo* chromosome aberration studies with GBFs are all subject to concerns regarding their reliability or biological relevance.
- There is limited evidence that glyphosate induces micronuclei (MN) in *vitro*. Since it is not clastogenic this would suggest the possibility of threshold-mediated aneugenic effects. However, there is strong evidence that glyphosate does not induce MN *in vivo*.
- Limited studies and potential technical problems do not present convincing evidence that GBFs or AMPA induce MN *in vitro*. The overwhelming majority of *in vivo* MN studies on GBFs gave negative results, but conflicting and limited data do not allow a conclusion on *in vivo* induction of MN by AMPA.
- There is evidence that glyphosate and GBFs can induce DNA strand breaks *in vitro*, but these might be secondary to toxicity since they did not lead to chromosome breaks. There is limited evidence of transient DNA strand breakage for glyphosate and GBFs *in vivo*, but for glyphosate at least these are not associated with DNA adducts. These results are assigned a lower weight than results from other more relevant endpoints, which were in any case more abundant.
- There is evidence that glyphosate and AMPA do not induce UDS in cultured hepatocytes.
- Some reports of induction of SCE *in vitro* by glyphosate and GBFs, and one positive report of SCE induction *in vivo* by a GBF, do not contrib-

ute to the overall evaluation of genotoxic potential since the mechanism of induction and biological relevance of SCE are unclear.

Although IARC policies prohibited the inclusion of additional data from unpublished studies or governmental reports, it was the Expert Panel's conclusion that the genetic toxicology studies published in reviews such as Kier and Kirkland (2013) (**Table 7**) should be included. The rationale supporting the inclusion of these 90 additional studies is that the supplementary tables presented in the Kier and Kirkland paper do contain sufficient detail concerning the robustness of the studies. Failure to evaluate and consider the large number of results included in the publication by Kier and Kirkland (2013) as well as other publicly available studies not reviewed by IARC, results in an inaccurate assessment of glyphosate, GBFs and AMPA's genotoxic hazard/risk potential.

**Table 7 Summary of studies presented in Kier and Kirkland 2013 and of other publically available studies not included in the IARC review**

| Test Category | Endpoint | Glyphosate (Pos/Neg) | GBFs (Pos/Neg) | AMPA (Pos/Neg) | Total (Pos/Neg) |
|---|---|---|---|---|---|
| Non-mammalian (Bacterial Reverse Mutation) | Gene Mutation | 0/19 | 0/20 | 0/1 | 0/40 |
| Mammalian *In Vitro* | Gene Mutation | 0/2 | ND | ND | 0/2 |
| | Chromosome Aberrations | 1/5 | 1/0 | ND | 2/5 |
| | Micronucleus | 2/0* | 1/0 | ND | 3/0 |
| | UDS | 0/1 | ND | 0/1 | 0/2 |
| | SCE | ND | 1/0 | ND | 1/0 |
| Mammalian *In Vivo* | Chromosome Aberrations | 0/1 | 2/0* | ND | 2/1 |
| | Micronucleus | 0/13* | 0/17 | 0/1 | 0/30 |
| | SCE | ND | 1/0 | ND | 1/0 |
| Total | | 3/41 | 6/37 | 0/3 | 9/81 |

*= inconclusive studies not included in count ND = Not Done

Based on the results of the WOE critique detailed above and the wealth of negative regulatory studies reviewed by Kier and Kirkland (2013) and Williams et al. (2000), the Expert Panel does not agree with IARC's conclusion that there is strong evidence for genotoxicity across the glyphosate or GBFs database. In fact the Expert Panel's WOE assessment provides strong support for a ***lack*** of genotoxicity, particularly in study categories closely associated with indications of potential genetic and carcinogenic hazard.

To provide greater emphasis to the Expert Panel's WOE conclusion, **Table 8** provides a comparison between a set of characteristics found in confirmed genotoxic carcinogens (Bolt et al., 2004; Petkov et al., 2015) and the genotoxic activity

profiles for glyphosate, AMPA and GBFs. There is virtually no concordance between the two sets of characteristics.

**Table 8. Comparison of test response profiles from Glyphosate, GBFs and AMPA to the profile characteristics of confirmed genotoxic carcinogens**

| Characteristic | Carcinogens with a Proven Genotoxic Mode of Action | | Glyphosate, GBFs , AMPA Study Data |
|---|---|---|---|
| Profile of Test Responses in Genetic Assays | Positive effects across multiple key predictive endpoints (i.e., gene mutation, chromosome aberrations, aneuploidy) both *in vitro* and *in vivo*. | | No valid evidence for gene mutation in any test; no evidence for chromosome aberrations in humans and equivocal findings elsewhere. |
| Structure Activity Relationships | Positive for structural alerts associated with genetic activity | | No structural alerts for glyphosate or AMPA suggesting genotoxicity |
| DNA binding | Agent or breakdown product are typically electrophilic and exhibit direct DNA binding | | No unequivocal evidence for electrophilic properties or direct DNA binding by glyphosate or AMPA |
| Consistency | Test results are highly reproducible both *in vitro* and *in vivo*. | | Conflicting and/or non-reproducible responses in the same test or test category both *in vitro* and *in vivo* |
| Response Kinetics | Responses are dose dependent over a wide range of exposure levels | | Many positive responses do not show significant dose-related increases |
| Susceptibility to Confounding Factors (e.g., Cytotoxicity) | Responses are typically found at non-toxic exposure levels | | Positive responses typically associated with evidence of overt toxicity |

Beyond the standard genetic toxicity assays, IARC concluded positive evidence of DNA breakage as determined by results in humans using the comet assay Paz-y-Mino et al.(2007), negative induction of chromosome aberrations (Paz-y-Mino et al. 2011), and positive induction of micronuclei (Bolognesi et al. (2009). These papers were critically reviewed by the Expert Panel and were found to be deficient on many fronts (identification of cells scored for comets, inconsistent observations, uncertainties with respect to “negative controls”, lack of statistical significance, and lack of effect relative to self-reported exposure). For the biomonitoring studies, in their evaluation section the IARC Monograph presents the results of the biomonitoring studies as positive without qualification. Due to the deficiencies cited in the biomonitoring studies above, along with the lack of scientific consensus regarding the relevance of micronuclei found in exposed humans, the Expert Panel concluded that there was little or no reliable evidence produced in these studies that would support a conclusion that GBFs, at levels experienced across a broad range of end-user exposures, poses any human genotoxic hazard/risk.

With respect to oxidative stress and genotoxic potential of glyphosate and its formulations, it is noted that many more oxidant stress studies are available for

GBFs than for glyphosate or AMPA. Unlike glyphosate, most of the GBF studies show evidence of oxidative stress suggesting that GBFs contain compounds that are likely to be toxic under some treatment conditions leading to reactive oxygen species followed by normal cellular protective responses. At predicted human exposure levels of less than 0.064 mg/kg bw/day, it is not anticipated that GBFs would induce toxicity likely to exceed endogenous detoxification capacities.

IARC claims of strong evidence supporting oxidative stress from AMPA seem to result from glyphosate and particularly GBF results rather than AMPA results. In fact, oxidative stress studies of AMPA are very limited. In the section on oxidative stress, IARC only cites one negative *in vitro* mammalian cell study of AMPA (Chaufan et al., 2014) and one positive *in vitro* mammalian cell study (Kwiatkowska et al., 2014). There is one other positive human cell study (Roustan et al., 2014) that was not cited; however, AMPA had unusually high toxicity in this report compared to other *in vitro* mammalian studies (see above) and no dose response was observed over an order of magnitude concentrations. The paucity of cited data does not seem to justify a conclusion of strong evidence for oxidative stress induction by AMPA.

Research on oxidative stress induced genotoxicity suggests that it is often a secondary response to toxicity and characterized by a threshold (Pratt and Barron, 2003). Therefore, the most appropriate conclusion supported by the oxidative stress data presented in the IARC Monograph (Section 4.2.3 of the IARC review) is, based on a WOE approach, that there is no strong evidence that glyphosate, GBFs or AMPA produce oxidative damage to DNA that would lead to induction of endpoints predictive of a genotoxic hazard or act as a mechanism for the induction of cancer in experimental animals or humans.

The WOE review does not provide relevant evidence for genotoxic activity of glyphosate, and moreover, there is no indication that genotoxic action through induction of oxidative stress is a biologically plausible mode of action for glyphosate, especially under anticipated conditions of use and estimated exposures to the human population.

## 3.4 Epidemiological Data

Following systemic collection, summary, and critique of 16 analytical epidemiological publications examining aspects of the possible relationship between reported use of glyphosate and two cancer types: NHL and MM, redundant publications (Cantor et al. (1992), Nordstrom et al. (1998), Hardell and Eriksson (1999), and Pahwa et al. (2012)) were excluded in favor of more recent published analyses of the same subjects. This resulted in a final evaluative dataset of 7 studies of glyphosate exposure and NHL (see **Table 9**) and 4 studies of glyphosate exposure and MM (see **Table 10**), considering Sorahan's (2015) publication as an extension of De Roos et al. (2005).

The descriptive characteristics of each of these studies were examined for the likely presence or absence of validity concerns (see **Table 11**). It is clear from **Table 11** (highlighted row) that only one study in the glyphosate literature – the Agricultural Health Study (AHS) cohort study (De Roos et al. 2005) – was designed to minimize selection bias and recall bias, had only firsthand respondents reporting about exposures (viz. no proxy respondents), and conducted analyses that controlled comprehensively for confounding by personal characteristics and occupational exposures. In addition, the AHS cohort study was the only study that attempted to look at exposure-response relationships while controlling for confounding exposures. As such, it deserves the highest weight in the current assessment of the literature. The other studies have so many validity concerns that they cannot be interpreted at face value. Indeed, there is evidence in many of these studies that virtually every exposure studied was associated with NHL or MM – a clear indication of widespread systematic bias and the unreliability of any of the reported exposure-disease associations.

The assessment of causality is a complex process that relies upon a family of well-recognized methods: the general scientific method (familiar to all scientists), study design and statistical methods, and research synthesis methods (e.g. the systematic narrative review, meta-analysis and pooled analysis, and the so-called criteria-based methods of causal inference). Of these, the criteria-based methods are often described and considered in causal assessments, with the most familiar having been proposed by Bradford Hill (1965) and utilized extensively in the 1964 Surgeon General's Committee on Smoking and Health and the many publications on the topic that dotted the scientific landscape in the late 1950's and early 1960's (Weed, 1995). These "criteria" or "considerations" are substantive components of the stated methodologies of agencies such as the U.S. Environmental Protection Agency (2005) and the International Agency for Research on Cancer (2015). In essence, all the causal frameworks in epidemiology focus on whether the observed associations are strong (viz. the size of the OR or RR is appreciably different than 1.0), whether the associations appear to have been estimated without bias, whether the OR or RR increases or decreases with increasing exposure (viz. exposure-response), whether the temporal relationship between exposure and effect is considered appropriate, and whether the results are statistically robust enough to rule out chance as an explanation (Hill 1965, Aschengrau and Seage 2003, or Bhopal, 2002).

With these considerations in mind, for NHL, it is justified scientifically to rely most on the results of the De Roos et al. (2005) cohort study as those best suited to reveal the existence (or not) of an association between exposure to glyphosate and NHL. This cohort study was the only study where information about pesticide use was collected independently of the participants' knowledge of cancer status, where there were no proxies providing information about pesticide use, where exposure-response was evaluated extensively, and where there was statistical adjustment for other pesticide exposures and personal factors in estimating RRs

for glyphosate. As De Roos et al. (2005) concluded "… the available data provided evidence of no association between glyphosate exposure and NHL incidence." On the other hand, all the case control studies had the potential limitation of recall bias, many had clear indications of selection bias (either in terms of subject participation or in the analysis), most had very small numbers of glyphosate exposed cases and controls, none showed evidence of an exposure-response relationship, and most did not control for the potential confounding effects of personal factors or other occupational exposures in their glyphosate risk estimates. We consider the case control studies to be inadequate for the assessment of a relationship between glyphosate and NHL and consider the AHS cohort study as the one reliable evaluation of NHL risk from glyphosate. The two limitations of the AHS study are the relatively small number of NHL cases (n = 92) and that the length of follow-up after enrollment was less than a decade. Those limitations speak to statistical robustness, not validity.

The glyphosate literature for MM is appreciably sparser than the literature for NHL. Again, the AHS cohort study (De Roos et al. 2005) is the best source of evidence when compared with the 3 available case control studies. De Roos et al. found that glyphosate users had about the same rate of MM as non-users adjusting for confounding factors (factoring in Sorahan's reanalysis of the fully adjusted MM results from DeRoos et al. (2005) to correct inadvertent selection bias. This bias results from the natural self-examination by cases of what might have caused their grievous illness. Recall bias is not a concern in the sole glyphosate cohort study (DeRoos et al. 2005) because exposure was determined from study participants at study entry before follow-up began for health outcomes. Recall bias tends to produce spurious positive associations between exposure and disease. Exposure-response analyses by De Roos et al. and Sorahan (2015) were relatively uninformative in light of the few MM cases split among exposure categories. More informative analyses await additional follow-up of the AHS cohort to increase the number of MM cases. The three MM case control studies are based on very small numbers, have concerns about recall bias and selection bias, and did not control for confounding by other exposures. Overall, then, we consider this literature inadequate to make an informed judgment about a potential relationship between glyphosate and MM.

In summary, in consideration of the questions;

1. Does the current published epidemiologic evidence establish a causal relationship between glyphosate exposure and NHL?
2. Does the current published epidemiologic evidence establish a causal relationship between glyphosate exposure and MM?

It is the opinion of the Expert Panel that review of the glyphosate epidemiologic literature and the application of commonly applied causal principles, does not indicate a relationship with glyphosate exposure and NHL. Likewise, there is no

substantive evidence to indicate a relationship between MM and glyphosate exposure.

**Table 9 Results for Glyphosate: Non-Hodgkin's Lymphoma (NHL)**

| Author, Year (study design) | # cases, controls total or exposed | OR/RR (95% CI) | Multivariate adjustments | Outcome |
|---|---|---|---|---|
| **McDuffie et al. 2001 (case-control)** | 517, 1506 [total]<br>51, 133<br>28, 97<br>23, 36 | Any use OR = 1.2 (95% CI 0.8, 1.7)<br>≤ 2 days/year OR = 1.0 (95% CI 0.6, 1.6)<br>> 2 days/year OR = 2.1 (95% CI 1.3, 2.7) | Age, province, medical conditions<br><br><br>Age, province | NHL |
| **Hardell et al. 2002 (case-control)** | 515, 1141 [total]<br>8, 8<br><br>8, 8 | <br>Any use OR = 3.0 (95% CI 1.1, 8.5)<br><br>Any use OR = 1.9 (95% CI 0.6, 6.2) | <br>None<br><br>Multivariate (unspecified) | NHL + HCL |
| **De Roos et al. 2003 (case-control)** | 650, 1933 [total]<br>36, 61<br><br>36, 61 | <br>Any use OR = 2.1 (95% CI 1.1, 4.0)<br><br>Any use OR = 1.6 (95% CI 0.9, 2.8) | <br>Age, other pesticides, study site<br><br>Age, other pesticides, study site, priors for chemical class and probability of being carcinogenic [hierarchical model] | NHL |
| **De Roos et al. 2005 (cohort, n = 57,311)** | **71 exposed cases**<br>**21 unexposed cases**<br><br>29 cases<br>15 cases<br>17 cases | **Any use RR = 1.1 (95% CI 0.7, 1.9)**<br><br><br>1 to 20 days RR = 1.0 (referent)<br>21 to 56 days RR = 0.7 (95% CI 0.4, 1.4)<br>57 to 2678 days RR = 0.9 (95% CI 0.5, 1.6) | Age, education, smoking, alcohol, family history, state, 10 pesticides<br><br><br>same | NHL |
| **Eriksson et al. 2008 (case-control)** | 910, 1016 [total]<br>29, 18<br><br>17, 9 | <br>Any use OR = 2.0 (95% CI 1.1, 3.7)<br><br>> 10 days OR = 2.4 (95% CI 1.0, 5.4) | <br>Age, sex, year of diagnosis or enrollment<br><br>same | NHL |
| **Orsi et al. 2009 (case-control)** | 244, 436 total<br>12, 24 | <br>Any use OR = 1.0 (95% CI 0.5, 2.2) | <br>Age, center, socioeconomic category | NHL |
| **Cocco et al. 2013 (case-control)** | 2348, 2462 [total]<br>4, 2 | <br>Any use OR = 3.1 (95% CI 0.6, 17.1) | <br>Age, sex, education, study center | B-cell lymphoma |

**Table 10 Results for Glyphosate: Multiple Myeloma (MM)**

| Author, Year | # cases, controls total or exposed | OR/RR (95% CI) | Multivariate adjustments |
|---|---|---|---|
| **Brown et al. 1993 (case-control)** | **173, 650 [total]<br>11, 40** | **Any use OR = 1.7 (95% CI 0.8, 3.6)** | **Age, vital status** |
| De Roos et al. 2005 (cohort, n = 57,311) | 24 exposed cases<br>8 unexposed cases<br><br>Not specified<br><br><br>8 exposed cases<br>5 exposed cases<br>6 exposed cases | Any use RR = 1.1 (95% CI 0.5, 2.4)<br><br>Any use RR = 2.6 (95% CI 0.7, 9.4)<br><br><br>1 to 20 days RR = 1.0 (referent)<br>21 to 56 days RR = 1.1 (95% CI 0.4, 3.5)<br>57 to 2678 days RR = 1.9 (95% CI 0.6, 6.3) | Age<br><br>Age, education, smoking, alcohol, family history, state, 10 pesticides<br><br><br>Age, education, smoking, alcohol, family history, state, 10 pesticides |
| Orsi et al. 2009 (case-control) | 56, 313 [total]<br>5, 18 | ~~3.1.47~~3.1.5 Any use OR = 2.4 (95% CI 0.8, 7.3) | Age, center, socioeconomic category |
| Kachuri et al. 2013 (case-control) | 342, 1357 [total]<br>23, 108<br><br>11, 78<br><br><br>10, 26 | Any use OR = 1.1 (95% CI 0.7, 1.9)<br><br>≤ 2 days/year OR = 0.7 (95% CI 0.4, 1.4)<br><br>> 2 days/year OR = 2.1 (95% CI 0.95, 4.7) | Age, province, smoking, selected medical conditions, family history of cancer<br><br>Same |
| Sorahan 2015[1]<br><br>Reanalysis of De Roos et al. 2005 | 24 exposed cases<br>8 unexposed cases<br><br>24 exposed cases<br>8 unexposed cases<br><br>8 cases<br>10 exposed cases<br>8 exposed cases<br>6 exposed cases | Any use RR = 1.1 (95% CI 0.5, 2.5)<br><br>Any use RR = 1.2 (95% CI 0.5, 2.9)<br><br>Never used RR = 1.0 (referent)<br>1 to 20 days RR = 1.1 (95% CI 0.4, 3.0)<br>21 to 57 days RR = 1.5 (95% CI 0.5, 4.3)<br>57 to 2678 days RR = 1.4 (95% CI 0.4, 4.5) | Age<br><br>Age, sex, education, smoking, alcohol, family history of cancer, education, state, 10 pesticides<br><br>Age, sex, education, smoking, alcohol, family history of cancer, education, state, 10 pesticides |

1. Reanalysis of De Roos et al. to assess the exclusion of 14,000 with some missing covariate data as the explanation for the difference in RRs adjusted for age (RR = 1.1) versus adjusted for age, education, smoking alcohol, family history, state, and 10 pesticides (OR = 2.6)

**Table 11 Validity Considerations Glyphosate Studies**

| 1st Author (year) | Recall bias | Exposure mis-classification | Exposure-response & trend test | Selection bias | Adjustment for con-founding from other pesticides yes/no | Adjusted for confounding from other variables yes/no | Pathology review of cases | proxies %cas-es/ %controls | Bias from sparse data | Blinding of inter-views | Consider-ation of latency |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Brown et al. (1993) | Likely | Moderate ever/ never | No | Unlikely | No | Yes | Yes | 42% for cases; 30% for controls | No | Unclear | No |
| McDuffie et al. (2001) | Likely | Moderate ev-er/never; appre-ciable days of use | Yes, no trend test | Likely | No | Yes and No | Yes | 21% cases 15% controls | No | Unclear | No |
| Hardell et al. (2002) | Likely | Moderate ev-er/never; appre-ciable days of use | No | Unlikely | Yes, but variables not specified | Unclear | Yes for NHL, unclear for HCL | 43% NHL cases and controls, 0% for HCL | Possible | Yes | No |
| De Roos et al. (2003) | Likely in origi-nal publi-cati-ons | Moderate ever/ never | No | Likely, in original publications | Yes | Yes | Yes | 31% for cases; 40% for controls | No | Yes | No |
| De Roos et al. (2005) | No | Moderate ev-er/never ap-preciable in days of use analysis | Yes, yes | Unlikely | Yes | Yes | Yes | No | Possi-ble in some anal-yses | N/A | No |
| Eriksson et al. 2008 | Likely | Moderate ev-er/never | Yes, no trend test | Unlikely | Yes | Age, sex, year of diagnosis | Yes | No | Possible in some analyses | Yes | Yes |
| Orsi et al. (2009) | Likely | moderate ev-er/never | No | Likely | No | Yes | Yes | No | Possible | Yes | No |
| Cocco et al. 2013. | Likely | Likely | No | Likely | No | No | 20% | No | Possible | Unclear | No |
| Kachuri et al. (2013) | Likely | Moderate ever/ never; apprecia-ble days of use | Yes, no trend test | Likely | No | Yes | Yes | Excluded | No | Unclear | No |

## 4.0 Discussion and Conclusions

IARC (2015), in their assessment and categorization process do not consider exposure and relevance of exposure in terms of dose and temporal pattern to toxicology and epidemiology findings. As a result, the IARC conclusion is "hazard" not "risk" based. With respect to exposures to glyphosate, even when using a number of worst-case assumptions, systemic doses of glyphosate in human applicators, bystanders, and the general public are very small. Those in the general public are three or more orders of magnitude less than the USEPA's RfD and in the most exposed applicators ($90^{th}$ centile) the systemic dose was estimated at 20-fold less that the RfD. Most exposures are in the range of 0.00001 to 0.01 mg/kg body weight/day and this includes occupational exposures. Exposures in this range cannot plausibly be associated with measurable (i.e., in experimental animals or in epidemiology studies) increase in cancer risk. In fact, one ***might*** perceive some increased risk for the most potent of genotoxic carcinogens known to date. This is not the case for glyphosate, as a result, the toxicology and epidemiology data need to be viewed in light of actual exposures attained and the resulting probability of observing a biologically relevant effect.

**Commented [wh24]:** Can we remove this sentence? We toxicologists really don't like it because it suggests that IARC actually found hazards, when they actually didn't for reasons well discussed elsewhere in the paper.

In addition, in the current IARC (2015) assessment of glyphosate, any numerical increase in tumors, sometime identified only after statistical manipulation, can be considered a treatment-related effect regardless of what the data from the study indicates. Furthermore, the overall weight-of-evidence from the full data sets of studies is not taken into account. Exposure to glyphosate, here clearly shown to be so low as to negate the cautionary note implicit in the IARC process, is ignored. IARC's non-standard process leads them to interpret study data differently from those groups informed about the relevant science. This is implicit in their process. However, their disregard of valid data without explanation cannot be considered to be a reasonable practice.

With respect to the cancer bioassay data, it appears to the Expert Panel that in the IARC working group review there was considerable selectivity in the choice of data reviewed. An example of how an informative data set was disregarded is found in the paper of Greim et al. (2015) who evaluated fourteen carcinogenicity studies, nine chronic/carcinogenicity studies in the rat, including one peer-reviewed published study, and five carcinogenicity studies with glyphosate in mice. All were submitted to support glyphosate Annex I renewal in the European Union. It is evident that neoplasms naturally occurring in rodents are widely represented in non-exposed animals as well as those exposed to doses well below those that might be expected in regulatory studies. The pattern of occurrence of these tumors is inconsistent across and within species and no "novel" neoplasms appeared; progression of non-neoplastic to neoplastic lesions was not seen. Further, the comparatively large number of studies performed might be ex-

pected to lead to "positive" results by chance; some evaluation of the biological significance of the findings should be made.

A number of scientific groups, regulatory agencies and individuals have commented on these data, the latter grouping in peer reviewed documents.

- **EFSA (2015)** – *"No, classification and labeling for carcinogenicity is not warranted. This is based on a large number of long-term studies in rats that did not reveal any evidence of carcinogenicity. In the mouse, a higher incidence of malignant lymphoma was observed in one out of five carcinogenicity studies at an exaggerated dose level in a strain with high background incidence of this tumor type.... Epidemiological studies in the whole did not provide evidence of carcinogenicity in man."*
- **APVMA (2013)** – *"The weight and strength of evidence shows that glyphosate is not genotoxic, carcinogenic, or neurotoxic."*
- **U. S. Environmental Protection Agency (2013)** – "*No evidence of carcinogenicity was found in mice or rats."*
- **U. S. Environmental Protection Agency (2012)** – "*No evidence of carcinogenicity was found in mice or rats."*
- **European Commission (2002)** – *"No evidence of carcinogenicity."*
- **U. S. Environmental Protection Agency (1993a,b)** – *"The Agency has classified glyphosate as a Group E carcinogen (signifies evidence of non-carcinogenicity in humans)."*
- **Health and Welfare Canada/PMRA (1991) [Doliner 1991]** – *"Health and Welfare Canada has reviewed the glyphosate toxicology data base, which is considered to be complete. The acute toxicity of glyphosate is very low. The submitted studies contain no evidence that glyphosate causes mutations, birth defects or cancer."*
- **JMPR (2006)** – *"In view of the absence of a carcinogenic potential in animals and the lack of genotoxicity in standard tests, the Meeting concluded that glyphosate is unlikely to pose a carcinogenic risk to humans."*
- **JMPR (1987)** – *"The chronic toxicity of glyphosate is low... There is no evidence of carcinogenicity."*
- **WHO (1994)** – *"The available studies do not indicate that technical glyphosate is mutagenic, carcinogenic or teratogenic."*

**Commented [wh25]:** I'm not sure all this should be in the summary. I suggest deleting it. I think it's fine to say that a number of regulatory agencies commented positively on these data, and that the actual comments can be found in the Animal Bioassay chapter/paper.

After review of all available glyphosate carcinogenicity data, the panel concludes:

(i) the renal neoplastic effects are not associated with glyphosate exposure, because they lack statistical significance strength, consistency, specificity, lack a dose-response pattern, plausibility, and coherence;

(ii) the strength of association of hemangiosarcomas in the liver of mice is absent, lacking consistency, and a dose-response effect;

(iii) the strength of association of pancreatic islet-cell adenomas in male S-D rats is absent, lacking a dose-response pattern (the highest incidence is in the low dose followed by the high dose), plausibility and pre-neoplastic/malignant effects;

(iv) n one of two studies, the significant positive trend in the incidence of hepatocellular adenomas in male rats did not materialize, no progression to malignancy was evident and no glyphosate-associated pre-neoplastic lesions were present;

**Commented [wh26]:** I'm confused by this. Does this mean one of two studies *cited by IARC?* Because obviously there wer more than 2 studies.

(v) in one of two studies, the significant positive trend in the incidence of thyroid C-cell adenomas in female rats did not materialize, although the adenomas were only slightly increased in mid and high doses, also there was no progression to malignancy;

**Commented [wh27]:** Same comment as above

A pattern of selective review of the data is also very evident in the IARC (2015) assessment of the genotoxicity data. Overall, extensive reviews of the genotoxicity of glyphosate, aminomethylphosphonic acid (AMPA) and glyphosate based formulations (GBFs) that were available prior to the development of the IARC Glyphosate Monograph all support a conclusion that glyphosate (and related materials) is inherently not genotoxic. Further, evidence indicative of an oxidative stress mechanism of carcinogenicity is largely unconvincing. The Expert Panel concluded that there is no new, valid evidence presented in the IARC Monograph that would provide a basis for altering these conclusions. The differences between the conclusions of the IARC review and the Expert Panel review were in large part due to IARC exclusion of numerous available studies and in some cases differences in interpretation of study results reported in the IARC monograph. Another significant source of difference was the Panel's weighting of different studies and endpoints by the strength of their linkage to mutagenic events associated with carcinogenic mechanisms. The Expert Panel concluded that without critically evaluating all available data, it is not possible to make an accurate WOE assessment.

The Expert Panel agreed that there was sufficient evidence to conclude that glyphosate and GBFs appeared to induce DNA strand breaks and possibly micronuclei in *in vitro* mammalian and non-mammalian systems and SCEs in *in vitro* mammalian systems. These results provide some evidence of genotoxicity, but it is not possible to accurately characterize or classify genotoxic hazard/risk or carcinogenesis mechanisms based on these results alone. As further stated in the OECD guidance comments (OECD, 2015) regarding test weights, "*When evaluating potential genotoxicants, more weight should be given to the measurement of permanent DNA changes than to DNA damage events that are reversible. In general, indicator tests should not be used in isolation and a substance should not be considered mutagenic (or non-mutagenic) on the results of indicator tests alone.*" Consequently, positive responses in genotoxic endpoints identified above as "indicator tests (i.e. DNA strand breaks, SCEs) are evidence of compound exposure but not sufficient to determine compound effect. In order to de-

termine compound effect, consideration must be given to available evidence clearly demonstrating the induction of gene mutations or stable chromosomal alterations, particularly *in vivo* in mammalian systems. The Panel concluded that the IARC assessment of classifications regarding strong evidence of genotoxicity and oxidative stress capabilities of glyphosate, GBFs and AMPA is not supported by the available data. A critical review of the complete dataset by the Expert Panel supports a conclusion that glyphosate (including GBFs and AMPA) does not pose a genotoxic hazard and therefore, should not be considered support for the classification of glyphosate as a genotoxic carcinogen.

The final set of data on which IARC (20150 based their conclusion was the epidemiology data with respect to glyphosate exposure/use in relation to the incidence of NHL and MM. The Expert Panel's review of the glyphosate epidemiologic literature and the application of commonly applied causal principles do not indicate a relationship with glyphosate exposure and NHL. In addition, the Panel considered the evidence for MM to be inadequate to judge a relationship with glyphosate. The maximum systemic dose found in a review of all glyphosate biomonitoring studies completed to date is 0.004 mg/kg (Niemann, 2015). For comparison, the USEPA's reference dose (viz. the daily oral exposure to the human population, including sensitive subgroups such as children, that is not likely to cause harmful effects during a lifetime) is 500-fold higher at 2 mg/kg/day (U.S. EPA 1993). The geometric mean systemic glyphosate dose for applicators is 0.0001 mg/kg/day. It is not plausible that an excess cancer risk could, if it indeed existed, could be detected given these levels of exposures. This argues strongly against the purported associations concluded by IARC to indicate "*limited*" evidence of carcinogenicity in humans. Moreover, a close inspection of the studies relied upon by IARC reveals a number of issues regarding the validity of the studies, not the least of which include selection bias, recall bias, inadequate/inappropriate measures of exposures, and confounding exposures to other chemicals. The study with the least amount of methodological issues, that of De Roos et al. (2005), shows no indication that glyphosate exposure is associated with increased risk for NHL.

**Commented [wh28]:** In Keiths Exposure section he uses the 1.75 mg/kg/day value. The value should be consistent throughout, don't you think?

At the end of the day, the totality of the evidence, especially in light of the extensive testing that glyphosate has received, as judged by the Expert Panel, does not support the conclusion that glyphosate is a "probable human carcinogen". Indeed, the data, inclusive of GLP-compliant unpublished studies, point to classification of "non-carcinogenic to humans". The IARC (2015) classification is flawed due to the selective review/analysis of data (especially the cancer bioassay and genetic toxicity data), lack of transparency in regards to data analysis, and most importantly, the lack of consideration of biological plausibility in light of exposure. In essence, the IARC (2015) "misclassification" of glyphosate is both the result of the hazard only paradigm employed and the selective/biased nature of the data reviewed and considered for analysis.

# 5 References