Message

From: HEYDENS, WILLIAM F [AG/1000] [/O=MONSANTO/OU=NA-1000-01/CN=RECIPIENTS/CN=230737]
Sent: 2/9/2016 11:43:08 PM
To: Ashley Roberts Intertek [redacted]
Subject: RE: summary article
Attachments: Summary Manuscript Draft 2 0 Feb 5 2016_jfa_wfh.docx

Ashley,

OK, I have gone through the entire document and indicated what I think should stay, what can go, and in a couple spots I did a little editing. I took a crack at adding a little text on page 10 to address John's comments about toxicologists' use of Hill's criteria – see what you think; it made sense to me, but I'm not sure if it will to others - please feel free to further modify and/or run by Gary.

After you have looked through this, let's discuss.

Thanks,

Bill

From: Ashley Roberts Intertek [redacted]
Sent: Monday, February 08, 2016 3:15 PM
To: HEYDENS, WILLIAM F [AG/1000]
Subject: FW: summary article

Hi Bill,

Please take a look at the latest from the epi group!!!!

Can you call me once you have digested this.

Thanks

Ashley

Ashley Roberts, Ph.D.
Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
[redacted]

From: John Acquavella [redacted]
Sent: February-08-16 4:00 PM
To: Ashley Roberts Intertek
Subject: summary article

Ashley:

Let me start by saying that I share your goal of having complete expert panel authorship on the summary article. I've had some initial correspondence from the panelists about the summary article and the consensus is that they will not be authors on an article that has inflammatory comments about IARC. Assuming those inflammatory comments were carried over from the animal carcinogenicity and genotoxicity articles, I'm sure the epi panelists would not want to be associated with those articles either.

To achieve the complete authorship goal, an extensive revision of the summary article is necessary. To facilitate, I've edited the entire summary article to take out most of the inflammatory statements about IARC. The view of the epi panelists is that the inflammatory comments are not necessary and will cause readers to disregard the outstanding scientific work that was done by the panels. Inflammatory statements will certainly

cause IARC and IARC's vocal supporters to push back hard to defend their evaluation and discredit Monsanto's expert panel process and panelists. I think you have seen the recent article in which many well known epidemiologists banded together to defend IARC (see Pearce et al. 2005 attached). Our strongest point is the quality of our scientific reviews, not disparaging the IARC process or the work of monograph 112 workgroups. To the extent that there are inflammatory comments about IARC in the articles by the other panels, I suggest you work with the authors to remove them.

In addition, I noted the following in my review of the summary article:

- Hill's criteria are misapplied by the toxicology panels. Please review applications of Hill's criteria with Doug Weed who is an expert on the intended meaning of each criterion. It will detract from the toxicology arguments to misuse these criteria. I suggest you also ask Doug to look at the animal carcinogenicity and genotoxicity articles to make sure that Hill's criteria are cited appropriately.
- With respect to exposure, I think the margin of safety is underestimated in various sections of the article because the RfD is a daily dose and the applicator exposures are very infrequent. I addressed this in an article in Annals of Epidemiology in 2003 that was the work of an ECPA taskforce. See reference below and article attached.

I expect to have specific suggestions from the epi panelists later this week. I will compile the unique suggestions and send them on to you asap.

Regards,

John

Acquavella JF, Doe J, Tomenson J, Chester G, Cowell J, Bloemen L. Epidemiologic Studies of Occupational Pesticide Exposure and Cancer: Regulatory Risk Assessments and Biologic Plausibility. Annals of Epidemiology 2003; 13: 1-7.

Glyphosate: Carcinogenic potential – the conclusions of IARC (2015) – A Critical review by an Expert Panel

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Keywords: Glyphosate, aminomethylphosphoric acid, Roundup, herbicide, cancer, genotoxicity

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Abstract

Introduction

Glyphosate, or N-(phosphonomethyl)glycine (CAS# 1071-83-6), 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 the synthesis of these amino acids stops rapidly growing plants such as weeds. Importantly, EPSPS 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 tolerant to glyphosate (i.e. allows for application after emergence of the crops). In addition, given its effectiveness and broad-spectrum activity, glyphosate is also used worldwide for forestry, rights of way, landscape, and household control of weeds.

The safety, including the potential carcinogenicity, of glyphosate has been ~~extensively~~ reviewed by experienced scientists and ~~many~~ regulatory authorities worldwide, including the US Environmental Protection Agency (US EPA), the European Commission, and the Canadian Pest Management Regulatory Agency (Health and Welfare Canada 1991; US EPA 1993, 2013; WHO 1994; Williams et al. 2000; European Commission 2002; Kier & Kirkland 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 to humans. As a result, glyphosate based herbicides have been approved for use in over 160 countries.

In 2015, the International Agency for Research on Cancer (IARC) published the Glyphosate Monograph of Volume 112 (IARC 2015). IARC (2015) categorized glyphosate as "*probably*

carcinogenic to humans" (Group 2A) based on ~~their conclusion that there is "~~*limited evidence*" of carcinogenicity in human studies, 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", genotoxicity and induction of oxidative stress. This mechanistic evidence conclusion was viewed as providing strong support for IARC classifying glyphosate as probably carcinogenic to humans, Group 2A.

Comment [wh1]: ASHLEY, I CAN LIVE WITH ANY OF THE DELETIONS BELOW ON THIS PAGE IF YOU ARE OK WITH THEM AS WELL

The classification of glyphosate as *probably carcinogenic to humans* differs from ~~is controversial as it is not consistent with~~ all previous and one subsequent glyphosate review ~~the views and opinions of~~ by scientific experts and regulatory bodies worldwide. ~~These regulatory bodies, including those outlined above 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 studies, including both data reported in the published literature as well as the results of the Good Laboratory Practices (GLP) and Organisation for Economic Co-operation and Development (OECD)/Redbook studies conducted by several companies as part of the normal series of studies conducted to support registration of an agricultural herbicide product.~~

~~Given that the IARC conclusion contradicts the conclusions reached by worldwide regulatory authorities, as well as of other independent scientists, and noting that the IARC classification ignores the important role exposure plays in a proper overall risk assessment~~ Accordingly, Intertek Scientific & Regulatory Consultancy Services (Mississauga, Ontario Canada) was commissioned by Monsanto Company to convened an Expert Panel ~~was convened~~ to assess independently the available data on glyphosate with respect to exposures, carcinogenicity studies conducted in experimental animals, genetic toxicity and mechanistic data, and epidemiological studies. ~~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 four ~~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 four areas of interest (exposure, animal cancer bioassays, genetic toxicity, and epidemiology) the data evaluated, ~~and~~ the method of evaluation, and the conclusions of the experts are summarized ~~outlined~~ in the sections below.

Exposures to glyphosate

Unpublished reports of studies on exposure to glyphosate in applicators were provided by Monsanto Company 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 100% ~~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) (US EPA 2009). Also, surface water measurements of glyphosate as part of the National Water-Quality Assessment (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 acid equivalents (a.e.)/L), these values were substituted with a dummy value of "zero". Although

chlorine and ozone are highly effective for removing glyphosate and AMPA during purification of drinking water (Jönsson et al. 2013), it was assumed that treatment did not remove any glyphosate. 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 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 2013, the Joint Meeting on Pesticide Residues (JMPR) reviewed dietary exposures to glyphosate (glyphosate, N-acetyl glyphosate, AMPA and N-acetyl AMPA) and calculated the international estimated daily intakes (IEDI) of glyphosate for 13 regional food diets (JMPR 2014). These IEDIs were based on estimated mean residues from supervised trials under normal or good agricultural practice. The US EPA has calculated exposures to glyphosate using the Dietary Exposure Evaluation Model (DEEM, ver 7.81), based on tolerance levels for all commodities and modeled estimates of exposures from food and drinking water for the overall US population (US EPA 2012).

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 (US EPA 2009), 10% penetration through clothing if not actually measured, 3% dermal penetration. 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. The median (50th centile) and 90th centile values were calculated from the raw data using the Excel function <=percentile>.

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.

Air Exposures

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 body mass (b.m.)/d. This is about six orders of magnitude less than the current US EPA's reference dose (RfD) of 1.75 mg/kg b.m./d, which is the US EPA's allowable limit for consumption of residues of glyphosate exposure based on toxicity studies.

Comment [JA2]: I believe this is the amount allowed daily. Seems worth mentioning as the potential for airborne exposure happens infrequently.

Water Exposures

"The concentrations of glyphosate measured in US surface waters ranged from 0.02-73 µg/L. The 90th centile value was 0.79 µg/L, which corresponds to a systemic dose of 2.25 x 10^{-5} mg/kg/d, which is approximately five orders of magnitude below the US EPA's RfD.

Exposures from Food and bystanders

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; Honeycutt and Rowlands (2014); Krüger et al. 2014; Markard, 2014). In these studies, the range for estimates

of systemic doses was 0.000022-00063 mg/kg/d. All of these estimates are at least three orders of magnitude less than the US EPA's RfD.

Exposure within Applicators

The 50th and 90th centiles in the dosimetry studies were 0.0015 and 0.064 mg/kg/d, respectively. Neither of these values is particularly large when compared to the current US EPA's RfD of 1.75 mg/kg/d. 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/d, respectively. These are several orders of magnitude less than the US EPA'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 an extremely large margin of ~~safety, no hazard~~ from exposure to glyphosate *via* normal uses.

Comment [wh3]: I M FINE WITH JOHN'S SUGGESTION

Comment [JA4]: Rather than say no hazard, perhaps say there is an extremely large margin of safety?

Cancer Bioassays

The recommended method for evaluating the results of 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 US EPA (Suter & 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

Comment [JA5]: One would expect a reference regarding who recommended the WOE approach

review, if certain studies are judged to be unreliable and thus not included ~~to be ignored~~, the reasons for this should be provided. The Expert panel reviewed the incidences of the tumors in the various studies with respect to dose-response, rate of occurrence relative to known spontaneous rates in control animals, and on the basis of biological plausibility.

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

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) a significant positive trend in the incidences of hepatocellular neoplasia in male SD rats and of thyroid C-cell neoplasia in female SD rats.

Comment [wh6]: I M PROPOSEING THIS AS A COMPROMISE, AS I STRONGLY DISAGREE WITH JOHN – THEY DID INTENTIONALLY IGNORE SOME STUDIES – THEY SAY SO IN THE MONOGRAPH

Comment [JA7]: The studies are not ignored. As mentioned, all are to be examined carefully. Perhaps you mean … if certain studies are considered to be unreliable for evaluative purposes …

Comment [JA8]: This seems a bit of a non-sequitur unless these are the reliability criteria the panel used. If so, state that explicitly.

Comment [wh9]: I WOULD IGNORE JOHN'S COMMENT

Comment [JA10]: Same strain as the previous finding?

Comment [JA11]: Later you say that IARC concluded that this data did not suggest a relationship to glyphosate. So, was this finding really important to their conclusion?

Comment [wh12]: YES IT WAS IMORTAT IN THEIR DECISION AND SHOULD BE INCLUDED

Kidney tubular-cell neoplasia in mice

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~~one 2-year oral mouse carcinogenicity stud~~ies~~y, (Monsanto 1983; Cheminova 1993a) excluding two 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; US EPA 1990).

Comment [wh13]: THE CHEMINOVA STUDY DID NOT HAVE ANY KIDNEY TUMOR ISSUE/QUESTION

In the ~~one~~ study referred to as Monsanto 1983 ~~considered by IARC (2015) to show evidence of renal tubular development associated with glyphosate treatment (Monsanto 1983)~~, the ~~overall final~~ incidence by dose 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 mid-dose group, followed by the control group, and the high-dose (HD) group. The low-dose (LD) group had no renal findings. It is informative to apply ~~to the study by Monsanto (1983)~~ a modified form of the Hill viewpoints, which were originally presented as aspects that should be considered when assessing causation in Occupational Medicine, to parameters/endpoints assessed in standard animal bioassays; such an evaluation, while not the intention of Hill's presentation originally, can be performed in a similar manner to address~~covering~~ eight of the nine criteria of causation (Hill 1965; Woodside & 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. When applied to the study by Monsanto (1983), s~~S~~everal conclusions were 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.

2. The association is not consistent, since four out of five mouse studies did not find ~~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.

Comment [wh14]: I THINK YOU SHOULD KEEP IN THE SENTENCE BELOW THAT JOHN DELETED

Comment [wh15]: I AM SUGGESTING ADDING THIS WORDING TO MORE GENERICALLY ADDRESS SOME OF JOHN'S COMMENTS THAT THE TOXICOLOGISTS AREN'T 'GETTING' THE HILL CRITERIA

Comment [JA16]: Specificity is not considered a viable Hill principle. Consider smoking that is not specific at all – heart disease, lung cancer, (protective Parkinson's disease), oral cancer, etc.

Comment [wh17]: JOHN IS WRONG – IT IS THERE – IT IS THE 3 ONE MENTIONED BY HILL

Comment [JA18]: Strong in Hill's article refers to the size of the difference between exposure groups, not presence/absence of statistical significance.

Comment [JA19]: This is not what Hill meant by specificity. He meant that the exposure only caused 1 disease. Also, specificity has been refuted as a helpful criterion – witness that smoking causes many types of cancers and other diseases.

To me, this might be a matter of inconsistency unless males are particularly susceptible.

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 four 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 plausibly 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 reported by Cheminova 1993b 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 1**). In addition, IARC (2015) did not comment on the lack of renal tumors in this mouse study.

Comment [JA20]: I don't think reduced latency is what Hill meant by temporality. Most interpret temporality as the exposure preceding the effect or occurring after a reasonable time period. So, an exposure that causes more of an illness at the time it usually occurs (e.g. smoking and lung cancer) does not violate Hill's sense of temporality.

Comment [wh21]: I DON'T SEE A REASON FOR DELETING THE TEXT THAT JOHN DID BELOW

Comment [JA22]: Seems repetitive to say this again.

Comment [JA23]: Since Williams and Greim are panelists, it does not strengthen the argument to say there is agreement. Perhaps say, this reationale appears in published articles by Williams and Griem.

Comment [wh24]: I DISAGREE WITH JOHN. THERE WERE ADDITIONAL SCIENTISTS BESIDES WILLIAMS AND GREIM INVOLVED IN THOSE REVIEWS, SO IT DOES STRENGTHEN THE ARGUMENT

Comment [JA25]: Rather than criticize IARC, it seems better to say how the panel evaluated the evidence. You have mentioned previously the basis for IARC's judgments.

Comment [wh26]: I DISAGREE WITH JOHN. I WOULD INCLUDE THE STATEMENT – IT IS A RELEVANT THAT THEY DID NOT PROVIDE A REASON FOR THEIR METHOD

Comment [JA27]: Is there some reason to question the Cochran-Armitage method in this instance?

Hemangiosarcomas in mice

If the likelihood of the occurrence of haemangiosarcoma is considered in terms of the recommended criteria ~~viewpoints~~ of Bradford Hill (Hill 1965), it is clear that the association is weak. ~~There is no strength in the association (Hill 1965).~~ For example, pairwise comparisons are not significant, there is no consistency (some mouse studies show no tumors of this type at all), and a dose/response effect is not seen (some HD groups have a lower incidence than lower doses). In terms of plausibility, recent studies emphasize 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 overall the evidence does not support the conclusion ~~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.

Comment [JA28]: Strength in Hill's paper does not refer to statistical significance. It refers to the size of the relative risk. Statistical significance depends on strength of the association and sample size. Here I assume they mean the number of excess tumors was small, they were sex specific, and other studies did not find the same results for males.

Comment [wh29]: I BELIEVE WE ARE SAYING THE SAME THING IN DIFFERENT WAYS

Comment [JA30]: This is unclear. Is the point that hemangiosarcoma is highly variable across studies?

Comment [wh31]: I CAN LIVE WITH EITHER

Liver tumors in rats

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 US EPA's Peer Review of Glyphosate (US EPA 1991a,b) (see **Table 2**)

The Stout and Ruecker (1990) study has been reviewed twice by the US EPA (1991a,b). The final interpretation of the US EPA Review committee was ~~appropriate~~: "D*espite 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" (US EPA 1991b). The US EPA ultimately concluded that glyphosate should be classified as a Group E (evidence of non-carcinogenicity for humans) chemical (US EPA 1991a,b).

There are other aspects of the Stout and Ruecker (1990) data that support the conclusion that glyphosate did not exert an 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 & 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 LD used (Chruscielska et al. 2000). Considered jointly, the animals were exposed through the diet to 24 different doses distributed across a wide range of 3.0-1290.0 mg/kg body weight (bw)/d. 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 hepatocellular carcinomas. These observations confirm the absence of carcinogenic potential of glyphosate on the rat liver.

Pancreatic tumors in rats and mice

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 two of the nine 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 the US EPA (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, 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%. 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 agrees 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 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 tumors 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 tumors. Based on this information the Expert Panel concludes that there is no evidence that glyphosate induces tumors in the pancreas.

Thyroid tumors in rats

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 US EPA's Second Peer Review of Glyphosate (US EPA 1991a). 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 3** below. Additionally, the US EPA (1991a) concluded that "the C-cell adenomas 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.

In sum, the Expert Panel is of the opinion that the ~~there is no reliable~~ evidence does not support a conclusion of ~~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.

Genetic Toxicity and Oxidative Stress Data

The genetic toxicology Expert Panel considered published studies reviewed in the IARC monograph and some additional published studies identified by literature searches or from ~~in~~ reviews ~~articles that were not considered by IARC.~~ These included both genetic toxicology studies and studies of oxidative stress. A large number of core genetic toxicology regulatory studies were also considered for which information was available from review supplements. These regulatory studies were not considered in the IARC monograph but the Expert Panel

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concluded that sufficient information was available to justify including these studies. The universally recommended method for evaluating the databases of the type associated with glyphosate (including GBFs and AMPA), involves the application of a WOE approach as discussed recently for genetic toxicology testing (US FDA 2006; Dearfield et al. 2011). One of the most important requirements of a WOE approach 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.

The weight of a category of evidence used in the Expert Panel evaluation is based on four considerations (i) Different categories of evidence (i.e. assay types) have different weights. (ii) The aggregate strength (robustness of protocols and reproducibility) and quality of evidence in the category also influence the weight (Klimisch et al. 1997), (iii) The number of pieces of evidence within a category influences the weight, and (iv) Tests with greater ability to extrapolate results to humans carry greater weight (e.g. test with non-human/mutated cell lines *vs* human donor derived cells). In general, human and *in vivo* mammalian systems have the highest test system weight, with a lower degree of weighting applied to *in vitro* mammalian cell systems and *in vivo* non-mammalian systems and lowest weight to *in vitro* non-mammalian systems (with the exception of the well validated bacterial reverse mutation-Ames test- using mammalian metabolic activation).

Publications in which glyphosate or GBFs have been tested for genotoxicity in a variety of non-mammalian species other than bacterial reverse mutation were included in the IARC review, ~~and apparently had significant weight in the IARC evaluation.~~ Many of these studies used non-standard species (e.g. fish) and exposure protocols (e.g. inclusion of surfactants in water exposure) and DNA damage endpoints. 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

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have significant weight in the overall genotoxicity evaluation, especially given the large number of standard core studies in the more relevant gene mutation and chromosomal effects categories available in mammalian systems. Support for this Expert Panel view 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 substantial results from validation studies suggesting concordance with rodent or human carcinogenicity. OECD guidelines specifically state that use of any non-standard tests require justification along with stringent validation including establishing robust historical negative and positive control databases (OECD 2014).

In addition, the IARC review seemed to apply significant weight to "indicator" tests such as DNA damage (comet assay) or SCE studies. These indicator tests are so called because the measured endpoint does not always lead to mutation, a change that can be passed on to subsequent generations. As stated by the OECD (2015), when evaluating potential genotoxicants, more weight should be given to the measurement of permanent DNA changes than to DNA damage events that are reversible. Therefore, the Expert Panel also considered that the data from these "indicator" tests with glyphosate, GBFs and AMPA should not have significant weight in the overall genotoxicity evaluation, especially given the large number of standard core studies in the more relevant gene mutation and chromosomal effects categories available in mammalian systems.

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

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suggests 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 regarding safety 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 2011; EFSA 2011). Therefore, the endpoints given the greatest weight in **Table 4** consist of gene mutation and chromosomal aberrations.

An evaluation of the studies in **Table 5** 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 (eight of nine) or from all studies combined (eight of 11).
- 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 six out of 15 studies identified as high weight being positive for the IARC evaluation, and only eight 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 contribute 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 5**) should be included in a WOE assessment. The rationale supporting the inclusion of these 90 additional studies is that the supplementary tables presented in the Kier and Kirkland (2013) paper 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.

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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 concluded that the available data ~~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 key study categories (mutation, chromosomal effects) considered relevant for or mechanistically associated with carcinogen prediction. As additional

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~~To p~~support for ~~rovide greater emphasis to~~ the Expert Panel's WOE conclusion, **Table 6** 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.

Beyond the standard genetic toxicity assays, IARC concluded for humans exposed to GBFs that there was positive evidence of DNA breakage as determined using the comet assay Paz-y-Miño et al. (2007), negative induction of chromosome aberrations (Paz-y-Miño 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 as evidence for GBF effects for many reasons (e.g. 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). In addition to questions about the significance of the comet endpoint there is also a lack of scientific consensus regarding the relevance of micronuclei found in exposed humans (Speit 2013; Kirsch-Volders et al. 2014). ~~The IARC Monograph placed special emphasis on the micronucleus study and qualifications for this study in the Monograph Mechanistic and Other Relevant Data section were not subsequently mentioned in the Monograph Evaluation and Rationale sections.~~ Important, very significant findings for the Bolognesi ~~is~~ study were that increases in micronuclei were not significantly correlated with self-reported GBF spray exposure and were not consistent with application rates. 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.

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With respect to oxidative stress and genotoxic potential of glyphosate and its formulations, it is noted that many more oxidative stress studies are available for GBFs than for glyphosate or AMPA. A higher proportion of the GBF studies show evidence of oxidative stress. This might be consistent with induction of oxidative stress by GBF components such as surfactants. IARC's statement that there is strong ~~IARC claims of strong e~~Eevidence supporting oxidative stress from AMPA seems to result from glyphosate and particularly GBF results rather than AMPA

results. In fact, oxidative stress studies of AMPA are very limited. The paucity of cited data does not seem to justify a conclusion of strong evidence for oxidative stress induction by AMPA.

One mechanism connecting oxidative stress to induction of carcinogenicity is oxidative damage to DNA and the generation of mutagenic lesions. Most of the endpoints used in oxidative stress studies cited by IARC are response endpoints and the number of studies examining oxidative DNA damage are very few and with mixed results. Further, research on oxidative stress induced genotoxicity suggests that it is often a secondary response to toxicity and characterized by a threshold (Pratt & Barron 2003). Comparison of GBF oxidative stress study results with predicted human exposure levels of less than 0.064 mg/kg bw/d, suggests that it is not likely that GBFs would induce oxidative stress likely to exceed endogenous detoxification capacities.

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.

A thorough WOE review of genotoxicity data does not indicate that glyphosate, GBFs or AMPA possess the properties of genotoxic hazards or genotoxic mechanisms of carcinogenesis

Epidemiological Data

The epidemiology panelists conducted a systematic review of the published glyphosate literature for the two cancers that were the focus of IARC's epidemiology review: non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM). Their approach was implemented to be consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews (Moher et al. 2009). Initially, an exhaustive search

of the medical literature was performed to identify all epidemiological studies that examined the relationships between reported use of glyphosate and NHL or MM. This resulted in seven unique studies for NHL and four studies for MM after removal of duplicates and focusing on the most recent findings for study populations that were the subject of more than one publication. Each study was then reviewed individually according to key validity considerations specified a priori and the results for NHL and MM separately were evaluated systematically according to widely used criteria for judging causal associations from epidemiologic studies (Hill 1965).

Data abstracted from each study included: first author, year of publication, outcome (NHL, MM), study design, study size, statistical methods, results (measure of relative risk [RR] with accompanying 95% confidence interval [95% CI]), exposure-response findings, and variables controlled in the analyses. Each study was evaluated for key features that relate to study validity, most importantly: recall bias, proxy respondents, selection bias, adequate statistical control for confounding, and evaluation of dose response (**Table 7**).

Of the seven NHL studies, only one study – the Agricultural Health Study (AHS) cohort study (De Roos et al. 2005) – was devoid of major concerns about recall bias and selection bias by virtue of the design, controlled comprehensively for confounding factors, and extensively considered relative risk by frequency and duration of glyphosate use. This study of more than 50,000 licensed pesticide farmers and applicators collected information about pesticide use before follow-up for health outcomes, had only firsthand respondents reporting about pesticide use (viz. no proxy respondents), had minimal potential for selection bias, and included statistical analyses that controlled confounding by myriad personal characteristics and non-glyphosate occupational exposures. In addition, De Roos et al. (2005) were the only investigators who conducted exposure-response analyses while controlling extensively for confounding exposures. In contrast, the NHL case control studies had major validity concerns including the strong potential for recall bias, selection bias (either appreciably lesser participation for controls

than cases or selecting controls that clearly did not reflect the population that gave rise to the cases [e.g. hospitals controls from rheumatology and orthopedic departments]), proxy respondents, and uncontrolled confounding in the statistical analyses. Indeed, in many of the case control studies virtually every pesticide exposure studied was associated with increased risk for NHL (or MM) – a clear indication of widespread systematic bias.

With these considerations in mind, for NHL, the results of the De Roos et al. (2005) cohort study were considered the only dependable epidemiologic findings. As De Roos et al. (2005) concluded "... the available data provided evidence of no association between glyphosate exposure and NHL incidence." Results from this study drove the panel's conclusion of no epidemiologic support for a relationship between reported glyphosate use and NHL.

The glyphosate literature for MM is appreciably sparser than the literature for NHL, both in terms of the number of available studies (one cohort and three case control studies) and the number of cases in those studies with reported glyphosate use. The three case control studies had important validity concerns, as noted for the NHL case control studies, and were unable to adjust analyses comprehensively for confounding factors due to the very small number of exposed cases. The AHS cohort study (De Roos et al. 2005 and re-analyzed by Sorahan 2015) found that glyphosate users had about the same rate of MM as non-users adjusting for confounding factors, but had too few exposed cases to conduct informative exposure response analyses. Overall, then, the available literature was considered inadequate to make an informed judgment about a potential relationship between glyphosate and MM.

In summary, the Expert Panel concluded that the glyphosate epidemiologic literature does not indicate a relationship with glyphosate exposure and NHL. For MM, the evidence was considered too sparse to judge a relationship between MM and reported glyphosate use.

Discussion and Conclusions

The expert panel focused on glyphosate exposure, animal carcinogenicity, genotoxicity, and epidemiologic studies. 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. With respect to exposure, s 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 US EPA's RfD, which is the allowable limit of daily exposure derived from toxicity studies and in the most exposed applicators (90th centile) the systemic dose was estimated at 20-fold less that the RfD. Most exposures are in the range of 0.00001-0.01 mg/kg bw/d and this includes occupational exposures. Exposures in this range cannot plausibly be associated with a measurable (i.e. in experimental animals or in epidemiology studies) increase in cancer risk and therefore even a potent genotoxic carcinogen would have minimal risk at such low exposure levels. Overall, the exposure to glyphosate is clearly shown to be so low as to negate the concerns implicit in the IARC process; however, IARC's non-standard process leads them to interpret study data differently from those groups informed about the relevant science.

In addition, in the current IARC (2015) assessment of glyphosate, any numerical increase in tumors, sometimes identified only after statistical manipulation, might be considered a treatment-related effect regardless of what the data from the study indicated. Furthermore, IARC's evaluation didn't consider all relevant data or to apply an overall WOE approach from the full data sets for animal carcinogenicity, genotoxicity, and epidemiology studies. In contrast, the Expert panel included a number of additional studies which were available for analysis within their overall evaluation. Therefore, IARC's disregard of valid data without explanation cannot be considered to be a reasonable practice.

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With respect to the cancer bioassay data, the Eexpert Ppanel conducted a thorough overall WOE evaluation that considered a much wider range of studies than IARC, all of which met GLP guidelines and ~~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 was highlighted in the paper of Greim et al. (2015) where a total of fourteen carcinogenicity studies, nine chronic/carcinogenicity studies in the rat, including one peer-reviewed published study, and five carcinogenicity studies with glyphosate in mice were evaluated. All these studies~~ were submitted to support glyphosate Annex I renewal in the European Union. These studies provided evidence 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 was found to be inconsistent across and within species and no "novel" neoplasms appeared; progression of non-neoplastic to neoplastic lesions also was not seen. Further, the comparatively large number of studies performed ~~might~~ would be expected to lead to several "positive" results by chance. In fact, Haseman (1983) has estimated that the overall false positive rate for animal bioassays that tested both sexes in two species, because of multiple comparisons, corresponds to 7-8% significance level for the study as a whole; the U.S. FDA has estimated that the overall rate can approach 10%.

~~A number of scientific groups, regulatory agencies and individuals have 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:

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(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;

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(ii) the ~~strength of~~ association of haemangiosarcomas in the liver of mice is ~~absent~~weak, lack~~ings~~ consistency, and there as no a dose-response effect;

(iii) the ~~strength of~~ association of pancreatic islet-cell adenomas in male SD rats is weak~~absent~~, not seen in the majority of rat studies, lack~~ings~~ a dose-response pattern (the highest incidence is in the low dose followed by the high dose), plausibility and pre-neoplastic/malignant effects;

(iv) in 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;

(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.

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~~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, AMPA and 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~~

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~~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.~~

~~Lastly, The final set of data on which IARC (2015) based their conclusion was the epidemiology data with respect to glyphosate exposure/use in relation to the incidence of NHL and MM. T~~The Expert Panel's review of the glyphosate epidemiologic literature and the application of commonly applied causal principles d~~id~~o 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 extremely large margin of safety found in exposure monitoring studies is considered to be supportive of these conclusions. ~~The maximum systemic dose found in a review of all glyphosate biomonitoring studies completed to date is 0.004 mg/kg (Niemann et al. 2015). For comparison, the US EPA'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 1.75 mg/kg/d (US EPA 1993). The geometric mean systemic glyphosate dose for applicators is 0.0001 mg/kg/d. 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~~

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~~methodological issues, De Roos et al. (2005), shows no indication that glyphosate exposure is associated with increased risk for NHL.~~

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.~~

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Tables

Table 1. 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

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Table 2. Sprague-Dawley male rats, hepatocellular tumor rates+ and Cochran-Armitage trend and Fisher's Exact tests results (p values).

	Dose (ppm)			
Tumors	0	2000	8000	20 000
Carcinomas	3/34	2/45	1/49	2/48†
(%)	(7)	(4)	(2)	(4)
p	0.324	0.489	0.269	0.458
Adenomas	2/44	2/45	3/49	7/48‡
(%)	(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¶	0/48
(%)	(0)	(0)	(2)	(0)
p	0.462	1.000	0.527	1.000

source: US EPA (1991a,b)
* Number of tumor-bearing animals/number of animals examined, excluding those that died or were sacrificed before week 55
† First carcinoma observed at week 85 at 20 000 ppm
‡ First adenoma observed at week 88 at 20 000 ppm
¶ First hyperplasia observed at week 89 at 8000 ppm
Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If then $p < 0.05$.

Table 3 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)

Table 4. 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 IARC	Gene Mutation	High	0/19	0/20	0/1	0/40
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)	2/0 (2/0)	1/1 (1/0)	8/3 (8/1)

ND, No Data
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.

Comment [jv51]: footnotes missing from table

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Table 5. 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	0/31
	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

Table 6. 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

AMPA, aminomethylphosphonic acid; GBF, glyphosate-based formulation

Table 7. Key validity considerations in glyphosate epidemiological studies

1st Author (year)	Study Design	Outcome	Recall bias	Selection bias	Proxy respondents	Adequate control for confounding	Exposure-response & trend test
De Roos et al. (2005)	Cohort	NHL, MM	No	Unlikely	No	Yes	Yes, yes
McDuffie et al. (2001)	Case control	NHL	Likely	Likely	21% cases 15% controls	No	Yes, no trend test
Hardell et al. (2002)	Case control	NHL, HCL	Likely	Unlikely	43% NHL cases and controls, 0% for HCL	No	No
De Roos et al. (2005)	Case control	NHL	Likely	Likely	31% for cases; 40% for controls	Yes	No
Eriksson et al. (2008)	Case control	NHL	Likely	Unlikely	No	No	Yes, no trend test
Orsi et al. (2009)	Case control	NHL, MM	Likely	Likely	No	No	No
Cocco et al. 2013	Case control	NHL	Likely	Likely	No	No	No
Brown et al. (1993)	Case control	MM	Likely	Unlikely	42% for cases; 30% for controls	No	No
Kachuri et al. (2013)	Case control	MM	Likely	Likely	Excluded in analysis	No	Yes, no trend test

NHL, non-Hodgkin's lymphoma; MM, multiple myeloma