Taylor & Francis
Taylor & Francis Group

Critical Reviews in Toxicology

ISSN: 1040-8444 (Print) 1547-6898 (Online) Journal homepage: http://www.tandfonline.com/loi/itxc20

Glyphosate rodent carcinogenicity bioassay expert panel review

Gary M. Williams, Colin Berry, Michele Burns, Joao Lauro Viana de Camargo & Helmut Greim

To cite this article: Gary M. Williams, Colin Berry, Michele Burns, Joao Lauro Viana de Camargo & Helmut Greim (2016) Glyphosate rodent carcinogenicity bioassay expert panel review, Critical Reviews in Toxicology, 46:sup1, 44-55, DOI: 10.1080/10408444.2016.1214679

To link to this article: http://dx.doi.org/10.1080/10408444.2016.1214679

© 2016 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.

Published online: 28 Sep 2016.

Submit your article to this journal

Article views: 17

View related articles

View Crossmark data

Citing articles: 1 View citing articles

Full Terms & Conditions of access and use can be found at
http://www.tandfonline.com/action/journalInformation?journalCode=itxc20

Download by: [209.112.18.114] **Date:** 30 September 2016, At: 06:29

ED_001560_00009050-00001

CRITICAL REVIEWS IN TOXICOLOGY, 2016
VOL. 46, NO. S1, 44–55
http://dx.doi.org/10.1080/10408444.2016.1214679

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

OPEN ACCESS

Glyphosate rodent carcinogenicity bioassay expert panel review

Gary M. Williams[a], Colin Berry[b], Michele Burns[c], Joao Lauro Viana de Camargo[d] and Helmut Greim[e]

[a]New York Medical College, Valhalla, NY, USA; [b]Queen Mary, University of London, London, UK; [c]Boston Children's Hospital, Boston, MA, USA; [d]Botucatu Medical School, Sao Paulo State University, UNESP, Sao Paulo, Brazil; [e]Technical University of Munich, Munich, Germany

ABSTRACT

Glyphosate has been rigorously and extensively tested for carcinogenicity by administration to mice (five studies) and to rats (nine studies). Most authorities have concluded that the evidence does not indicate a cancer risk to humans. The International Agency for Research on Cancer (IARC), however, evaluated some of the available data and concluded that glyphosate probably is carcinogenic to humans. The expert panel convened by Intertek assessed the findings used by IARC, as well as the full body of evidence and found the following: (1) the renal neoplastic effects in males of one mouse study are not associated with glyphosate exposure, because they lack statistical significance, strength, consistency, specificity, lack a dose-response pattern, plausibility, and coherence; (2) the strength of association of liver hemangiosarcomas in a different mouse study is absent, lacking consistency, and a dose-response effect and having in high dose males only a significant incidence increase which is within the historical control range; (3) pancreatic islet-cell adenomas (non-significant incidence increase), in two studies of male SD rats did not progress to carcinomas and lacked a dose-response pattern (the highest incidence is in the low dose followed by the high dose); (4) in one of two studies, a non-significant positive trend in the incidence of hepatocellular adenomas in male rats did not lead to progression to carcinomas; (5) in one of two studies, the non-significant positive trend in the incidence of thyroid C-cell adenomas in female rats was not present and there was no progression of adenomas to carcinomas at the end of the study. Application of criteria for causality considerations to the above mentioned tumor types and given the overall weight-of-evidence (WoE), the expert panel concluded that glyphosate is not a carcinogen in laboratory animals.

Abbreviations: APVMA: Australian Pesticides and Veterinary Medicines Authority; EC: European Commission; EFSA: European Food Safety Authority; FAO: Food and Agriculture Organization; IARC: International Agency for Research on Cancer; ICH: International Conference on Harmonization; IPCS: International Program on Chemical Safety; JMPR: Joint FAO/WHO Meeting on Pesticide Residues; OECD: Organization for Economic Co-operation and Development; US EPA: United States Environmental Protection Agency; US FDA: United States Food and Drug Administration; WHO: World Health Organization

ARTICLE HISTORY
Received 8 April 2016
Revised 7 June 2016
Accepted 15 July 2016

KEYWORDS
Glyphosate; aminomethylphosphoric acid; Roundup; herbicide; cancer; genotoxicity

Table of contents

Introduction ... 44
Background to the IARC evaluation ... 45
Rodent carcinogenicity studies ... 45
Background ... 45
Evaluation of IARC's conclusions ... 47
Kidney tubular-cell neoplasia in mice ... 47
Hemangiosarcomas in mice ... 49
Pancreatic tumors in rats ... 49
Liver tumors in rats ... 50
Thyroid tumors in rats ... 51
Evaluations by regulatory agencies, scientific bodies and third party experts ... 52
Regulatory agencies ... 52
Scientific bodies ... 52
Independent experts ... 52
Conclusions ... 52
Acknowledgements ... 52
Declaration of interest ... 53
References ... 53

Introduction

An expert panel was convened by Intertek, as described above (Williams et al. 2016) in response to the scientifically surprising conclusion of an International Agency for Research on Cancer (IARC 2015) panel's conclusion that data on glyphosate were sufficient to be classified by IARC as category 2a – "probably carcinogenic to humans". This conclusion contradicts a number of reviews and regulatory approvals that previously evaluated the carcinogenic and genotoxic potential of glyphosate (N-(phosphonomethyl)glycine) and its metabolite aminomethyl phosphonic acid. Glyphosate-based formulations (GBFs) were also in use prior to the

CONTACT Gary M. Williams, MD gary_williams@nymc.edu New York Medical College, Department of Pathology, BSB413, Valhalla, NY 10595, USA

© 2016 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.

development of IARC Monograph 112 (Health and Welfare Canada 1991; US EPA 1993a, 2013; WHO 1994; Williams et al. 2000; European Commission 2002; Kier & Kirkland 2013). The consensus among these reviews was that glyphosate was not considered to be an animal or human carcinogen and that the use of glyphosate and GBFs does not pose a genotoxic or carcinogenic hazard or risk. As a result, glyphosate-based herbicides have been approved for use in over 160 countries.

Background to the IARC evaluation

In this section, direct quotes from the IARC documentation are italicized so as to better define their stated objectives.

In examining what are called "agents", IARC refers to "specific chemicals, groups of related chemicals, complex mixtures, occupational or environmental exposures, cultural or behavioral practices, biological organisms and physical agents". A consistent pattern of consideration of this extraordinarily wide range of categories is clearly hard to achieve by a single mode of action (MoA).

Any of these categories might be considered in a monograph, which is stated to be the first step in carcinogen risk assessment – more precisely described as hazard identification. The monographs are intended to identify cancer hazards even when the perceived risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher. In some IARC monographs, epidemiological studies used to identify a cancer hazard can also be used to estimate a dose-response relationship. The epidemiological review in the IARC document makes clear that this would not be appropriate regarding glyphosate.

IARC indicates that the outcome of these deliberations represent only one part of the body of information on which public health decisions may be based. It is nevertheless important that the data presented are the result of a set of deliberations, which acknowledge the characteristics of the scientific method in terms of the consideration of the available data.

Rodent carcinogenicity studies

Background

In considering any potential human carcinogen, information from many fields of science can be of value and none should be ignored, unless there are cogent and properly defined reasons for so doing. Studies that are poorly designed and thus inherently flawed may be excluded from consideration and developments in science subsequent to testing or new information may make it clear that the conclusions of earlier studies were not valid; this is how science progresses.

Animal testing over a significant portion of their lifespan is an integral part of the regulatory process and is clearly intended to provide information, which aids in the identification of potentially carcinogenic properties of a chemical. These properties are those that might result in an increased incidence of neoplasms in treated animals when compared with concurrent control groups. The studies may identify target organ(s) for carcinogenicity, characterize a tumor dose/response relationship, identify a no-observed-adverse-effect level (NOAEL) or point of departure for establishment of a benchmark dose, provide information allowing the extrapolation of carcinogenic effects to low-dose human exposure levels, and may also provide data to test hypotheses regarding a possible MoA (Williams et al. 2014).

Methods for evaluating the results of an extensive database of toxicology and carcinogenicity bioassays, as exist for glyphosate, have evolved from the application of WoE approaches (US EPA, 2005; Suter and Cormier, 2011) to approaches built on the systematic and rigorous methods of systematic evidence-based reviews (James et al. 2015). These approaches recommend that all reliable information be evaluated. Transparent descriptions of studies to be included and excluded are a key component of this approach. For example, if certain studies are determined to be invalid and thus not included, the reasons for these exclusions should be provided.

The majority of carcinogenicity studies are carried out in rodent species, most commonly with dosing via the oral route. In regulatory toxicology, the Organization for Economic Co-operation and Development (OECD) guidelines are commonly followed and these have been reviewed over a number of years, most recently in 2008 (OECD 2009). 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 any studies are to be ignored, the reasons for this should be provided.

The panel members were of the opinion that the IARC evaluation showed selectivity in the choice of data reviewed, with some omissions for which reasons were not clearly presented. These points will be considered below in more detail with regard to particular tumors, but an example of how an informative data set was not included in the IARC review is highlighted by the paper of Greim et al. (2015) who evaluated 14 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 (European Commission, 2002) and were detailed in a supplement to the Greim et al. (2015) paper. The IARC Monograph reviewed only six rat and two mouse studies.

The dosing regimens in regulatory studies are determined on the basis of internationally agreed frameworks and in general, some evidence of an effect is sought. The attempt to demonstrate a potential toxic effect with a nontoxic compound, such as glyphosate has meant that the highest doses studied may utilize the compound at dosages of tens of thousands of parts per million in the diet, levels that are considered to be orders of magnitude greater than would be achieved from human exposure. Unusually, for glyphosate, there are also a number of studies in which lower doses are used.

Table 1 from Greim et al. (2015) provides a summary of the results of eight different rat studies conducted on glyphosate. As the studies used dietary exposure, the achieved dose levels in each study vary. Table 1 presents a tabulation of the

Table 1. Summary of select neoplasms in male rats (studies 1–8) listed in the legend .

	Tumor incidence/number of animals examined by dose in mg/kg bw/day (ppm diet)											
Select neoplasm	Controls– 0 [range in %]	3† (30)	7.4§ (100)	10† (100)	10¶ (adjust)¶¶¶	31† (300)	73.9§ (1000)	86†† (1500)	89‡ (2000)	100¶ (adjust)¶¶¶	104# (3000)	121 (2000)
Pancreas islet cell adenoma	20/397 [0–14]	5/49	0/30	2/50	1/24	2/50	0/32	1/51	8/57	2/17	1/74	2/64
Pituitary adenoma	153/398 [6–57]	19/49	4/30	20/48	12/24	18/47	3/31	11/51	32/58	8/19	41/75	17/63
Pituitary carcinoma	4/98 [2–6]	2/49	NF	3/48	1/24	1/47	NF	NF	NF	0/19	NF	NF
Testes interstitial cell (Leydig)	14/447 [0–8]	3/50	0/37	1/50	1/25	6/50	2/32	3/51	0/60	0/19	2/75	2/63
Thyroid C cell adenoma	35/391 [4–18]	1/49	0/26	0/49	1/21	2/49	1/29	#1/51	5/58	1/17	10/74	#1/63
Hepatocellular adenoma	30/351 [0–48]	NF	22/50	NF	1/50	NF	10/48	2/51	2/60	1/49	0/75	2/64
Hepatocellular carcinoma	22/384 [0–42]	0/50	28/50	1/50	1/50	2/50	18/48	0/51	2/60	1/49	1/75	NF
Benign keratoacanthoma (skin)	8/250 [2–5]	NF	NF	NF	NF	NF	NF	3/51	3/60	NF	3/75	0/64

	Tumor Incidence/number of animals examined by dose mg/kg bw/day (ppm diet)													
Select neoplasm	150| (3000)	285†† (5000)	300¶ (adjust)¶¶¶	354# (10000)	361 (6000)	362† (8000)	740.6§ (10000)	780| (15000)	940‡ (20000)	1000¶ (adjust)	1077†† (15000)	1127# (30000)	1214 (20000)	1290| (25000)
Pancreas islet cell adenoma	NF	2/51	2/21	1/80	0/64	5/60	1/49	NF	7/59	1/49	1/51	1/78	1/64	NF
Pituitary adenoma	NF	10/51	7/21	33/80	18/64	34/58	5/49	NF	32/59	17/50	20/51	42/78	19/63	NF
Pituitary carcinoma	NF	NF	1/21	NF	NF	NF	NF	NF	NF	0/50	NF	NF	NF	NF
Testes interstitial cell (Leydig)	1/49	1/51	0/21	0/80	2/63	3/60	3/50	2/49	2/60	2/50	1/51	2/78	2/64	0/47
Thyroid C cell adenoma	NF	‡‡0/51	2/21	5/79	‡‡1/63	8/58	1/50	NF	7/60	8/49	‡‡3/51	6/78	‡‡0/64	NF
Hepatocellular adenoma	NF	0/51	2/50	2/80	0/64	3/60	21/50	NF	8/60	2/50	1/51	1/78	5/64	NF
Hepatocellular carcinoma	1/49	0/51	0/50	2/80	NF	1/60	24/50	0/49	2/60	0/50	0/51	1/78	NF	0/47
Benign keratoacanthoma (skin)	NF	0/51	NF	0/80	1/64	4/60	NF	NF	5/59	NF	6/51	7/78	1/63	NF

The 25 doses result from the multiple doses per individual study.
Taken from Greim et al. 2015.
†Study 1 (Monsanto) (CD) SD rats, rated unreliable for carcinogenicity evaluation.
‡Study 2 (Monsanto) (CD) SD rats, including interim sacrifice groups.
¶Study 3 (Cheminova) SD rats.
§Study 4 (Feinchemic Schwebda) Wistar rats.
|Study 5 (Excel) SD rats, rated unreliable for carcinogenicity evaluation.
#Study 6 (Arysta Life Sciences) Crj:CD SD rats, including interim sacrifice groups.
Study 7 (Syngenta) Alpk:APfSD Wistar rats, including interim sacrifice groups.
††Study 8 (Nufarm) Wistar Han Crl:WI rats.
‡‡Recorded as parafollicular adenoma.
¶¶¶Dietary concentrations adjusted weekly to achieve target mg/kg bw/day dose.
NF: not found/not reported.

relevant tumor data for each of these eight studies in ascending order of achieved dose (lowest to highest). This allows a comparison of the incidence of specific neoplasms in each of the eight studies at all dose levels. As can be seen from Table 1, some of the benign tumors in male rats that appear to concern IARC in terms of the potential risk to humans, are widely represented in non-exposed animals as well as those exposed to doses well below those that might be expected in standard carcinogenicity studies conducted for regulatory purposes. The incidence of tumors shows no clear or consistent pattern, either across dose or individual study. Such a distribution of findings strongly indicates that these incidences represent spontaneous variations.

Neoplasm data can be analyzed using a survival-adjusted trend test that discriminates among fatal, incidental, and palpable neoplasms (Peto et al., 1980). If one or more tumor types in a valid bioassay show a significant positive trend in incidence rates, the significance level (p value) for rare (└ 1% background incidence) neoplasms would be 0.025 and for common neoplasms 0.005 (US FDA 2001; Williams et al. 2014). For pairwise comparisons (control vs high dose), the significance of rare neoplasms would be 0.05 and of common 0.01 (US FDA 2001; Williams et al. 2014).

In the Monograph, IARC concluded that there is sufficient evidence in experimental animals for the carcinogenicity of glyphosate, reaching this opinion by the use of trend analysis in the absence of statistical significance in pairwise comparisons. Furthermore, the level of significance which differs between rare and common tumors was not taken into account.

Evaluation of IARC's conclusions

IARC concluded that glyphosate induced:

1. A significant positive trend in the incidence (p¼.037) of renal tubule carcinomas and of adenomas and carcinomas (p¼.034) in male CD-1 mice of one study only. This is a rare tumor type.
2. In a second feeding study in the same strain of mice, a significant positive trend in the incidence ($p < .001$) of hemangiosarcomas in male mice.
3. In two dietary studies in SD rats, a significant positive trend ($p < .05$) in the incidence of pancreatic islet cell adenomas occurred in male rats.
4. In the first dietary study in SD rats, a significant positive trend (p¼.016) in the incidence of hepatocellular adenomas occurred in males.
5. In the first dietary study in SD rats, a significant positive trend (p¼.031) in the incidence of thyroid C-cell adenomas occurred in females.

The expert panel evaluated each of these conclusions further below.

Kidney tubular-cell neoplasia in mice

The expert panel noted that the conclusions of the IARC monograph 112 (IARC 2015) with respect to kidney neoplasms in male CD-1 mice were based on only one of two oral mouse two-year carcinogenicity studies (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 mouse studies were considered by expert groups to meet the guidelines for carcinogenicity bioassay in mice (US EPA 1990; ICH 1997). The two mouse studies evaluated by IARC, which were the first two studies reported, were also reviewed by Williams et al. (2000).

This section examines the renal neoplasms that occurred in the first two-year, oral chronic toxicity, and carcinogenicity study in CD-1 mice (Monsanto 1983), which was subsequently reevaluated by a pathology working group (PWG) (Dr. R M Sauer, Dr. MR Anver, Dr. JD Strandberg, Dr. JM Ward, and Dr. DG Goodman) and peer review experts including Dr. Marvin Kuschner M.D., Dean, School of Medicine, State University of New York at Stony Brook; Dr. Robert A. Squire, Robert A. Squire Associates Inc., Ruxton Maryland; Klaus L. Stemmer M.D., Kettering Laboratory, University of Cincinnati Medical Center, and; Robert E. Olson, M.D., Ph.D., Professor of Medicine and Pharmacological Sciences, State University of New York at Stony Brook (Sauer 1985; US EPA 1985a, 1985b, 1986, 1991a; McConnell 1986) and compares these findings to the other four chronic toxicity and carcinogenicity mouse studies with oral glyphosate (GLY) administration. These latter four studies did not produce renal neoplasms (Cheminova 1993a; Arysta Life Sciences 1997; Feinchemie Schwebda 2001; Nufarm 2009).

In the first two-year bioassay reported by Monsanto in 1983, male and female CD-1 mice were dosed with GLY at 0 (M0/F0, control group), 1000 [157/190, low-dose (LD) group], 5000 [814/955, mid-dose (MD) group] or 30,000 [4841/5874 mg/kg/d, high-dose (HD) group] ppm in the diet. In this and all the other carcinogenicity studies, HD animal survival was high. Some of the pertinent, but not significant, GLY-related effects were observed only in the high-dose group in males. They included: decrease in body weight gain, a centrilobular hepatocellular hypertrophy, and a urinary bladder hyperplasia. In addition, initially, neoplastic (benign) renal tubule adenomas were found microscopically in male mice only (0/49, 0/49, 1/50 (2%), 3/50 (6%) at the terminal necropsy. The initial diagnosis in one MD mouse (mouse #3023), and three HD mice (mouse #'s 4029, 4032, 4041) was that of renal cell adenoma (Monsanto 1983). This rare neoplasm is designated as renal cell adenoma or tubular cell adenoma (Greaves 2012). Macroscopically, the location and dimensions of these adenomas were as follows: In #3023, a mass was found on the right kidney (2.4┘ 1.8 cm), in #4029, a very small area was suspected (no location and dimensions were given), in #4032, a suspicious area was found on the left kidney (0.5┘ 0.4 cm), in #4041, a suspicious area was found on the left kidney (0.6 cm in diameter). Subsequently, reevaluation was made by a PWG that resulted in a report by Sauer (1985) and McConnel (1986). This was also reflected in four US EPA submissions (US EPA 1985a, 1985b, 1986, 1991a). The final evaluation of the

Table 2. Final evaluation of pertinent renal histopathology findings from Monsanto Study (1983).

Diagnosis	Mouse and group identification	Group incidence
Tubular-cell adenoma	1028	Control 1/49
Tubular-cell carcinoma	3023*,	Mid dose 1/50
	4029, 4032, 4041	High dose 3/50
Tubular-cell hyperplasia	1018,	Control 1/49
	3031, 3039,	Mid dose 2/50
	4008, 4049	High dose 2/50
Intercurrent† papillary hyperplasia	1008, 1041,	Control 2/49
	3008, 3050	Mid dose 2/50

Bold numbers indicate the original histopathological diagnosis of tubular-cell adenoma in four male mice; TCA/TCC, this combination was utilized in the IARC 2015 evaluation, only the trend analysis was p¼.034, a value level, which is not significant for rare tumors (US FDA 2001); , this neoplasm was the largest of all neoplasms; †, intercurrent occurring indicates while another process/renal toxic change was in progress.

kidney pathology produced the following incidences of pertinent renal findings detailed in Table 2.

The overall final incidence of renal neoplasms in male mice was as follows: 1/49, 0/49, 1/50, and 3/50, with the largest neoplasm being in the MD (#3023) group. The important non-neoplastic renal findings of hyperplasia were as follows: 3/49, 0/49, 4/50, and 2/50, indicating absence 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.

Based on the pattern of pre-neoplasia and neoplasia described above, the PWG recommendation was that the renal neoplasms were not compound related, since they were not preceded by dose-related proliferative changes (hyperplasia). Thus, there was no dose-response for pre-neoplasia. In addition, no multiple renal neoplasms and no nephrotoxic lesions were found in any of the mice; many mice had proliferative/cystic lesions in the parietal layer of the Bowmans' capsule and proximal convoluted tubules. These changes, however, were more severe in controls. In addition, the females from the HD group of the study had no renal neoplasms and only proximal tubule epithelial basophilia and hypertrophy. No discrepancies were noted in any of the histopathology reporting among the various expert panel groups (Sauer 1985; US EPA 1985a, 1985b, 1986; McConnel 1986).

In addition to the PWG recommendations (above), a review of the renal lesions, which occurred only in 14 out of 198 male mice at the termination of the first (Monsanto 1983) study, showed clearly that none of the occurrences of hyperplasia (tubular-cell hyperplasia or intercurrent papillary hyperplasia were present in mice that had tubular-cell adenoma or tubular-cell carcinoma (Table 2). The absence of hyperplasia indicates that all renal proliferative and neoplastic lesions occurred de novo in male mice in all experimental groups (including controls), i.e. they were spontaneous or background lesions, and were not compound related. Moreover, the female mice, which had received 1.2-times, 1.1-times, or 1.2-times more GLY, within the LD, MD, or HD groups, respectively, had no renal neoplastic lesions.

Thus, the Monsanto (1983) report concluded that for male and female mice, the lower NOAEL was 157 mg/kg/d, and the lowest observed adverse effect level was 814 mg/kg/d.

Three additional oral carcinogenicity studies were conducted in CD-1 mice and one in Swiss Albino mice (Cheminova 1993a; Arysta Life Sciences 1997; Feinchemie Schwebda 2001; Nufarm 2009).

The Cheminova (1993a) report, was a two-year mouse study. In this study, no renal neoplasms were evident up to 1000 mg/kg/d (HD) of GLY in CD-1 mice of both sexes.

In an 18-month diet study in CD-1 mice, histopathological evaluations of groups dosed up to 4200 mg/kg/d of GLY (HD), did not show any evidence of renal neoplasms in male or female mice (Arysta Life Sciences 1997).

In an 18-month diet study in Swiss Albino mice, up to 1460 mg/kg/d (HD) of GLY produced no statistically significant neoplastic lesions (Feinchemie Schwebda 2001) and finally, in a 18-month diet study in CD-1 mice at dosages up to 946 mg/kg/d (HD) of GLY was shown not to be carcinogenic to the kidney (Nufarm 2009).

In the last four mouse carcinogenicity studies, multiple-section sampling of kidneys for histopathology was utilized according to Eustis et al. (1994).

Thus, for the five glyphosate mouse carcinogenicity studies, only the first conducted study showed any neoplastic renal lesions and these occurred only in male mice of the MD at 814 mg/kg/d, and HD groups at 4841 mg/kg/d. All of these general and renal neoplastic findings indicating a lack of a glyphosate renal carcinogenic response were reported in key regulatory submission updates (US EPA 1985a, 1985b, 1986, 1991a, 1993a, 1993b, 2012, 2013; JMPR 1987, 2006, 2014, 2016; IPCS 1996, 2005; European Commission 2002; EFSA 2009, 2015), and one review publication (Greim et al. 2015).

In conclusion, 14 GLY carcinogenicity studies (nine rat and five mouse) were evaluated for their reliability, and selected neoplasms were identified for further evaluation across all databases (Greim et al. 2015). The mouse renal neoplasms occurred only in males of the first study. In the other four, the HD of 1000 mg/kg/d (Cheminova 1993a), 4200 mg/kg/d (Arysta Life Sciences 1997), 946 mg/kg/d (Nufarm 2009), and 1460 mg/kg/d (Feinchemie Schwebda 2001) produced no renal neoplasms in either male or female mice.

The assessment of this study (Monsanto 1983) based on the PWG of the US EPA (1986) evaluation and which was reported by IARC (2015), concluded that the incidence of renal tubule adenoma: 1/49 (2%), 0/49, 0/50, 1/50 (2%), was not statistically significant, whereas, the incidence of renal tubule carcinoma: 0/49, 0/49, 1/50 (2%), 2/50 (4%), was significant at p¼.037 (in the Cochran–Armitage trend test). When the adenomas and carcinomas were combined: 1/49 (2%), 0/49, 1/50 (2%), 3/50 (6%), then the value was p¼.034 (in the Cochran–Armitage trend test). While both these p values (p¼.037 and p¼.034) were reported to be significant in this one study, it is important that these p values are not considered significant for rare neoplasms, for which authorities require a level of significance for trend at $p < .025$ (US FDA 2001).

Furthermore, the Panel applied to the kidney neoplasms noted within the Monsanto (1983) study a set of logical considerations for causation similar to those proposed for evaluation of epidemiologic data (Hill, 1965; Woodside & Davis, 2013) to assess 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 following this evaluation were made:

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 control group.
2. The association is not consistent, since four out of five 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 GLY did not develop renal neoplasms. Also, there were no renal findings (hyperplasia or neoplasia) in the LD group, whereas the control group had four incidences of hyperplasia or adenoma (Table 2).
4. The time required between exposure and effect, i.e. a reduced latency time was not present; all tumors were observed only at termination. Also, no mouse with neoplasia had also hyperplasia, and the largest tubular-cell carcinoma (#3023) was in the MD group.
5. The biological gradient of association or the dose-response curve was absent, since the females and the males in LD group had no neoplasms, whereas the controls had one.
6. A plausible explanation for the association was absent, since a MoA for induction of these renal neoplasms was not established.
7. Coherence of the association was also absent, 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 GLY.

Hemangiosarcomas in mice

This is a common neoplasm in this strain of mice with historical control values for both males and females ranging from 2 to 12%. This tumor was observed only in the liver.

The IARC conclusion was that "there was a significant ($p < .001$) positive trend in the incidence of hemangiosarcoma in high dose male CD-1 mice" (Control 0%, 0%, 0%, 8%) based on their interpretation of the Joint Meeting of the FAO panel of experts on Pesticide Residues in Food and the Environment (JMPR) 2006 study. Yet in females, the highest incidence (4%) was in the low-dose group followed by the high dose (2%) (Table 3).

In the CD-1 mouse study reported by Cheminova (1993a), the animals were fed diets providing intakes of glyphosate at dose levels of 100, 300, or 1000 mg/kg bw/d for 104 weeks. There were no treatment related effects on survival or body weight, nor were there any notable intergroup differences in the incidences of externally palpable masses. There were no statistically significant increases in the incidence of any tumors when compared with the control groups and no dose response was evident.

Based on their own statistical analysis, IARC concluded that there was an increase in the incidence of hemangiosarcoma in males [$p < .001$, Cochran–Armitage trend test].

IARC did not comment on the absence of hemangiosarcomas in Nufarm (2009), an 18-month diet study in CD-1 mice providing intakes up to 946 mg/kg bw/d of glyphosate similar to the previous study high dose. IARC also failed to note the historical control data, which have a range of 2–12% for both sexes (Charles River Labs 2000). Therefore, the statistically significant tumors were within the control data range (Table 3).

If the likelihood of the occurrence of hemangiosarcoma is considered in terms of the criteria for causality, it is clear that there is no strength in the association. For example, pairwise comparisons are not significant, there is no consistency (other mouse studies show no tumors of this type at all), a dose/response effect was not seen (some HD groups have a lower incidence than lower dose groups). In addition, the dose (about 170 mg/kg bw/d) associated with the highest incidence in males, did not produce any renal neoplasia in this study. Moreover, the female mice which have received higher doses of GLY had no significant incidence of hemangiosarcomas. Thus, despite the significantly positive trend in high dose males only, the incidence of this neoplasm was not compound related.

Pancreatic tumors in rats

Pancreatic islet cell tumors are common in this strain of rat (Williams et al. 2014). 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, 1991b, 1991c).

In the first study, SD rats received 0, 30 (3), 100 (10), and 300 (31 mg/kg bw/d) ppm ad libitum in diet for 26 months. No pancreatic islet carcinomas were observed. The incidence of adenoma was found to have a positive trend ($p < .05$) in the study. However, the level of significance for common tumors should be $p < .005$. The following islet cell adenoma

Table 3. Incidences of hemangiosarcoma in CD-1 mouse study (Cheminova 1993b).

	Tumor incidence/number of animals examined (mg/kg bw/d)							
	Males				Females			
	0	100	300	1000	0	100	300	1000
Hemangiosarcomas	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) supplemental data, doses were administered in the diet, with dietary concentrations adjusted regularly to achieve target mg/kg bw/day dose.

Table 4. Liver tumor incidences/number of Sprague–Dawley rats/group (Stout and Ruecker 1990).

	Males				Females			
mg/kg bw/d (ppm)	0 (0)	89 (2000)	362 (8000)	940 (20,000)	0 (0)	113 (2000)	457 (8000)	1183 (20,000)
Interim sacrifice (12th month)								
Hepatocellular adenoma	0/10	0/10	0/10	0/10	0/10	0/10	1/10	0/10
Hepatocellular carcinoma	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
Unscheduled deaths								
Hepatocellular adenoma	2/36	1/31	0/33	4/33	0/28	1/28	2/33	1/32
Hepatocellular carcinoma	2/36	1/31	1/33	2/33	0/28	0/28	0/33	1/32
Scheduled sacrifices								
Hepatocellular adenoma	1/14	1/19	3/17	4/17	6/22	1/22	3/17	0/18
Hepatocellular carcinoma	1/14	1/19	0/17	0/17	1/22	0/22	1/17	1/18
All deaths								
Hepatocellular adenoma	3/60	2/60	3/60	8/60	6/60	2/60	6/60	1/60
Hepatocellular carcinoma	3/60	2/60	1/60	2/60	1/60	0/60	1/60	2/60

incidences were observed for controls, low, mid and high doses respectively in males: 0/50, 5/49 (10%), 2/50 (4%), 2/50 (4%). This incidence data shows no dose-response patterns and preneoplastic effects are absent. In addition, in the first study in males, the adenomas also did not progress to carcinomas. Thus, the pancreatic islet cell adenomas were not compound-related. In females, the corresponding values were: 2/50 (4%), 1/50 (2%), 1/50 (2%), and 0/50.

In the second study, male and female Sprague–Dawley (SD) rats were fed 0, 2000 (89/113), 8000 (362/457), or 20,000 (940/1183 mg/kg bw/d) ppm glyphosate (96.5% pure) ad libitum in diet for 24 months. The following islet cell tumor incidences were observed in males: adenomas – 1/58 (2%), 8/57 (14%), 5/60 (8%), 7/59 (12%); carcinomas – 1/58 (25%), 0/57, 0/60, 0/59. In females, the corresponding incidences were: adenomas – 5/60 (8%), 1/60 (2%), 4/60 (7%), 0/59; carcinomas – 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 panel disagrees with the conclusion of IARC that there is a significant positive trend ($p < .05$) in the incidence of pancreatic adenomas in males, since the level of significance for trend should be $p < .005$ (US FDA 2001; Williams et al. 2014). Moreover, there was no progression of adenomas to carcinomas.

Four additional studies in rats, described by Greim et al. (2015), but not evaluated by IARC, similarly did not show pancreatic islet cell tumors. Based on this information, the panel concluded that there is no evidence that glyphosate induces islet cell neoplasia in the pancreas.

Liver tumors in rats

Hepatocellular neoplasms are common for this strain of rat (about 5% in males and 3% in female controls) (Williams et al. 2014). The IARC evaluation indicated that there was "…a significant positive trend ($p ¼ .016$) 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 1991b, 1991c).

In the Stout and Ruecker (1990) carcinogenic bioassay, SD rats were exposed through the diet to 0, 2000, 8000, and 20,000 ppm of 96.5% pure glyphosate for 24 months. These dietary concentrations corresponded to 0, 89, 362, and 940 mg/kg bw/d for males and 0, 113, 457, and 1183 mg/kg bw/d for females, the highest tested dose (HTD) being close to the limit dose for long-term studies with rats (OECD 2009). No glyphosate-related clinical signs or influence on survival were observed. At term, there was no influence on body weights or body weight gain by males; in the females there was a 6.4% decreased body weight gain. The original data on tumor incidence in this study are available in Greim et al. (2015). The all-deaths incidences of hepatocellular adenomas or carcinomas in the glyphosate-exposed groups were not significantly different from the controls (Table 4). At the 12th month (interim sacrifice), no adenomas or carcinomas were observed in the male groups, but a single adenoma case was noted in a female at 457 mg/kg/d. The rates of hepatocellular adenomas in females and of hepatocellular carcinomas in each sex followed no dose-response pattern at any time. In males, the first liver adenoma and carcinoma were observed at week 88 and 85, respectively, in animals exposed to the HTD of 940 mg/kg/d. A non-significant numerically greater ($p ¼ .101$, Fisher Exact) incidence of hepatocellular adenomas occurred in male rats exposed to the highest dose, since it is a common tumor type, the level of significance required is $p < .01$. There was no progression from adenoma to carcinoma. The authors did not highlight the occurrence of hepatocellular tumors in their final report and concluded that "an oncogenic effect was not observed".

The Stout and Ruecker (1990) study has been reviewed twice by the US EPA (1991b, 1991c). The US EPA memoranda indicate that the incidences of hepatocellular adenomas in males were within the range (1.4–18.3%) of historical controls from the Monsanto Environmental Health Laboratory (EHL), where the study was conducted. Additional statistical analyses developed by US EPA on liver tumor rates of male rats surviving after the 55th week indicated that the incidence of adenomas in the HTD males did not differ significantly from the control by the Fisher's Exact Test pair-wise comparison, but detected a significant trend ($p ¼ .016$) by the Cochran–Armitage trend test (see also above) (Table 5). Since liver adenoma is a common tumor type, the significance level for trend should be 0.005 (US FDA 2001; Williams et al. 2014). It should be noted that the incidences of hepatocellular adenomas in animals exposed to the two intermediate doses were of the same magnitude as the controls, i.e. there was no linear ascending trend of incidence across doses, but a "hockey-stick"-type slope. The biological importance of the

Table 5. Sprague–Dawley male rats: hepatocellular tumor rates† and Cochran–Armitage trend and Fisher's exact tests results (p values).

	Dose mg/kg bw/d (ppm)			
Tumors	0 (0)	89 (2000)	362 (8000)	940 (20,000)
Carcinomas	3/34	2/45	1/49	2/48‡
(%)	(7)	(4)	(2)	(4)
p	.324	.489	.269	.458
Adenomas	2/44	2/45	3/49	7/48¶
(%)	(5)	(4)	(6)	(15)
p	.016	.683	.551	.101
Adenoma þ Carcinoma	5/44	4/45	4/49	9/48
(%)	(11)	(9)	(8)	(19)
p	.073	.486	.431	.245
Hyperplasia only	0/44	0/45	1/49§	0/48
(%)	(0)	(0)	(2)	(0)
p	.462	1.000	.527	1.000

Adapted from Table 3 (US EPA 1991a) or Table 7 (US EPA 1991b).
(p < .05) Significance of trend indicated at control (0 ppm). Significance of pair-wise comparison with control denoted at dose level, if occurred.
†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.

observed data should be taken into account (OECD 2012) and in this case the result of the trend test should not override the absence of significance found by the pair-wise test.

The final interpretation of the US EPA 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" (US EPA 1991b). As noted previously, the US EPA ultimately concluded that glyphosate should be classified as a Group E (evidence of non-carcinogenicity for humans) chemical (US EPA 1991b, 1991c).

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, chemical-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, hyperplasia, and preneoplasia, i.e. altered hepatocellullar foci, and malignant tumors (Williams 1980; Bannasch et al. 2003; Maronpot et al. 2010). Identification and analyses of these liver changes – that span from adaptative to irreversible adverse effects – can support characterization of key events along the carcinogenesis process and inform the MoA of the tested chemical (Williams & Iatropoulos 2002; Holsapple et al. 2006; Carmichael et al. 2011). None of these alterations were significantly found in this study.

It is clear that there was a non-significant numerically greater incidence of liver adenomas in a long-term bioassay with male rats exposed to glyphosate, at a dose that was close to the limit dose. There was no progression to malignancy and no compound-associated pre-neoplastic lesions were induced.

Table 6. Tumor Incidence/number of animals examined (mg/kg bw/d) (Stout and Ruecker 1990 all deaths reported).

	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

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 doses used (Chruscielska et al. 2000). Considered jointly, these animals were exposed through the diet to 24 different doses distributed across a wide range of 3.0–1290.0 mg/kg 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.

Thyroid tumors in rats

C-cell tumors of the thyroid are a common tumor in this strain of rat (Williams et al. 2014).

The incidence of thyroid C-cell adenoma in females was reported in the Monograph (IARC 2015) to have a significant positive trend (p¼.031). 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 (1990) study, no statistically significant difference was reported in the incidence of thyroid C-cell neoplasms, as shown in Table 6. 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 numerically greater 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. However, IARC concluded that "there was also a statistically significant positive trend in the incidence of thyroid C-cell adenoma in females (p¼.031)." But, because this is a common tumor type, the trend significance value should be p < .005 (US FDA 2001; Williams et al. 2014). Thus, the incidence of this tumor is not statistically significant.

In the Arysta Life Sciences (1997) study, no increase in C-cell adenomas up to 1247 mg/kg/d was reported. The Chruscielska et al. (2000) study in Wistar rats is not informative and this work fails to meet appropriate standards for inclusion.

Thus, in one of the two studies, the significant 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, but there was no progression to malignancy. Thus, only one out of nine life-time

studies in rats showed a slight not significant increase in C-cell adenomas, which however did not progress to carcinomas.

Evaluations by regulatory agencies, scientific bodies and third party experts

A number of scientific groups, regulatory agencies and individuals have evaluated and commented on these data with the latter grouping from third party experts appearing in peer reviewed documents. The expert panel agrees with the opinions expressed below that glyphosate was not carcinogenic to rodents.

Regulatory agencies

- EFSA 2015: "No evidence of carcinogenicity was confirmed by the large majority of the experts (with the exception of one minority view) in either rats or mice due to a lack of statistical significance in pair-wise comparison tests, lack of consistency in multiple animal studies and slightly increased incidences only at dose levels at or above the limit dose/maximum tolerated dose, lack of preneoplastic lesions and/or being within historical control range. The statistical significance found in trend analysis (but not in pair-wise comparison) per se was balanced against the former considerations." (EFSA 2015)
- APVMA (2013) – "The weight and strength of evidence shows that glyphosate is not genotoxic, carcinogenic, or neurotoxic."
- US EPA (2013) – "No evidence of carcinogenicity was found in mice or rats."
- US EPA (2012) – "No evidence of carcinogenicity was found in mice or rats."
- European Commission (2002) – "No evidence of carcinogenicity."
- US EPA (1993a, 1993b) – "The Agency has classified glyphosate as a Group E carcinogen (signifies evidence of non-carcinogenicity in humans)."
- Health and Welfare Canada (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."

Scientific bodies

- JMPR (2016) – "Glyphosate is not carcinogenic in rats, but could not exclude the possibility that it is carcinogenic in mice at very high doses."
- 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."
- WHO (1994) – "The available studies do not indicate that technical glyphosate is mutagenic, carcinogenic or teratogenic."
- JMPR (1987) – "The chronic toxicity of glyphosate is low … There is no evidence of carcinogenicity."

Independent experts

- Williams et al. (2000) – "It was concluded that, under present and expected conditions of use, Roundup herbicide does not pose a health risk to humans."
- Greim et al. (2015) – "There was no evidence of a carcinogenic effect related to glyphosate treatment. The lack of a plausible mechanism, along with published epidemiology studies, which fail to demonstrate clear, statistically significant, unbiased and non-confounded associations between glyphosate and cancer of any single etiology, and a compelling weight of evidence, support the conclusion that glyphosate does not present concern with respect to carcinogenic potential in humans."

Conclusions

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

i. The rare renal tubule tumors in one male (CD-1) mouse study were not associated with glyphosate exposure, because they lacked statistical significance, strength, consistency, specificity, dose-response patterns, plausibility, and coherence.
ii. In a different mouse (CD-1) study, there was a lack of association of exposure to glyphosate and a statistically significant positive trend for the incidence of liver hemangiosarcoma (a common tumor) because the findings were inconsistent, there was no dose-response effect, and the incidences were within the historical control range.
iii. The strength of association of pancreatic islet-cell adenomas (a common tumor) to glyphosate exposure in two studies of male SD rats was absent. There was a lack of a dose-response pattern (the highest incidence is in the low dose followed by the high dose), plausibility and absence of pre-neoplastic effects and progression to islet-cell carcinomas.
iv. In one of two studies, a significant positive trend in the incidence of hepatocellular adenomas (a common tumor) in male SD rats did not occur, and no progression to carcinomas 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 SD rats was not evident. The adenomas were only slightly increased in mid and high doses, within the historical ranges. Also, there was no progression to carcinomas.

Application of criteria for causality considerations to the above mentioned tumor types and given the overall WoE, the expert panel concluded that glyphosate is not a carcinogen in laboratory animals.

Acknowledgements

The authors gratefully acknowledge the extensive comments received from seven independent reviewers selected by the Editor and who were

anonymous to the authors. Their comments were very helpful in revising the manuscript.

Declaration of interest

The employment affiliation of the authors is as shown on the cover page. However, it should be recognized that each individual participated in the review process and preparation of this paper as an independent professional and not as a representative of their employer.

The expert panel Members recruitment and evaluation of the data was organized and conducted by Intertek Scientific & Regulatory Consultancy (Intertek). The expert panelists were engaged by, and acted as consultants to, Intertek, and were not directly contacted by the Monsanto Company. Funding for this evaluation was provided to Intertek by the Monsanto Company, which is a primary producer of glyphosate and products containing this active ingredient. Neither any Monsanto company employees nor any attorneys reviewed any of the expert panel's manuscripts prior to submission to the journal.

Intertek (previously Cantox) is a consultancy firm that provides scientific and regulatory advice, as well as safety and efficacy evaluations for the chemical, food, and pharmaceutical industries. While Intertek has not previously worked on glyphosate related matters for the Monsanto Company, previous employees (Ian Munro, Barry Lynch) of Cantox, have worked in this capacity. These employees of Cantox, and Gary Williams, prepared a safety and risk assessment, including the carcinogenicity, of Roundup herbicide (glyphosate), which was published in 2000 (Williams GM, Kroes R, Munro IC (2000). Safety evaluation and risk assessment of the herbicide roundup and its active ingredient, glyphosate, for humans. Regul Toxicol Pharmacol 31(2):117–165).

Gary Williams, Sir Colin Berry, João Lauro Viana de Camargo, and Helmut Greim have previously served as independent consultants for the Monsanto Company, some on the European Glyphosate Task Force. Gary Williams has consulted for Monsanto on litigation matters involving glyphosate. Michele Burns has not previously been employed by the Monsanto Company or previously been involved in any activity involving glyphosate and as such declare no potential conflicts of interest. Furthermore, other than Gary Williams, none of the aforementioned authors have been involved in any litigation procedures involving glyphosate.

This article is part of a supplement, sponsored and supported by Intertek Scientific & Regulatory Consultancy. Funding for the sponsorship of this supplement was provided to Intertek by the Monsanto Company, which is a primary producer of glyphosate and products containing this active ingredient.

References

APVMA. 2013. A review of the earth open source (EOS) report roundup and birth defects: is the public being kept in the dark?. Prepared by Canberra (Australia): scitox assessment services for Canberra (Australia): Australian pesticides and veterinary medicine authority (APVMA). Available from: http://archive.apvma.gov.au/news_media/docs/glyphosate_scitox_review_july_2013.pdf.

Arysta Life Sciences. 1997. HR-001: 18-month oral oncogenicity study in mice. Tokyo (Japan): The Institute of Environmental Toxicology (Cited in: Greim et al. 2015).

Bannasch P, Haertel T, Su Q. 2003. Significance of hepatic preneoplasia in risk identification and early detection of neoplasia. Toxicol Pathol. 31:134–139.

Carmichael N, Bausen M, Boobis AR, Cohen SM, Embry M, Fruijtier-Pölloth C, Greim H, Lewis R, Meek ME, Mellor H, et al. 2011. Using mode of action information to improve regulatory decision-making: an ECETOC/ILSI RF/HESI workshop overview. Crit Rev Toxicol. 41:175–186.

Charles River Labs. 2000. Spontaneous neoplastic lesions in the crl:CD-1® BR mouse. Wilmington (MA): Charles River Laboratories Inc.

Cheminova. 1993a. Glyphosate: 104 week dietary carcinogenicity study in mice. [Unpublished Report] Tranent (Scotland): inveresk research international Ltd. Submitted to WHO by Lemvig (Denmark): Cheminova A/S. (Report No. 7793, IRI project No. 438618).

Cheminova. 1993b. 104 week combined chronic feeding/oncogenicity study in rats with 52 week interim kill (results after 104 weeks). [Unpublished report] Tranent (Scotland): inveresk research nternational Ltd. Submitted to WHO by Lemvig (Denmark): Cheminova A/S. (Report No. 7867, IRI project No. 438623).

Chruscielska K, Brzezinski J, Kita K, Kalhorn D, Kita I, Graffstein B, Korzeniowski P. 2000. Glyphosate – evaluation of chronic activity and possible far-reaching effects. Part 1. Studies on chronic toxicity. Pestycydy (Warsaw). (3/4):11–20.

EFSA. 2009. 2007 Annual report on pesticide residues according to article 32 of regulation (EC) no 396/2005 (reasoned opinion of EFSA prepared by the pesticides unit/PRAPeR) (EFSA-Q-2008-714). Parma (Italy): European food safety authority (EFSA). EFSA scientific report 305, p. 1–106; [cited 2009 Jun 10]. Available from: http://www.efsa.europa.eu/en/efsajournal/pub/305r.

EFSA. 2015. Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate (EFSA-Q-2014-00546, EFSA-Q-2015-00279, by European food safety authority). EFSA J. 13:4302 [107 p.]. doi:10.2903/j.efsa.2015.4302; [cited 2015 Oct 30]. Available from: http://www.efsa.europa.eu/en/efsajournal/pub/4302.

European Commission. 2002. Review report for the active substance glyphosate. Finalized in the standing committee on plant health at its meeting on 29 June 2001 in view of the inclusion of glyphosate in annex I of directive 91/414/EEC. Brussels (Belgium): European commission (EC), health and consumer protection directorate general. (6511/VI/99-final). Available from: http://ec.europa.eu/food/fs/sfp/ph_ps/pro/eva/existing/list1_glyphosate_en.pdf.

Eustis SL, Hailey JR, Boorman GA, Haseman JK. 1994. The utility of multiple-section sampling in the histopathological evaluation of the kidney for carcinogenicity studies. Toxicol Pathol. 22:457–472.

Excel. 1997. Combined chronic toxicity/carcinogenicity study of glyphosate technical in Sprague–Dawley rats. Pune, India: Indian Institute of Toxicology.

Feinchemie Schwebda. 2001. Carcinogenicity study with glyphosate technical in Swiss Albino mice. [Unpublished report]. Bangalore (India): Rallis India, Ltd.

Greaves P. 2012. Urinary tract [renal neoplasms] (chapter 10). In: Histopathology of preclinical toxicity studies. 4th ed. New York (NY): Elsevier B.V. p. 545–626 [See p. 593].

Greim H, Saltmiras D, Mostert V, Strupp C. 2015. Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies. Crit Rev Toxicol. 45:185–208.

Health and Welfare Canada. 1991. Preharvest application of glyphosate (roundup) herbicide. Ottawa (ON): health and welfare Canada, pest management regulatory agency (PMRA), plant industry directorate. Pesticide information division. (pesticides directorate discussion document). 91. p. 92.

Hill AB. 1965. The environment and disease: association or causation. J R Soc Med. 58:295–300.

Holsapple MP, Pitot HC, Cohen SM, Boobis AR, Klaunig JE, Pastoor T, Dellarco VL, Dragan YP. 2006. Mode of action in relevance of rodent liver tumors to human cancer risk. Toxicol Sci. 89:51–56.

IARC. 2015. Glyphosate. In: Some organophosphate insecticides and herbicides: diazinon, glyphosate, malathion, parathion, tetrachlorvinphos. IARC working group, Lyon (France). Lyon (France): World Health Organization (WHO), International Agency for Research on Cancer (IARC). (IARC monographs on the evaluation of carcinogen risks to humans, vol 112). p. 1–92; [cited 2015 Mar 3–10]. Available from: http://monographs.iarc.fr/ENG/Monographs/vol112/index.php.

ICH. 1997. Testing for carcinogenicity of pharmaceuticals: S1B. Geneva: International Conference on harmonization of technical requirements for registration of pharmaceuticals for human use (ICH). (ICH harmonized tripartite guideline – current step 4 version); [cited 1997 Jul 16]. Available from: http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html [Open S1B].

IPCS. 1996. Glyphosate. (Geneva: World Health Organization (WHO), International program on chemical safety (IPCS). WHO/FAO data sheets on pesticides no 91; WHO/PCS/DS/96.91). Available from: http://apps.who.int/iris/handle/10665/63290.

IPCS. 2005. Glyphosate. Luxembourg: commission of the European union/ International program on chemical safety (IPCS). (international chemical safety card, ICSC-0160). Available from: http://www.inchem.org/documents/icsc/icsc/eics0160.htm.

James RC, Britt JK, Halmes NC, Guzelian PS. 2015. Evidence-based causation in toxicology: a 10-year retrospective. Hum. Exp. Tox. 34:1245–1252.

JMPR. 1987. Glyphosate. In: pesticide residues in food – 1986: part II – toxicology. Joint meeting of the FAO panel of experts on pesticide residues in food and the environment (JMPR) and the WHO expert group on pesticide residues, Sep. 29-Oct. 8, 1986, Rome. Rome: food and agriculture organization of the United Nations (FAO)/FAO panel of experts on pesticide residues in food and the environment/WHO expert group on pesticide residues joint FAO/WHO meeting on pesticide residues (JMPR). (FAO plant production and protection paper, vol 78). p. 63–76. Available from: http://www.inchem.org/documents/jmpr/jmpmono/v86pr08.htm.

JMPR. 2006. Glyphosate. In: pesticides residues in food – 2004. Evaluations 2004 part II–toxicological. Joint meeting of the FAO panel of experts on pesticide residues in food and the environment and the WHO core assessment group (JMPR), Sep 20–29, 2004, Rome. Rome: food and agriculture organization of the United Nations (FAO)/Geneva: World Health Organization (WHO), International program on chemical safety (IPCS). (WHO/PCS/06.1). p. 95–169; [cited 2004 Sep 20–29]. Available from: http://www.inchem.org/documents/jmpr/jmpmono/v2004pr01.pdf.

JMPR. 2014. 5.21. Glyphosate ('158) and metabolites. In: pesticide residues in food 2013. Joint FAO/WHO meeting on pesticide residues and the WHO core assessment group on pesticide residues, Geneva. Rome: food and agriculture organization of the United Nations/Geneva, World Health Organization (WHO). (FAO plant production and protection paper No. 219). p. 225–228, 484–486; [cited 2013 Sep 17–26]. Available from: http://www.fao.org/publications/card/en/c/299ca869-ae51-5093-8407-9cb0782b9f5/.

JMPR. 2016. Diazinon, glyphosate and malathion. Summary report from a core assessment group on pesticide residues (JMPR) held at WHO headquarters, Geneva, Switzerland, from 9 to 13 of May, 2016; [cited 2016 May 16].

Kier LD, Kirkland DJ. 2013. Review of genotoxicity studies of glyphosate and glyphosate-based formulations. Crit Rev Toxicol. 43:283–315.

Maronpot RR, Yoshizawa K, Nyska A, Harada T, Flake G, Mueller G, Singh B, Ward JM. 2010. Hepatic enzyme induction: histopathology. Toxicol Pathol. 38:776–795.

McConnel R. 1986. A chronic feeding study of glyphosate (Roundup® technical) in mice: pathology report on additional kidney sections. final report. Confidential. [Unpublished report] prepared by Bio/dynamics Inc. Division of biology and safety evaluation for St Louis (MO): Monsanto Company for submission to Washington (DC): Washington (DC): U.S. environmental protection agency (US EPA), office of pesticides, and toxic substances. (Project No. 77-2061A; BDN-77-420).

Monsanto. 1983. A chronic feeding study of glyphosate (roundup® technical) in mice. [Unpublished report]. East Millstone (NJ): Bio/dynamics Inc. (project #77-2062, 1981).

Nufarm. 2009. Glyphosate technical: dietary carcinogenicity study in the mouse [Unpublished Report] Derbyshire (UK): Harlan Laboratories Ltd. (Cited by Greim et al. 2015).

OECD. 2009. Combined chronic toxicity\carcinogenicity studies. In: OECD guidelines for the testing of chemicals. Paris (France): organization for economic co-operation and development (OECD). (OECD guideline no 453); [cited 2009 Sep 7]. Available from: http://www.oecd-ilibrary.org/environment/test-no-453-combined-chronic-toxicity-carcinogenicity-studies_9789264071223-en.

OECD. 2012. Guidance document 116 on the conduct and design of chronic toxicity and carcinogenicity studies, supporting test guidelines 451, 452 and 453. 10th ed. Joint meeting of the chemicals committee and the working party on chemicals, pesticides, and biotechnology. Paris (France): organization for economic co-operation and development (OECD), environment directorate, health and safety publications. (OECD series on testing and assessment; ENV/JM/MONO(2011)47). Available from: http://www.oecd.org/officialdocuments/publicdisplay-documentpdf/?cote¼ENV/JM/MONO(2011)47&doclanguage¼en.

Peto R, Pike MC, Day NE, Gray RG, Lee PN, Parish S, Peto J, Wahrendorf J. 1980. Guidelines for simple, sensitive significance test for carcinogenic effects in long-term animal experiments. In: Long-term and short-term screening assays for carcinogens: a critical appraisal, edited by R Montesano, H Bartsh, L Tomatis, IARC monogrphas on the evaluation of the carcinogenic risk of chemicals to humans, Suppl. 2, pp. 311–426. Lyon Franc: International Agency for Research on Cancer.

Sauer RM. 1985. Pathology working group report on glyphosate in CD-1 mice. (10/10/85). Reported In: http://www.cdpr.ca.gov/docs/risk/toxsums/pdfs/1855.pdf [See p. 16].

Stout LD, Ruecker FA. 1990. Chronic study of glyphosate administered in feed to Albino rats. [Unpublished report] St Louis (MO): Monsanto agricultural company. (No. MSL-10495, job/project No. ML-87-148/EHL 87122).

Suter GWII, Cormier SM. 2011. Why and how to combine evidence in environmental assessments: weighing evidence and building cases. Sci Total Environ. 409:1406–1417.

US EPA. 1985a. Glyphosate; EPA Reg.#: 524-308; mouse oncogenicity study [memo]. Washington (DC): U.S. environmental protection agency (US EPA). (Document No. 004370). Available from: http://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/html/103601.html.

US EPA. 1985b. EPA Reg.#: 524-308; Roundup; glyphosate; pathology report on additional kidney sections [memo]. Washington (DC): U.S. Environmental protection agency (US EPA). (document No. 004855). Available from: http://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/html/103601.html.

US EPA. 1986. Glyphosate; EPA Reg.#: 524-308; roundup; additional histopathological evaluations of kidneys in the chronic feeding study of glyphosate in mice [memo]. Washington (DC): U.S. Environmental protection agency (US EPA). (Document No. 005590). Page 7, point 5. Letter of October 10, 1985, from pathology working group (PWG) to Monsanto. Available from: http://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/html/103601.html.

US EPA. 1990. Determination of glyphosate in drinking water by direct-aqueous-injection HPLC, post column derivatization, and fluorescence detection. In: methods for the determination of organic compound in drinking water – supplement I. Washington (DC): U.S. Environmental protection agency (US EPA), office of research and development. (EPA/600/4-90/020). Available from: http://nepis.epa.gov/Exe/ZyPDF.cgi/30000UX8.PDF?Dockey¼30000UX8.PDF.

US EPA. 1991a. Second peer review of glyphosate [memo]. Washington (DC): U.S. Environmental protection agency (US EPA). Available from: http://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/html/103601.html.

US EPA. 1991b. Glyphosate; 2-year combined chronic toxicity/carcinogenicity study in Sprague–Dawley rats – list A pesticide for reregistration [memo]. Washington (DC): U.S. Environmental protection agency (US EPA). (Document No. 008390). Available from: http://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/html/103601.html.

US EPA. 1991c. Peer review on glyphosate [memo]. Washington (DC): U.S. environmental protection agency (US EPA), office of pesticides, and toxic substances.

US EPA. 1992. Determination of glyphosate in drinking water by direct-aqueous-injection HPLC, post column derivatization, and fluorescence detection. In: Methods for the determination of organic compound in drinking water – supplement II. Washington (DC): U.S. environmental protection agency (US EPA), office of pesticides, and toxic substances. (EPA/600/R-92-129).

US EPA. 1993a. Reregistration eligibility decision (RED): glyphosate. U.S. environmental protection agency (US EPA), office of prevention, pesticides, and toxic substances. (EPA 738-R-93-014). Washington (DC). Available from: http://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-417300_1-Sep-93.pdf.

US EPA. 1993b. RED facts: glyphosate. Washington (DC): U.S. environmental protection agency (US EPA), office of prevention, pesticides, and

toxic substances. (EPA 738-F-93-011). Available from: http://archive.epa.gov/pesticides/reregistration/web/pdf/0178fact.pdf.

US EPA 2005. Guidelines for carcinogen risk assessment [EPA/630/P-03/001F]. Washington (DC): US. Environmental Protection Agency (U.S. EPA), Risk assessment forum, National Center for Environmental Assessment (NCEA). Available from: http://www.epa.gov/risk/guidelines-carcinogen-risk-assessment.

US EPA. 2012. Memo from Tom Bloem et al. (RAB/HED) through Charles W. Smith III, George F. Kramer (RA/HED) to Barbara Madden and Andrew Ertman (RD) Re: glyphosate. section 3 registration concerning the application of glyphosate to carrots, sweet potato, teff and oilseeds (crop group (CG) 20) and to update the CG definitions for bulb vegetable (CG 3-07), fruiting vegetable (CG 8-10), citrus fruit (CG 10-10), pome fruit (CG 11-10, berry (CG 13-07). Washington (DC): U.S. environmental protection agency (US EPA), office of chemical safety and pollution prevention. (D398547).

US EPA. 2013. Glyphosate pesticide tolerances; final rule (40 CFR Part 180) [EPA–HQ–OPP–2012–0132; FRL–9384–3]. Fed regist (US). 78:25396-25401. Available from: http://www.regulations.gov/#%21documentDetail;D¼EPA-HQ-OPP-2012-0132-0009.

US FDA. 2001. Draft guidance for industry on the statistical aspects of the design, analysis, and interpretation of chronic rodent carcinogenicity studies of pharmaceuticals. Availability [Docket No. 01N–0006]. Fed Regist (US). 66:23266-23267.

WHO. 1994. Glyphosate. Geneva: World Health Organization (WHO)/International program on chemical safety (IPCS)/United Nations environment program (UNEP). (Environmental health criteria, no 159). Available from: http://www.inchem.org/documents/ehc/ehc/ehc159.htm.

Williams GM. 1980. The pathogenesis of rat liver cancer caused by chemical carcinogens. Biochem Biophy Acta. 605:167–189.

Williams GM, Iatropoulos MJ. 2002. Alteration of liver cell function and proliferation: differentiation between adaptation and toxicity. Toxicol Pathol. 30:41–53.

Williams GM, Kroes R, Munro IC. 2000. Safety evaluation and risk assessment of the herbicide roundup and its active ingredient, glyphosate, for humans. Regul Toxicol Pharmacol. 31:117–165.

Williams GM, Iatropoulos MJ, Enzmann HG, Deschl UF. 2014. Carcinogenicity of chemicals. In Hayes' principles and methods of toxicology. In: Hayes AW, Kruger CL, editors. Boca Raton, FL, USA: CRC Press Taylor & Francis Group. pp 1251–1303.

Williams G, Aardema M, Acquavella J, Berry C, Brusick D, Viana de Camargo JL, Garabrant D, Greim H, Kier L, Kirkland D, et al. 2016. A review of the carcinogenic potential of glyphosate by four independent expert panels and comparison to the IARC assessment. Crit Rev Toxicol., in this issue. doi: 10.1080/10408444.2016.1214677.

Woodside FC III, Davis AG. 2013. The Bradford Hill criteria: the forgotten predicate. Thomas Jefferson Law Rev. 35:103–125.