

Responses to Subpoena
"Roundup Products Liability Litigation – Civil Action No. 3:16-MD-2741-VC"
Served on Roger O. McClellan on November 26, 2018

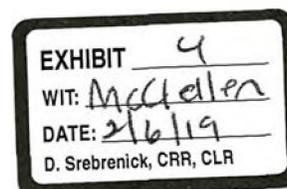
The Subpoena identified above was served on November 26, 2018 on Roger O. McClellan, Editor-in-Chief of Critical Reviews in Toxicology, an international journal published by Taylor and Francis. Attachment A to the Subpoena contains a section identified as "Documents and Things to be Produced" including a list of 19 items.

This document is a summary of the responses to the 19 items.

- (1) All agreements and contracts between YOU and Monsanto

Response:

There are no past or current agreements or contracts between Roger O. McClellan and Monsanto.



RM 000001

(2) All invoices from You to Monsanto

Response:

There are no invoices from Roger O. McClellan to Monsanto.

- (3) All communications and documents related to unrestricted research grants from Monsanto to You

Response:

There are no communications or documents related to unrestricted research grants from Monsanto to Roger O. McClellan

- (4) All communications and documents related to unrestricted research grants from Monsanto to Critical Reviews in Toxicology

Response:

Roger O. McClellan is not aware of any communications or documents related to unrestricted research grants from Monsanto to Critical Reviews in Toxicology.

- (5) All communications and documents related to peer-review reports for Monsanto-sponsored and/or authored manuscripts related to the potential adverse human health effects of GBFs, AMPA, ad/or surfactants for GBF's published in Critical Reviews in Toxicology during your tenure at the journal.

Response:

I have served as Editor-in-Chief of Critical Reviews in Toxicology since 1987 (see attached Biography). Most recently, Critical Reviews in Toxicology has been published by Taylor and Francis and earlier by Informa Healthcare, both a part of Informa UK Limited.

I have not searched issues of Critical Reviews in Toxicology published prior to 2013 to determine if any papers on GBFs, AMPA, and/or surfactants for GBFs were published in Critical Reviews in Toxicology prior to 2013.

From 2013 to the present time, 9 manuscripts, authored by Monsanto scientists and/or scientists funded directly or indirectly by Monsanto, have been published in Critical Reviews in Toxicology. The 9 papers and a Foreword to a Special Supplement are listed below and copies are provided with this response.

Kimmel, G.L., C.A. Kimmel, A.L. Williams and J.M. DeSesso (2013). Evaluation of Developmental Toxicity Studies of Glyphosate with Attention to Cardiovascular Development. Crit. Rev. in Toxicology 43(2): 79-95.

Kier, L.D. and D.I. Kirkland (2013). Review of Genotoxicity Studies of Glyphosate and Glyphosate-Based Formulations. Crit. Rev. in Toxicology 43(4): 283-315.

Greim, H., D. Saltmiras, V. Mostert and C. Strupp (2015) Evaluation of the Carcinogenic Potential of the Herbicide Glyphosate Drawing on Tumor Incidence Data from Fourteen Chronic/Carcinogenicity Rodent Studies. Crit. Rev. in Toxicol 45(3): 185-208.

Kier, L.D. (2015). Review of Genotoxicity Biomonitoring Studies of Glyphosate-Based Formulations. Crit. Rev. Toxicol. 45(3): 209-218.

McClellan, Roger O. (2016). Foreword: Evaluating the Potential Carcinogenic Hazard of Glyphosate. Crit. Rev. Toxicol. 46(S1): 1-2. [Prepared independently in Roger O. McClellan's role as Editor-in-Chief of Critical Reviews in Toxicology]

Williams, Gary, Marilyn Aardena, John Acquavella, Sir Colin Berry, David Brusick and Michele M. Burns (2016). A Review of the Carcinogenic Potential of Glyphosate by Four Independent Expert Panels & Comparison to IARC Assessment. Crit. Rev. Toxicol. 46(S1): 3-20.

Solomon, Keith R. (2016). Glyphosate in the General Population and in Applications: A Critical Review of Studies on Exposures. *Crit. Rev. Toxicol.* 46(S1): 21-27.

Acquavella, John, David Garabrant, Gary Marsh, Tom Sorahan and Douglas L. Weed. (2016). Glyphosate Epidemiology Expert Panel Review: A Weight of Evidence Systematic Review of the Relationship Between Glyphosate Exposure and Non-Hodgkin's Lymphoma or Multiple Myeloma. *Crit. Rev. Toxicol.* 46(S1): 28-43.

Williams, Gary, Colin Berry, Michele Burns, Joao Lauro Viana de Camargo and Helmut Greim. (2016). Glyphosate Rodent Carcinogenicity Bioassay Expert Panel Review. *Crit. Rev. Toxicol.* 46(S1): 44-55.

Brusick, David, Marilyn Aardema, Larry Kier, David Kirkland and Gary Williams. (2016). Genotoxicity Expert Panel Review: Weight of Evidence Evaluation of the Genotoxicity of Glyphosate, Glyphosate-Based Formulations, and Aminomethylphosphonic Acid. *Crit. Rev. Toxicol.* 46(S1): 56-74.

All of these manuscripts, excluding my Foreword to the Supplement, were submitted to Critical Reviews in the same manner as the 100 or so manuscripts received by the journal each year. The entry point for manuscripts is an electronic manuscript management review system [Manuscript Central/Scholar One] provided by the publisher. The system may be accessed at <https://mc.manuscriptcentral.com/btxc>.

This electronic system has provision for:

- (1) authors to submit manuscripts in an electronic format,
- (2) the Editor to identify potential reviewers and solicit review comments.
- (3) reviewers to return comments to the Editor,
- (4) the Editor to send review comments (blind as to identity) to the author(s),
- (5) the author to return revised manuscript to the Editor,
- (6) the Editor to make a decision on the revised manuscript (accept, further revisions or reject),
- (7) the Editor to advise author of the editorial decision, and
- (8) the Editor to forward accepted manuscripts to the publisher.

The integrity of the manuscript management and review system and its successful use is dependent upon all parties recognizing the confidential nature of the communications between authors, Editor, reviewers and the publisher.

The following material taken from the Manuscript Central/Scholar One instructions to reviewers illustrates the emphasis given to ensuring confidentiality.

"Agreeing to review an article for this Journal implies that you as the reviewer will adhere to the accepted ethical standards of scientific, medical and academic publishing.

Material submitted for peer review is a privileged communication that should be treated in confidence. Material under review should not be shared or discussed with anyone outside the designated review process, unless approved by the editor. All communications relating to the paper in review should also be treated in confidence. Any breach of confidentiality in the review process is taken seriously by the journal and will be investigated according to the advice of COPE (<http://publicationethics.org>). Any conflict of interest, suspicion of duplicate publication, fabrication of data, plagiarism or other ethical concerns must immediately be reported to the Editor. By agreeing to review this manuscript, you are stating that you are the person completing this review. If you wish to collaborate with a colleague and/or trainee to perform this review, or wish to assign this review to a trainee for completion under your guidance, please contact the Editor for permission before sharing the manuscript. If the Editor agrees please provide the name, affiliation and e-mail address for the trainee/colleague so he or she may be assigned as a reviewer directly. If you have any conflict of interest (for example, collaborate with the author(s) or are currently working on a similar study), please decline to review this manuscript and, if possible, suggest appropriate alternate reviewers."

The publisher uses a second electronic system to manage the production and publication of the accepted manuscripts; that system operated by Taylor and Francis is called the Central Article Tracking System (CATS).

- (14) All communications with any of the authors of Williams, et al., *A Review of the Carcinogenic Potential of Glyphosate by Four Independent Expert Panels and Comparison to the IARC Assessment* 46 Crit. Rev. Toxicol. 3-20 (2016), including all communications with any of the authors of the four companion papers by the Intertek Expert Panel, related to GBs, AMPA, and/or surfactants for GBFs.

Response:

As noted above, the primary communications between authors and the Editor are initially conducted electronically using the Manuscript Central/Scholar One system provided by the publisher, Taylor and Francis. After critical review and acceptance by the Editor-in-Chief, the accepted manuscripts are electronically transferred to the Central Article Tracking System (CATS) operated by Taylor and Francis. The CATS system is used for processing of the accepted manuscripts, including production of galley proofs for review and approval by the authors before proceeding to on-line publication. CATS is maintained and used by Taylor and Francis to publish the approximate 2600 journals in its portfolio.

As Editor-in-Chief, I do not maintain files to duplicate the CATS system.

BIOGRAPHY – 2018

ROGER O. McCLELLAN, DVM, MMS, DSc (Honorary),
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ROGER O. McCLELLAN serves as an advisor to public and private organizations on issues of air quality in the ambient environment and work place using his expertise in inhalation toxicology, comparative medicine, aerosol science and human health risk analysis. He received his Doctor of Veterinary Medicine degree with Highest Honors from Washington State University in 1960 and a Master of Management Science degree from the University of New Mexico in 1980. He is a Diplomat of the American Board of Toxicology and the American Board of Veterinary Toxicology and a Fellow of the Academy of Toxicological Sciences.

He served as Chief Executive Officer and President of the Chemical Industry Institute of Toxicology (CIIT) in Research Triangle Park, NC from September 1988 through July 1999. During his tenure, the organization achieved international recognition for the development of scientific information under-girding important environmental and occupational health decisions and regulations. Prior to his appointment as President of CIIT, Dr. McClellan was Director of the Inhalation Toxicology Research Institute, and President and Chief Executive Officer of the Lovelace Biomedical and Environmental Research Institute, Albuquerque, New Mexico. The Institute continues operation today as a core element of the Lovelace Respiratory Research Institute. During his 22 years with the Lovelace organization, he provided leadership for development of one of the world's leading research programs concerned with the health effects of airborne radioactive and chemical materials. Prior to joining the Lovelace organization, he was a scientist with the Division of Biology and Medicine, U.S. Atomic Energy Commission, Washington, DC (1965-1966), and Hanford Laboratories, General Electric Company, Richland, WA (1957-1964). In these assignments, he conducted and managed research directed toward understanding the human health risks of internally deposited radionuclides.

Dr. McClellan is an internationally recognized authority in the fields of inhalation toxicology, aerosol science, comparative medicine, and human health risk analysis. He has authored or co-authored over 400 scientific papers and reports and edited 10 books. In addition, he frequently speaks on risk assessment and air pollution issues in the United States and abroad. He is active in the affairs of a number of professional organizations, including past service as President of the Society of Toxicology and the American Association for Aerosol Research. He serves in an editorial role for a number of journals, including service since 1987 as Editor of Critical Reviews in Toxicology. He serves or has served on the Adjunct Faculty of 8 universities.

Dr. McClellan has served in an advisory role to numerous public and private organizations. He has served on senior advisory committees for eight major federal agencies concerned with human health. This included service as Chairman of the Clean Air Scientific Advisory Committee, Environmental Health Committee, Research Strategies Advisory Committee, and Member of the Executive Committee, Science Advisory Board, U. S. Environmental Protection Agency; Member for 30 years, National Council on Radiation Protection and Measurements; Member, Advisory Council for Center for Risk Management, Resources for the Future; a former Member, Health Research Committee, Health Effects Institute; and service on National Academy of Sciences/National Research Council Committee on Toxicology (served as Chairman for 7 years), Risk Assessment for Hazardous Air Pollutants, Health Risks of Exposure to Radon, Research Priorities for Airborne Particulate Matter, as well as the Committee on Environmental Justice of the Institute of Medicine. He has served on the Board of Scientific Councilors for the Center for Environmental Health Research of the Centers for Disease Control and Prevention and the Agency for Toxic Substances and Disease Registry and on the National Institutes of Health Scientific Advisory Committee on Alternative Toxicological Methods. He served on the National Aeronautics and Space Administration Lunar Airborne Dust Toxicity Advisory Group.

Dr. McClellan's contributions have been recognized by receipt of a number of honors, including election in 1990 to membership in the National Academy of Medicine. He is a Fellow of the Society for Risk Analysis, the American Association for Aerosol Research, the Health Physics Society, the International Aerosol Research Assembly, and the American Association for the Advancement of Science and American Thoracic Society Fellow. In 1985, he received the American Conference of Governmental industrial hygienist Herbert Stokinger Award for pioneering research on the health effects of exposure to diesel engine exhaust. In 1997, he received the Thomas T. Mercer Prize for research on inhalable materials from the International Society for Aerosols in Medicine and the American Association for Aerosol Research. In 1998, he received the International Achievement Award of the International Society of Regulatory Toxicology and Pharmacology for outstanding contributions to improving the science used for decision making on chemical safety and the International Aerosol Fellow Award of the International Aerosol Research Assembly for outstanding contributions to aerosol science and technology. In 2002, he was inducted into the University of New Mexico Anderson School of Management Hall of Fame for contributions to the effective management of multi-disciplinary research organizations. He received the Society of Toxicology Arnold J. Lehman Award in 1992 for contributions to chemical safety, the Society's Merit Award in 2003 for a distinguished career in toxicology, the Society's Founders Award in 2009 for contributions to science-based safety/risk decision-making and the Society's Distinguished Toxicology Scholar Award in 2018 for contributions to understanding the toxicity of inhaled radionuclides. In 2012, he received a career achievement award from the International Dose-Response Society and the American Association for Aerosol Research, and in 2014 from the Academy of Toxicological Sciences. In 2016, he received the American Veterinary Medical Association Meritorious Service Award for public service. In 2018, he was designated as an American Thoracic Society Fellow. In 2005, The Ohio State University awarded him an Honorary Doctor of Science degree for his contributions to comparative medicine and the science under-girding improved air quality. In 2006, he received the New Mexico Distinguished Public Service Award. In 2008, Washington State University presented Dr. McClellan the Regents Distinguished Alumnus Award, the highest recognition the University can bestow on an Alumnus.

Dr. McClellan has a long-standing interest in environmental and occupational health issues, especially those involving risk assessment and air quality and in the management of multidisciplinary research organizations. He is a strong advocate of science-based decision-making and the need to integrate data from epidemiological, controlled clinical, laboratory animal and cell studies to assess human health risks of exposure to toxic materials and to inform policy makers in developing standards and guidance to protect public health. He is internationally recognized for his knowledge of the health issues associated with a range of energy technologies, including nuclear power, coal combustion, oil/gas extraction and internal combustion engines, including the transition from traditional to clean diesel technology.

REVIEW ARTICLE

Evaluation of developmental toxicity studies of glyphosate with attention to cardiovascular development

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Abstract

The herbicide glyphosate has undergone multiple safety tests for developmental toxicity in rats and rabbits. The European Commission's 2002 review of available glyphosate data discusses specific heart defects observed in several individual rabbit developmental toxicity studies, but describes the evidence for a potential causal relationship as equivocal. The present assessment was undertaken to analyze the current body of information generated from seven unpublished rabbit studies in order to determine if glyphosate poses a risk for cardiovascular malformations. In addition, the results of six unpublished developmental toxicity studies in rats were considered. Five of the seven rabbit studies (dose range: 10–500 mg/kg/day) were GLP- and testing guideline-compliant for the era in which the studies were performed; a sixth study predated testing and GLP guidelines, but generally adhered to these principles. The seventh study was judged inadequate. In each of the adequate studies, offspring effects occurred only at doses that also caused maternal toxicity. An integrated evaluation of the six adequate studies, using conservative assumptions, demonstrated that neither the overall malformation rate nor the incidence of cardiovascular malformations increased with dose up to the point where severe maternal toxicity was observed (generally >150 mg/kg/day). Random occurrences of cardiovascular malformations were observed across all dose groups (including controls) and did not exhibit a dose-response relationship. In the six rat studies (dose range: 30–3500 mg/kg/day), a low incidence of sporadic cardiovascular malformations was reported that was clearly not related to treatment. In summary, assessment of the entire body of the developmental toxicity data reviewed fails to support a potential risk for increased cardiovascular defects as a result of glyphosate exposure during pregnancy.

Keywords

Cardiac, heart, interventricular septal defect, rabbit, rat

History

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Introduction

Glyphosate, the active ingredient in popular herbicide formulations such as Roundup, AquaMaster and Vision branded products, is the most commonly used herbicide in the US (Grube, 2011). Specific usage statistics are not readily available for Europe, but are assumed to mirror those of the US. Glyphosate acts by targeting the enzyme enolpyruvylshikimate phosphate synthase in plants (Williams et al., 2012). Although this enzyme is important in the synthesis of several essential amino acids in plants, it is not found in animals. For this reason, glyphosate is considered to be generally safe to people and other mammals when used according to the manufacturer's instructions. Nevertheless, due to its widespread use and the large number of glyphosate manufacturers, glyphosate has been subjected to numerous safety tests to protect health. In a monograph developed

to support the European Commission's 2002 review of glyphosate (BBA, 1998–2000; European Commission, 2002), the authors discuss specific heart defects observed in individual rabbit developmental toxicity studies of glyphosate, however they describe the evidence for a potential causal relationship as equivocal. Based on data selected from these studies, others have alleged there is evidence of teratogenicity and have called for a new risk assessment of glyphosate (Antoniou et al., 2012).

The present critical analysis assesses the glyphosate developmental toxicity database available to European regulatory agencies in order to determine if there is, in fact, a cause for concern for cardiovascular defects or other malformations. Rabbit and rat developmental toxicity studies on glyphosate conducted by member companies of the European Union (EU) Glyphosate Task Force were made available to the authors of this paper for the purpose of this analysis. These included seven developmental toxicity studies conducted in rabbits as well as six developmental toxicity studies conducted in rats. A PubMed search of the peer-reviewed literature through May 2012 was also conducted in an attempt to identify other studies of developmental glyphosate exposure and heart/cardiovascular malformations. No studies were

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found to be focused on cardiovascular defects as a result of *in utero* glyphosate treatment. A few published studies examined the effects on the fetal development of *in utero* exposure to glyphosate-based herbicide formulations (Dallegrave et al., 2003, 2007; Darwich et al., 2001); none of these studies, however, addressed visceral malformations. Therefore, the focus of the present analysis is on developmental toxicity studies of glyphosate that were conducted to fulfill regulatory requirements, particularly those in the rabbit. Each of the seven rabbit developmental toxicity studies has been critically evaluated with attention to whether the database as a whole is of sufficient quality to determine glyphosate's teratogenic potential in rabbits, particularly for the cardiovascular system. Details of these analyses are found in the Appendix. The findings from six rat developmental toxicity studies conducted with glyphosate for regulatory purposes are also addressed, paying particular attention to heart and cardiovascular defects. Finally, the rabbit and rat data are briefly discussed in the context of the available epidemiological data for glyphosate.

Rabbit developmental toxicity database

A total of seven developmental toxicity studies of glyphosate have been conducted in the rabbit, the designs of which are summarized in Table 1. These studies, which are critically evaluated in the Appendix, involved testing in three different rabbit strains (New Zealand white, Japanese white and Dutch belted) and covered a wide range of glyphosate doses, from 10 to 500 mg/kg/day. This range includes doses that caused overt maternal toxicity (150 mg/kg/day and above); in some cases, the maternal toxicity observed was substantial. Two of these studies (Suresh, 1993; Tasker, 1980a) had insufficient numbers of fetuses available for assessment at the high dose (500) and 350 mg/kg/day, respectively).

The seven rabbit developmental toxicity studies vary considerably in their quality: the numbers of animals per dose group, the spacing of doses, the extent of documentation and detail provided and the specific types of data reported. Five of the studies stated that they followed good laboratory practices (GLP) specific to the time period in which they were conducted (Brooker et al., 1991a; Coles and Doleman, 1996; Hojo, 1995; Moxon, 1996; Suresh, 1993). Another study was conducted prior to the establishment of GLP requirements, but appears to have generally adhered to GLP principles (Tasker et al., 1980a). In the seventh study (Bhide & Patil, 1989),

it is not clear to what extent GLP practices were followed, but it is unlikely that this study was fully GLP-compliant because the description of study results is extremely limited and inappropriate animals appear to have been included in the calculations for certain endpoints. All these studies were conducted according to developmental toxicity testing guideline requirements current at the time they were initiated and provided quality assurance audits.

As these studies were all done in different laboratories, there is considerable disparity across studies in the classification of various anomalies as major malformations, minor malformations or variations and in the terminology used to describe these findings. Further, three of the studies (Bhide & Patil, 1989; Hojo, 1995; Suresh, 1993) did not report anomalies by individual fetus. Therefore, for these studies, it is not possible to determine whether certain fetuses showed multiple anomalies or if anomalies occurred in combination. The study by Suresh (1993) also used some terminology that is not standard for heart defects in developmental toxicity studies (e.g. seal-shaped heart, dilated heart), which makes interpretation of the findings difficult. Certain cardiovascular changes reported in the Brooker et al. (1991a) study (e.g. retroesophageal right subclavian artery) are considered variations in other laboratories (Appendix); these are discussed in more detail below. Because of inappropriate methods and the poor reporting of data, the Bhide & Patil (1989) study was considered inadequate for assessing glyphosate's potential for developmental toxicity in rabbits. The remaining six rabbit studies formed the basis for our analysis. While the individual studies may fall short of current guidelines (mainly because the desired number of rabbits per group has increased and the exposure period has been extended beyond GD18), these shortcomings are overcome when one considers the overall database. More specifically, the exposure period in each of these studies extends well before and after the period of organogenesis for the cardiovascular system. Additionally, the studies cover a broad and well-distributed range of 15 different glyphosate exposures ranging from 10 to 500 mg/kg/day. Finally, the combined database from these studies includes evaluation of 347 total litters (99 controls and 247 treated) and 2990 fetuses (834 controls and 2156 treated). Based on these elements, the overall database of six adequate rabbit developmental studies is considered to be robust for the purposes of risk assessment.

To address whether the six adequate studies exhibited evidence of selective offspring sensitivity to glyphosate

Table 1. Maternal and developmental NOAELs from six sufficient rabbit developmental toxicity studies of glyphosate.

Study	No. of animals per group	Exposure period	Doses (mg/kg/day)	Maternal NOAEL (mg/kg/day)	Offspring NOAEL (mg/kg/day)
Moxon (1996)	20	GD 7-19	0, 100, 175, 300	100	175
Coles & Doleman (1996)	18	GD 7-19	0, 50, 200, 400	200	≥400
Brooker et al. (1991a)	16-20	GD 7-19	0, 50, 150, 450	50	150
Hojo (1995)	18	GD 7-19	0, 10, 100, 300	100	≥300
Tasker et al. (1980a)	16-17	GD 6-27	0, 75, 175, 350	75	≥175
Suresh (1993)	15-26	GD 6-18	0, 20, 100, 500	100	≥100
Bhide & Patil (1989)	15	GD 6-18	0, 125, 250, 500	- ¹	- ²

¹Moxon (1996) designated the day of insemination as GD 1 and Hojo (1995) designated the day after insemination as GD 0. The exposure periods here have been adjusted to be comparable to the other studies which used GD 0 as the day of insemination.

²Due to significant limitations in study design and data reporting, this study was considered inadequate for determining NOAELs.

treatment *in utero*, the no observed adverse effect levels (NOAELs) for maternal toxicity and developmental effects were determined (Table 1). Maternal toxicity was most commonly evidenced in the rabbit studies by diarrhea and reduced food intake, which generally occurred at doses of 150 mg/kg/day or higher. Additionally, maternal weight loss and deaths generally occurred at the highest doses. Table 1 also shows that offspring effects due to glyphosate, when observed in a particular rabbit developmental toxicity study, always occurred at the same dose or doses as those associated with maternal toxicity. This does not mean that injury to the fetus necessarily occurred as a direct result of maternal toxicity, but rather, when exposures to glyphosate were kept below the doses that cause maternal toxicity, the developing offspring did not exhibit any adverse effects. Therefore, selective offspring sensitivity to glyphosate is not apparent from these studies.

Post-implantation loss was quite variable across studies. Four of the six adequate studies (Hojo, 1995; Moxon, 1996; Suresh, 1993; Tasker, 1980a) reported no statistically significant increase in post-implantation loss in three different strains of rabbits at exposure levels as high as 500 mg/kg/day. In comparison, Coles & Dolenian (1996) reported an increase in post-implantation loss at 200 mg/kg/day, but not at 400 mg/kg/day; consequently, a dose-response pattern was not established in this study. Brooker et al. (1991a) reported increased post-implantation loss at doses of 50 mg/kg/day and above (mean = 19.5 ± 19.8%, 15.3 ± 17.2% and 21.0 ± 11.8% for the 50, 150 and 450 mg/kg/day dose groups, respectively), but noted that post-implantation loss in the concurrent control group (5.7 ± 7.2%) was lower than in historical controls (mean: 12.9%, range: 6.5–17.5%), while post-implantation loss in treated litters was within or slightly higher than the historical control range. Post-implantation loss has a high degree of variability as demonstrated by the standard deviations around this endpoint in the six studies reviewed. This variability is common in the rabbit. Other historical control databases have reported mean percent post-implantation loss in the rabbit of 8.1% (range: 2.8–17.7%) and 9.1% (range: 0.6–23.4%) (Holson et al., 2006 and MARTA, 1997, respectively). Consequently, without a clear dose-response pattern established across the six studies reviewed, it is unlikely that these findings are biologically significant.

As previously noted, the rabbit developmental toxicity data for glyphosate have been previously described as equivocal with regard to cardiovascular defects (BBA, 1998–2000; European Commission 2002). To address this issue, data were extracted from each study for malformations and variations (Appendix). Two of the studies (Brooker et al., 1991a; Suresh, 1993) suggested a possible association of cardiovascular anomalies with treatment, but the data were not clear-cut; these are discussed in more detail in the Appendix. In addition, two studies (Hojo, 1995; Moxon, 1996) reported an increase in skeletal defects at the high dose of 300 mg/kg/day. These anomalies appeared to be the result of reduced ossification, which is likely related to delayed development (evidenced by reduced fetal body weights observed at the high dose), or were not clearly dose-related. Based on this information and our evaluation of the combined

data, we concluded that glyphosate treatment was not associated with an increase in malformations in rabbits. The remaining discussion focuses on cardiovascular defects only.

Examination of the data from the six rabbit studies showed a variety of malformations of the heart and great vessels. These included: dilated aorta/narrow pulmonary artery; narrow aorta/dilated pulmonary artery; hypoplasia of the pulmonary artery; interventricular (IV) septal defect; cardiomegaly; single ventricle; thickened ventricle walls; dilated ventricle; retro-esophageal right subclavian artery; interrupted aorta; right subclavian artery arising from aortic arch; "scal-shaped" heart. If glyphosate treatment was associated with congenital heart defects and malformation of the great vessels in rabbits, then the prevalence of these defects would be anticipated to increase with dose and the overall malformation rate would also be anticipated to increase. However, as can be seen from the malformation incidence tables in the Appendix, cardiovascular malformations generally occurred in the rabbit studies at a low incidence across all dose groups. Further, in most studies, they did not exhibit a positive dose-response, and oftentimes, clusters of malformations occurred in the same fetuses.

In order to further discern whether there might be an association between exposure of rabbits to glyphosate and cardiovascular malformations, the following conservative assumptions were made so that the malformation data from the six adequate studies could be combined. First, all three rabbit strains (Japanese white, New Zealand white and Dutch belted) were assumed to be equally sensitive to glyphosate. Second, small differences in treatment duration across studies were assumed not to affect the incidence of cardiovascular malformations because all treatment paradigms covered the critical period of heart and great vessel development (i.e. GD 8–17; DeSesso, 2012). Third, cardiovascular malformations were categorized depending on the type of cardiovascular defect and what is known about the underlying morphogenetic processes. For instance, several defects are related to development of the aorticopulmonary septum and are grouped together. As an example, Brooker et al. (1991a) reported that many fetuses with IV septal defects exhibited other cardiovascular defects that included enlarged aorta/stenotic pulmonary artery or the converse (stenotic aorta/enlarged pulmonary artery). During formation of the outflow tract from the ventricles, neural crest cells migrate from the hindbrain region into the truncus arteriosus where they contribute to and direct the growth of the aorticopulmonary septum (Hutson & Kirby, 2003; Kirby et al., 1983; Sadler, 2011). The aorticopulmonary (spiral) septum (Figure 1) grows as a pair of ridges that divide the truncus arteriosus into equally sized halves: the aorta and the pulmonary artery (DeSesso & Venkat, 2010). At its inferior end, the aorticopulmonary septum forms the upper portion (membranous portion) of the IV septum. Consequently, malformations relating to a disproportionately sized aorta and pulmonary septum, as well as IV septal defects of the upper region, are all related to displacement of the developing aorticopulmonary septum (DeSesso & Venkat, 2010).

Based on this information, those cardiac defects that involved perturbations of aorticopulmonary septum development were combined based on the premise that glyphosate

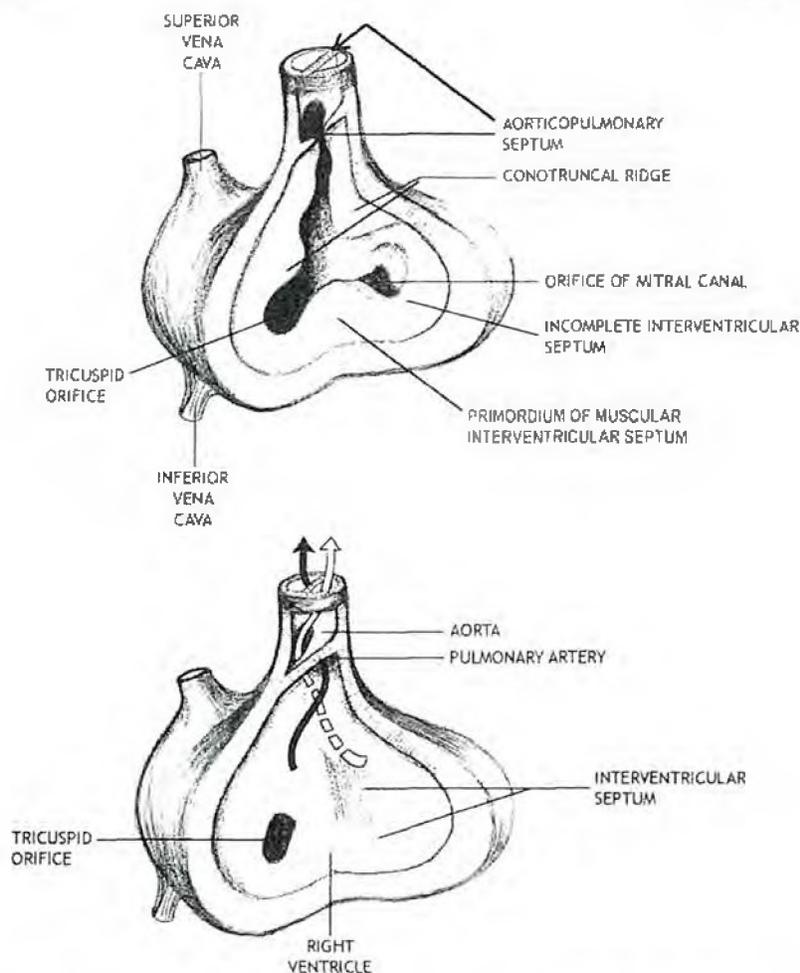


Figure 1. Division of the outflow tract by the aorticopulmonary (spiral) septum. In the top diagram, the aorticopulmonary septum is forming by the growth and merging of the conotruncal ridges in the walls of the outflow tract. This process divides the outflow tract into the atriioventricular canals (precursors of the aorta and pulmonary artery). In the lower diagram, the spiral septum has completed the separation of the outflow tract into the equally sized aorta (for systemic circulation) and pulmonary artery (for the pulmonary circulation). The most inferior part of the spiral septum will contribute to the upper membranous portion of the IV septum. (Modified from DeSesso & Venkat. 2010).

might cause all or any of these defects by acting on a single developmental process. Data from all numerically similar dose groups (e.g. data from all three studies that treated rabbits at 100 mg/kg/day) were combined into a single entry.

Evaluation of the resulting tabulation (Table 2) shows that there was no increase in cardiovascular malformations at doses that were not overtly toxic to the pregnant rabbits (i.e. generally at doses over 150 mg/kg/day). The two most commonly observed malformations involved the aorticopulmonary septum and dilated heart. The incidence of aorticopulmonary septum-related defects in the combined control groups was 1/770 (0.1%); in the combined glyphosate-treated groups the incidence was 6/1939 (0.3%). More than half of these affected fetuses were found in litters exposed to one of the highest doses (450 mg/kg/day). Doses of 150 mg/kg/day and above were generally associated with maternal

toxicity, including severe weight loss and death. If doses of 300 mg/kg/day and above are not considered because of the confounding maternal toxicity issues, then the incidence of the defects in glyphosate-treated animals is 2/1388 (0.1%). Thus, these data show that the overall incidence of aorticopulmonary septum-related defects in offspring from mothers exposed to glyphosate at doses below those that cause severe maternal toxicity is similar to that seen in non-exposed rabbits.

The other prevalent cardiovascular malformation reported was dilated heart. All observations of this finding occurred in a single study (Suresh, 1993). There was also one case of cardiomegaly at 100 mg/kg/day in the same study. None of the other five adequate studies reported dilated hearts or cardiomegaly. Furthermore, neither the criteria used to diagnose dilated heart nor measurements of the hearts were provided in the study report, so it is not possible to directly

Table 2. Combined and grouped (number and percentage) cardiovascular malformations from six rabbit developmental toxicity studies

Dose (mg/kg/day)	0	10	20	50	75	100	150	175	200	300	350	400	450	500
Total number of fetuses evaluated at each dose	770	130	78	261	114	374	112	200	119	256	38	134	95	28
Defects related to displaced aorticopulmonary (spiral) septum including ventricular septal defects	1 ^H (0.1%)					1 ^H (0.3%)	1 ^H (0.9%)						4 ^H (5.0%)	
Dilated heart			4 ^S (5.1%)			4 ^S (1.1%)								2 ^S (7.1%)
Dilated ventricles	1 ^S (0.1%)					1 ^S (0.2%)								1 ^S (3.6%)
Cardiomegaly						1 ^S (0.2%)								
Single heart ventricle, thickened ventricle walls						1 ^M (0.2%)				1 ^M (0.4%)				
Retroesophageal right subclavian artery							3 ^B (2.7%)							2 ^H (2.1%)
"Seal-shaped" heart	1 ^X (0.1%)					1 ^S (0.2%)								
Acephalic animal with heart defects				1 ^H (0.4%)						1 ^C (0.8%)				
Cebocephalic animal with heart defects	1 ^M (0.1%)													

B = Brooker et al. (1991a); C = Coles & Doleman (1996); H = Hojo (1995); M = Moxon (1996); S = Suresh (1993).

Table 3. Maternal and developmental NOAELs from six sufficient rat developmental toxicity studies of glyphosate.

Study	No. of animals per group	Exposure period	Doses (mg/kg/day)	Maternal NOAEL (mg/kg/day)	Offspring NOAEL (mg/kg/day)
Moxon (2002)	22-24	GD 6-15†	0, 250, 500, 1000	≥1000	≥1000
Wood (1996)	22-25	GD 6-15	0, 100, 500, 1000	≥1000	≥1000
Hatakenaka (1995)	22-24	GD 6-15	0, 30, 300, 1000	300	≥1000
Brooker et al. (1991a)	23-25	GD 6-15	0, 300, 1000, 3500	1000	1000
Suresh (1991)	20-30	GD 6-15	0, 1000	≥1000	≥1000
Tasker et al. (1980b)	20-23	GD 6-19	0, 300, 1000, 3500	1000	1000

†Moxon (1995) designated the day of finding sperm as GD 1. The exposure period here has been adjusted to be comparable to the other studies which used GD 0 as the day of insemination.

compare the dilated heart findings to the hearts of the more than 2500 fetuses in the other studies.

Finally, an examination of the overall rate of cardiac malformations across the six studies did not support a dose-response correlation with glyphosate exposure. Based on this analysis, it appears that prenatal glyphosate exposure is not associated with increased cardiovascular defects in rabbits.

Rat developmental toxicity database

The six developmental toxicity studies of glyphosate conducted in the rat are discussed in the Appendix and summarized in Table 3. These studies involved testing in two different rat strains (Wistar and Sprague-Dawley) and covered a wide range of glyphosate doses up to 3500 mg/kg/day, which is well above the current limit dose for toxicity studies of 1000 mg/kg/day. With the exception of Tasker et al. (1980b), all studies conformed to internationally accepted general principles of GLPs and were conducted according to OECD 414 (1981) and US EPA 83-3 guideline requirements. The study by Tasker et al. (1980b) predated the establishment of US EPA and OECD guidelines, but it received quality

assurance audits by the testing facility and appeared to be well-conducted and essentially guideline-compliant. As with the rabbit studies, the rat developmental toxicity studies of glyphosate varied in the numbers of animals per dose group, the spacing of doses, the extent of documentation and detail provided, and the specific types of data reported. Nevertheless, for the purposes of this evaluation, all six rat studies were considered adequate for assessing the developmental toxicity potential of glyphosate.

The NOAELs for maternal toxicity and developmental effects as assessed for the six rat developmental toxicity studies are shown in Table 3. Maternal body weight was not affected in any of the studies at exposure levels lower than 3500 mg/kg/day. Further, there were no dose-related effects on intrauterine parameters at doses of 1000 mg/kg/day and below. Maternal NOAELs were determined to be ≥1000 mg/kg/day for all studies except Hatakenaka (1991) (Table 3), which reported loose stools in a few dams at that exposure. No treatment-related effects were observed in the offspring at doses of 1000 mg/kg/day and below. Consequently, the offspring NOAELs for these studies were ≥1000 mg/kg/day and equal to or greater than the maternal

NOAELs in each study (Table 3). Further, no treatment-related effects of glyphosate on structural development of the offspring were observed (Table A10). Generally, malformations (including cardiovascular malformations) were limited to 1-3 fetuses in 1-2 litters in the exposed groups and occurred at incidences as low as or lower than those in the control group. Overall, the rat developmental toxicity studies do not show any evidence of cardiovascular or other types of malformations as a result of glyphosate exposure at doses of up to 3500 mg/kg/day.

Discussion and conclusions

The 13 developmental toxicity studies summarized above and discussed in detail in the Appendix have been submitted to regulatory agencies in support of the registration of glyphosate. Analyses by the regulatory agencies have not supported the claim that glyphosate causes cardiovascular defects or other developmental effects (BBA, 1998-2000; EPA, 1993; European Commission, 2002). At the time of the US EPA's assessment, only the studies by Tasker et al. (1980a,b) were available for evaluation. The European Commission's review (European Commission, 2002), however, included the examination of four of the rabbit studies (Bhide & Patil, 1989; Brooker et al., 1991a; Suresh, 1993; Tasker et al., 1980a) and three of the rat studies (Brooker et al., 1991b; Suresh 1991; Tasker et al., 1980b) discussed herein. In a related monograph (BBA, 1998-2000), the results from two of the rabbit studies reviewed by the European Commission were characterized as equivocal for cardiovascular developmental effects. None of the three rabbit developmental toxicity studies that were not evaluated by the European Commission (Coles & Doleman, 1996; Hojo, 1995) showed a potential for cardiovascular defects.

Based on our assumptions underlying the integrated assessment of data across studies (equal strain sensitivity, insignificant differences in timing of exposure and shared morphogenetic processes of certain defects), the overall conclusion of our analysis of the potential for glyphosate to cause malformations, and cardiovascular defects in particular, is that there is no increased risk at the levels of exposure below those that caused maternal toxicity. This conclusion is in agreement with that of regulatory agency reviews as well as the limited data available from epidemiology studies showing no increased risk of congenital defects with exposure (Bell et al., 2001a,b,c; Garry et al., 2002; Rull et al., 2006; reviewed in Williams et al., 2012). It should be noted, however, that these studies investigated exposures to several pesticides and were not specific to glyphosate. More recently, a detailed review of epidemiology studies of glyphosate and non-cancer endpoints found no evidence of a causal relationship between glyphosate exposures and malformations (Mink et al., 2011). Finally, a review of the available biomonitoring data demonstrates that human exposure as a result of normal glyphosate application practices is extremely low, often below the limits of analytical detection (Williams et al., 2012). In conclusion, this analysis of the developmental toxicity data available for glyphosate exposure confirms that there is no evidence of an increased risk of cardiovascular defects as a result of glyphosate exposure.

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Declaration of interest

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Appendix

Rabbit developmental toxicity studies

A total of seven developmental toxicity studies of glyphosate have been conducted in the rabbit and are summarized in detail below. The studies vary considerably in their quality, the extent of documentation and detail provided and the specific types of data reported. They have been ordered on the basis of quality, with studies of higher quality, and therefore greater relevance in the overall evaluation, detailed first. Although some of these studies reported the results of preliminary range-finding experiments, only the results of the definitive studies are detailed here for the purposes of this review. Typically, doses for the definitive studies were selected based on maternal toxicity observed in the preliminary range-finding studies. Five of the studies stated that they followed GLP specific to the time period in which they were conducted (Brooker et al., 1991a; Coles & Dolanau, 1996; Hojo, 1995; Moxon, 1996; Suresh, 1993). Another study was conducted prior to the establishment of GLP requirements, but generally adhered to GLP principles (Tasker et al., 1980b). In the seventh study (Bhude & Patil, 1989), it is not clear to what extent GLP practices were followed, but it appears that this study was not fully GLP-compliant because the description of study results is extremely limited and inappropriate animals appear to have been included in the calculation of certain endpoints. All the studies were conducted according to current testing guideline requirements at the time of the study and provided quality assurance audits. The animal supply and husbandry were described, although detailed husbandry data were not provided in the study reports. No other deviations were detailed by the study authors. In the summaries that follow, we address issues of data quality where appropriate. In two cases (Brooker et al., 1991a; Suresh, 1993), we have tabulated the malformations reported in some detail. This was done because these two studies reported increases in malformations which appeared to be related to increases in cardiovascular defects. All other studies had very low levels of cardiovascular malformations, so no further details were given.

Moxon (1996)

This study was conducted according to OECD 414 (1981) and US EPA 83-3 testing guideline requirements. Female virgin New Zealand White rabbits (age unknown) were paired with males (day of insemination = gestational day (GD) 1) and delivered to the testing laboratory on either GD 2 or 3. The designation of the day of insemination as GD 1 is different than that for the majority of the rabbit studies, which designated the day of insemination as GD 0. For the purposes of comparing to other studies, the day of mating has been corrected to GD 0 in the following discussion with succeeding gestational days changed accordingly. The maternal animals were assigned by a randomized design to minimize (but not necessarily to prevent) the number of animals in the same group that were sisters or mated to the same male. Glyphosate acid (purity: 95.6%) was formulated in deionized water, was stable over the test period and was shown to have an adequate homogeneity. The achieved concentrations were within 12% of the target concentrations. The doses were administered 0, 100, 375 or 300 mg/kg/day by oral gavage on GD 7–19 (20 rabbits per group). The dosing volume was 2 mL/kg body weight; the dosing vehicle was deionized water. The rabbits were evaluated daily for mortality, behaviour and clinical signs of toxicity. Body weights were recorded on GDs 3, 7–19, 22, 25 and 29. Food consumption was recorded every 3–4 days from GD 3 to GD 25. Does were sacrificed on GD 29 and the men and ovaries were examined for the numbers of corpora lutea, implantations, live and dead fetuses, and intra-uterine deaths (both early and late). The does were further evaluated for any gross pathological changes. Fetuses were weighed and examined for external, visceral (via fresh dissection) and skeletal (by means of alizarin red S staining) anomalies. The degree of bone ossification was scored visually based on the extent of alizarin staining.

Clinical symptoms of toxicity observed in the 175 and 300 mg/kg/day dose groups included diarrhea, few feces and/or staining in the genital

Table A1 Maternal and fetal outcome data for New Zealand white rabbits treated with glyphosate on gestational days 7-19 (Moxon 1996).

	0 mg/kg/day	100 mg/kg/day	175 mg/kg/day	300 mg/kg/day
Maternal data				
No. animals on study	20	30	20	20
No. non-gravid	2	0	1	1
No. gravid does dead or sacrificed <i>in extremis</i>	1	2	2	2
No. that aborted	1	2	1	2
Embryofetal data				
Total No. litters examined	17	18	17	17
Mean No. corpora lutea	10.8 ± 2.2	11.0 ± 1.6	11.1 ± 1.3	11.2 ± 1.4
Mean No. implantations	9.65 ± 2.06	9.00 ± 1.78	9.12 ± 2.50	9.82 ± 1.88
Mean % pre-implantation loss	10.7 ± 11.0	18.2 ± 11.1	18.1 ± 20.8	12.8 ± 11.9
Mean No. embryo/fetal death	NR	NR	NR	NR
Mean No. viable fetuses	8.41 ± 1.80	8.17 ± 2.20	7.94 ± 2.19	8.47 ± 2.32
Mean % post-implantation loss	11.7 ± 12.0	9.5 ± 16.7	12.1 ± 9.7	13.6 ± 16.6
Mean fetal body weight (g)	44.4 ± 4.3	43.3 ± 3.9	43.2 ± 5.7	40.7 ± 7.8*
Total fetuses (litters) with malformations				
Major external/visceral	2 (2)	1 (1)	0 (0)	2 (2)
Minor external/visceral	12 (8)	7 (5)	9 (8)	11 (7)
Major skeletal	3 (2)	0 (0)	0 (0)	1 (1)
Minor skeletal	58 (16)	82 (18)**	59 (16)	79 (17)**
Total fetuses (litters) with variations				
External/visceral	0	0	0	0
Cardiovascular	1 (1)	1 (1)	0	1 (1)
Skeletal	119 (17)	129 (18)	116 (17)	132 (17)**

NR = Not reported.

*Moxon (1995) designated the day of insemination as GD 1. The exposure period here has been adjusted to be comparable to the other studies which used GD 0 as the day of insemination. See text for details.

†Includes litters that were aborted in the analysis.

* $p < 0.05$, ANOVA; litter is statistical unit.** $p < 0.05$, Fisher's exact test.

area. Dose-dependent reductions in food consumption and body weight gains were observed in these two dose groups as well.

Pregnancy outcome and delivery data are shown in Table A1. Two does died or were sacrificed *in extremis* in each dose group except the control, in which there was a single animal death. Abortions occurred in 1, 2, 1 and 2 rabbits in the 0, 100, 175 and 300 mg/kg/day dose groups, respectively. All animals that aborted or had total litter resorptions died or were sacrificed *in extremis*. No macroscopic findings related to treatment were found in does at necropsy.

Glyphosate treatment had no effect on the number of corpora lutea, implantations, viable fetuses per litter or the incidences of pre- and post-implantation loss. Mean fetal body weights were significantly reduced at the high dose of 300 mg/kg/day compared to controls; this difference was attributed to two litters for which fetal weights were particularly low. The fetal sex ratio was skewed toward males at the intermediate dose of 175 mg/kg/day. Since this endpoint tends to be highly variable and no dose response trend was evident, the difference was not considered to be treatment-related.

Table A1 also shows the number of fetuses and litters in each dose group with major and minor external/visceral and skeletal defects and the incidence of fetuses with variations in each. The only changes that appeared to increase with dose were minor skeletal defects and variants, and these were increased almost exclusively in the 300 mg/kg/day group. The increase in minor skeletal defects and variants can be attributed to reduced ossification in several bones, including transverse processes of cervical and lumbar vertebrae, sternbrae and bones of the hindpaw. These are likely related to the reduced fetal body weights seen at the highest dose level.

The type and incidence of major malformations within individual fetuses did not increase with dose. Only five fetuses in the entire study had major malformations, two in the control group, one at 100 mg/kg/day and one at 300 mg/kg/day. Three fetuses had heart defects involving effects on separation of the heart, one in the controls, one at 100 mg/kg/day and one at 300 mg/kg/day. Thus, none of the malformations noted were associated with exposure to glyphosate.

Based on clinical signs of toxicity and on reduced food intake and body weight gain, the NOAEL for maternal toxicity is considered to be 100 mg/kg/day. Based on reduced fetal weights observed at the high dose, the NOAEL for developmental toxicity is considered to be 175 mg/kg/day.

Coles & Doleman (1996)

This study was conducted according to OECD 414 (1981) and US EPA 83-3 (1984) testing guideline requirements. Female New Zealand White rabbits (2.7-4.1 kg) of 17-19 weeks of age were mated with "stud" males by the supplier and delivered to the test facility at or before GD 3. The day of mating was considered GD 0. Glyphosate technical (purity: 95.3%) was formulated in 1% carboxymethyl cellulose, was stable over the test period and was shown to have an adequate homogeneity. The averaged achieved concentrations were within 11% the target concentrations over the test period. Although doses were described as "mg/kg" in the study report, based on the dosing description, it is assumed that these are daily doses (i.e. mg/kg/day). The does were administered 0, 50, 200 or 400 mg/kg/day by oral gavage on GD 7-19 (18 rabbits per group). The dosing volume was 5 mL/kg body weight. Individual dose volumes were based on the most recent body weight. Animals were examined at least once daily for mortality and clinical signs. Body weights were recorded on GD 3, 7, 10, 13, 16, 19, 22, 25 and 29 (body weight change was based on BW at GD 7); food consumption was measured using the same time intervals (e.g. GD 3-7, 7-10). All surviving animals were sacrificed on GD 29 and the uteri and ovaries were examined. The numbers of corpora lutea, implantations, and live and dead fetuses were recorded. The does were further evaluated for gross pathological changes. All fetuses were sexed, weighed and examined for external and internal abnormalities. The heads of alternate fetuses were fixed and examined separately. The skeletons were stained with alizarin red and examined.

No dose-related clinical signs were reported except soft/liquid feces and mucus in the feces. This was observed most frequently in the 400 mg/kg/day group, but was also observed at 50 and 200 mg/kg/day. During the treatment period, maternal food consumption was reduced from that of controls at 400 mg/kg/day (GD 10-19). In the post-treatment period, food consumption in the treated groups tended to be higher than the controls; however, the differences did not attain statistical significance. There was a statistically significant reduction in body weight gain (GD 7-29) at 400 mg/kg/day, and a non-statistically significant reduction at 200 mg/kg/day.

Pregnancy outcome and delivery data are presented in Table A2. The numbers of non-pregnant animals were 3, 0, 2 and 1 in the 0, 50, 200 and 400 mg/kg/day groups, respectively. The numbers of does dead or

Table A2. Maternal and fetal outcome data for New Zealand white rabbits treated with glyphosate on gestational days 7-19 (Coles & Doleman, 1996).

	0 mg/kg/day	50 mg/kg/day	200 mg/kg/day	400 mg/kg/day
Maternal data				
No. animals in study	18	18	18	18
No. non-gravid	3	0	2	1
No. gravid does dead or sacrificed <i>in extremis</i>	1	0	1	2†
No. that aborted	0	0	0	0
Embryofetal data				
Total No. litters examined	14	18	15	15
Mean No. corpora lutea	10.9 ± 2.2	10.5 ± 2.3	10.7 ± 2.1	11.5 ± 1.8
Mean No. implantations	9.5 ± 2.5	9.1 ± 2.3	8.9 ± 2.5	10.3 ± 2.3
Mean % pre-implantation loss	12.5 ± 18.2	13.6 ± 9.4	16.4 ± 15.5	9.3 ± 12.5
Mean No. embryofetal death	0.36 ± 0.63	0.33 ± 0.77	1.00 ± 1.00 [‡]	1.40 ± 2.35
Mean No. viable fetuses	9.1 ± 2.5	8.7 ± 2.4	7.9 ± 2.5	8.9 ± 2.6
Mean % post-implantation loss	3.7 ± 6.5	3.6 ± 8.5	13.5 ± 11.4*	12.1 ± 18.6
Mean fetal body weight (g)	41.5 ± 5.5	39.4 ± 5.6	41.7 ± 4.5	38.2 ± 5.2
Total fetuses (litters) with malformations	1 (1)	3 (2)	2 (2)	1 (1)
Total fetuses (litters) with cardiovascular malformations	0	0	1 (1)	0
Total fetuses (litters) with variations‡	41 (13)	50 (17)	39 (15)	51 (14)

†At least one of these deaths/sacrifices at 400 mg/kg/day was likely treatment-related.

‡Fetuses with both malformations and variations are included in the malformations tally; fetuses with only variations are captured here.

* $p < 0.05$, Kruskal-Wallis followed by the Mann-Whitney U test; litter was the statistical unit.

sacrificed *in extremis* were 1, 0, 1 and 2 in the 0, 50, 200 and 400 mg/kg/day groups, respectively. At least one maternal death at 400 mg/kg/day appeared to be treatment-related; deaths in the control and mid-dose groups were attributed to dosing technical errors. None of the animals aborted.

The total litters included in the data evaluation were 14, 18, 15 and 15 for the 0, 50, 200 and 400 mg/kg/day groups, respectively. Compared to controls, glyphosate treatment exerted no effects on the numbers of corpora lutea, implantations, pre-implantation loss, fetal sex ratios or fetal weights. There was a statistically significant increase in embryo/fetal death and post-implantation loss at 200 mg/kg/day, and a non-statistically significant increase at 400 mg/kg/day. The standard deviations within these data are considerable and Coles & Doleman (1996) point out that at 200 mg/kg/day, there was a preponderance of 'early fetal deaths', and at 400 mg/kg/day, the increase could be attributed to one animal with nine late deaths or a post-implantation loss of 69.2%. If the one litter with high implantation loss is excluded, the mean ± standard deviation for post-implantation loss in the remaining litters is 8.0 ± 10.2 . With no consistent, statistically significant dose-response pattern, the biological significance of these data is questionable. No historical control data were provided in Coles & Doleman (1996) to compare with these results.

Table A2 also shows the number of fetuses and litters in each dose group with external/visceral and skeletal malformations and variations. There was no apparent increase in morphological findings with increasing dose in any group. There was a variety of malformations seen, but no particular pattern of malformations and no apparent dose-response relationship. Only one case of a heart and great vessel defect was seen in the 200 mg/kg/day group in a fetus with a number of other severe abnormalities. A number of skeletal variations were noted, but there did not appear to be a dose-related increase.

Based on clinical signs and a decrease in maternal weight gain at 400 mg/kg/day, the NOAEL for maternal toxicity is considered to be 200 mg/kg/day. It is possible that similar treatment-related clinical signs were observed at exposures lower than 400 mg/kg/day, but there was no clear dose-response. Assuming that the increase in post-implantation loss discussed above is not biologically significant, the NOAEL for developmental toxicity is ≥ 400 mg/kg/day.

Brooker et al. (1991a)

This study was conducted according to OECD 414 (1981) and US EPA 83-3 (1984) guideline requirements. Female New Zealand White rabbits of 11-24 weeks of age were used; there did not appear to be a period of acclimatization. The females were mated with proven males, followed by an injection of luteinizing hormone to promote ovulation. The day of mating (sperm positive) was considered GD 0. Glyphosate acid (purity: 95.3%) was formulated in 1% methylcellulose, was stable over the test

period and was shown to have an adequate homogeneity. The achieved concentrations were within 6% of the target concentrations, with the exception of a single measurement in Group 2 which was 19% below the target concentration. It is unclear how often samples for analysis were taken during the study. The does were administered 0, 50, 150 or 450 mg/kg/day by oral gavage on GD 7-19 (16-20 rabbits per group). The reason for including different numbers of animals per dose group was not reported. The dosing volume was 5 mL/kg body weight. Individual dose volumes were based on individual body weights on GD 7 and adjusted according to body weights on GD 9, GD 11 and GD 15. Animals were examined daily for mortality and signs of toxicity. Body weights were recorded on GD 1, 7, 9, 11, 15, 20, 24 and 29; food consumption was measured using the same time intervals (e.g. GD 1-7, 7-9). Does that did not survive until the end of the study were weighed and necropsied. All surviving animals were sacrificed on GD 29, and the ovaries and uteri were examined for the numbers of corpora lutea, implantations, and live and dead fetuses. The does were further evaluated for gross pathological changes. All fetuses were weighed and examined for external abnormalities, then dissected to examine for visceral abnormalities and to determine sex. The heads were fixed and examined separately. The skeletons were stained with alizarin red and examined. Structural changes were reported by study investigators as malformations (defined as rare and/or probably lethal changes), anomalies (defined as relatively frequent minor differences from 'normal') and variants (defined as alternative structures occurring regularly in the control population).

There were no dose-related clinical signs except soft/liquid faeces; this finding was observed at all exposure levels, but not in the controls, and was substantially increased at the high dose (450 mg/kg/day). During the treatment period, maternal food consumption was reduced from that of controls at 150 mg/kg/day (GD 11-19) and 450 mg/kg/day (GD 7-19). In the post-treatment period, both of these groups demonstrated a rebound and food consumption was greater than that in controls. No dose-related differences in maternal body weights were observed.

Pregnancy outcome and delivery data for this study are shown in Table A3. Two does were excluded from the study for non-experimental reasons (one control doe was found with a congenital malformation of the uterus at autopsy, one 450 mg/kg/day doe¹ was found to have a broken leg prior to treatment). The numbers of non-pregnant animals were 0, 6, 1 and 5 in the 0, 50, 150 and 450 groups, respectively; there did not appear to be a correlation between age of the animals (assumed based on body weights) and the occurrence of non-pregnancy. One

¹The authors state that this animal was replaced, but this does not appear to be the case from Appendix 1 in Brooker et al. (1991a).

Table A3. Maternal and fetal outcome data for New Zealand white rabbits treated with glyphosate on gestational days 7-19 (Brooker et al., 1991a).

	0 mg/kg/day	50 mg/kg/day	150 mg/kg/day	450 mg/kg/day
Maternal data				
No. animals on study	19	19	16	20
No. excluded from study	1	0	0	1
No. non-gravid	0	6	1	5
No. gravid does dead or sacrificed <i>in extremis</i>	0	0	0	1
No. that aborted	0	1	0	0
Embryo/fetal data				
Total No. litters examined	18	12†	15‡	13
Mean No. corpora lutea ^a	11.5	12.4	11.7	11.3
Mean No. implantations ^a	9.7	10.5	9.0	9.2
Mean % pre-implantation loss ^a	14.6	15.4	23.4	18.8
Mean No. embryo/fetal death ^a	0.6	1.8 ^b	1.5 ^a	1.8 ^{a,c}
Mean No. viable fetuses ^a	9.1	8.7	7.5	7.3
Mean % post-implantation loss ^b	5.7 ± 7.2	19.5 ± 19.8 ^c	15.3 ± 17.2 ^a	21.0 ± 11.8 ^{a,c}
Mean fetal body weight (gms) ^b	43.9	43.3	44.0	44.5
Total fetuses (litters) with malformations	3 (3)	3 (3)	5 (3)	6 (5)
Total fetuses (litters) with cardiovascular malformations	1 (1)	1 (1)	4 (3)	5 (4)
Total fetuses (litters) with variations "anomalies" [†]	29 (13)	26 (9)	26 (11)	16 (10)

†Analysis does not include the one litter that was aborted at this dose.

‡Includes one female which aborted one embryonic death - referred to as "partial abortion".

^aStandard deviation was not provided.

^bStandard deviation values calculated from individual animal data in Brooker et al. (1991a).

^cExclusion of retroesophageal right subclavian artery reduces the numbers to 1 (1), 1 (1), 1 (1) and 4 (4) for 0, 50, 150 and 450 mg/kg/day, respectively.

^d*p* < 0.05; ^e*p* < 0.01. Kruskal-Wallis test followed by non-parametric equivalent of Williams' test. litter was the statistical unit.

Table A4. Types and incidence of malformations by individual fetus (Brooker et al., 1991a).

	0 mg/kg/day	50 mg/kg/day	150 mg/kg/day	450 mg/kg/day
No. fetuses examined	163	104	112	95
Narrow ascending aorta, dorsally displaced pulmonary trunk, IV septal defect	1		1	1
Dilated ascending aorta/aortic arch, narrow pulmonary trunk; IV septal defect with enlarged left, reduced right ventricle				2
Retroesophageal right subclavian artery [†] (1 fetus at 150 mg/kg/day also had forelimb flexure; 1 fetus at 450 mg/kg/day with IV septal defect)			3	2
Accephaly; single dilated arterial trunk and carotid artery; right-sided descending aorta; IV septal defect, forelimb flexure and hindlimb brachydactyly		1		
Sacral meningocele occulta with slightly flattened cranium and minimal protrusion in occipital region	1			
Bilateral small eye (areas of retinal folding and dysplasia)		1		
Hydrocephaly and cebocephaly with fused and reduced nasals and premaxillae, fused nares, absent upper incisors			1	
Cleft palate; forelimb flexure and brachydactyly				1
Reduced and fused thoracic vertebral arches with absent centrum; connected, branched and absent ribs	1			
Spina bifida with lumbar kyphosis and flattened cranium; malrotated hindlimb		1		

[†]Retroesophageal right subclavian artery is considered a variation by other laboratories. Removing this endpoint as a malformation would reduce the number of fetuses in this group to one fetus with forelimb flexure at 150 mg/kg/day and one fetus with IV septal defect at 450 mg/kg/day.

maternal death occurred at 450 mg/kg/day following abortion, gastrointestinal disturbances, reduced food intake and body weight loss. One doe aborted in the 50 mg/kg/day group.

The total litters included in the data evaluation were 18, 12, 15 and 13 for the 0, 50, 150 and 450 mg/kg/day groups, respectively. Compared to controls, glyphosate treatment exerted no marked effects on the numbers of corpora lutea, implantations, pre-implantation loss, fetal sex ratios or fetal weights. There was a statistically significant increase in embryo/fetal death and post-implantation loss at all exposure levels. The study investigators questioned the biological significance of these findings for several reasons: (1) No dose-response pattern was evident; (2) the control value was at the lower end of the historical control range, while those of the exposed groups were at the higher end and (3) the values

in all groups were within or slightly above the historical control range. The latter two statements are supported by the historical control data provided in the study report. There was also considerable variance around the mean for post-implantation loss.

A dose-related increase in malformations (fetuses and litters) was observed with 3, 3, 5 and 6 fetuses malformed at 0, 50, 150 and 450 mg/kg/day, respectively. The increase at 450 mg/kg/day appeared to be due to an increase in IV septal and other heart defects, which were seen in 1, 1, 4 and 5 fetuses in the 0, 50, 150 and 450 mg/kg/day groups, respectively (Table A4).

Although the authors indicated retroesophageal right subclavian artery as a malformation in three fetuses at 150 mg/kg/day and in two at 450 mg/kg/day, other laboratories suggest that this is a fairly common

Table A5 Maternal and fetal outcome data for Japanese white rabbits treated with glyphosate on gestational days 7–19 (Hojo, 1995)

	0 mg/kg/day	10 mg/kg/day	100 mg/kg/day	300 mg/kg/day
Maternal data				
No. animals on study	18	18	18	18
No. non-gravid	0	0	0	0
No. gravid does dead or sacrificed <i>in extremis</i>	0	0	0	1
No. that aborted	0	2	0	2
No. with only resorptions	0	1	2	1
Embryo/fetal data				
Total No. litters examined [†]	18	15	16	14
Mean No. corpora lutea	10.2 ± 2.0	11.7 ± 2.2	12.1 ± 2.0	10.1 ± 2.3
Mean No. implantations	8.5 ± 2.8	9.8 ± 2.9	10.4 ± 2.9	8.6 ± 3.3
Mean % pre-implantation loss [*]	17.8 ± 22.4	16.6 ± 17.0	15.2 ± 18.0	14.6 ± 25.2
Mean No. embryo/fetal death [‡]	0.7	1.1	1.0	0.6
Mean No. viable fetuses	7.8 ± 2.4	8.7 ± 3.2	9.4 ± 2.7	8.0 ± 3.2
Mean % post-implantation loss [§]	7.1 ± 8.8	13.8 ± 14.1	8.7 ± 10.5	6.5 ± 9.8
Mean fetal body weight (g) MALES	35.8 ± 8.1	37.3 ± 5.4	36.7 ± 3.3	36.2 ± 5.4
Mean fetal body weight (g) FEMALES	35.7 ± 6.7	36.1 ± 5.1	36.0 ± 3.9	34.9 ± 4.4
Malformations and variations				
Total # litters (%) with malformations	1 (5.6)	3 (20.0)	3 (18.8)	5* (35.7)
Total # litters (%) with variations	16 (88.9)	14 (93.3)	16 (100.0)	8* (57.1)
Total # Fetuses (%) with malformations				
External	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)
Visceral	0 (0.0)	1 (0.8)	3 (2.0)	0 (0.0)
Cardiovascular	0	0	1 (1)	0
Skeletal	1 (0.7)	4 (3.1)	6 (4.0)	5 (5.4)
Total # Fetuses (%) with variations				
Visceral	4 (2.9)	5 (3.8)	5 (3.3)	1 (0.9)
Skeletal	4† (28.6)	32 (24.6)	61* (40.7)	31 (27.7)

[†]Day of insemination adjusted to GD0 for comparison with other studies. See text for details.

[‡]Analysis does not include the litters that were aborted.

^{*}Mean and standard deviations not reported. Calculated from individual animal data in Hojo (1995).

[‡]Standard deviations calculated from individual animal data in Hojo (1995).

^{*}*p* < 0.05, Fisher's exact test; litter is the statistical unit.

variation in rabbits (MARTA, 1997; Stump et al., 2012) and it occurs in 0.5–2.0% of humans (Berko et al., 2009; Epstein & DeBord, 2002; Fazan et al., 2003). The historical control data provided by Brooker et al. (1991a) indicate that various studies have included 1–3 of such defects in control groups. Removing this defect as a malformation would reduce the total incidence of malformed fetuses to 3, 3, 3 and 5, and the incidence of fetuses with cardiovascular defects to 1, 1, 1 and 4 in the 0, 50, 150 and 450 mg/kg/day dose groups, respectively. Glyphosate treatment had no significant effect on the incidence of fetuses with variations when compared to the control group.

Based on clinical signs and decreased food consumption at 150 and 450 mg/kg/day, the NOAEL for maternal toxicity is considered to be 50 mg/kg/day. There was a slight increase in fetuses with malformations at 450 mg/kg/day. Several of the cardiovascular malformations that were observed, particularly in the high dose group, occurred in the same animals (Table A4) and are related to a single morphogenetic mechanism (i.e. displacement of the developing aorticopulmonary septum), which may adjust during the postnatal period as some of these improve during the first few months of life in humans (Hoffman and Kaplan, 2002). These mechanistically related findings, which often cluster together, include dilated/narrow aorta and narrow/dilated pulmonary artery; IV septal defect and disproportionately sized right and left ventricles. These malformations and the associated morphogenetic mechanism are discussed in greater detail in the integrated assessment below. These findings in the heart were also observed (often in clusters) in the historical control data provided by Brooker et al. (1991a). Overall, the malformation data showed an increase at 450 mg/kg/day (not statistically significant) and all findings in the glyphosate-treated groups were within historical control ranges. Although there were statistically significant increases in embryo/fetal death and post-implantation loss at 50 mg/kg/day and above, this was due to unusually low values in the concurrent control group. Although embryo/fetal death was within the historical control range, post-implantation loss was above historical control values in the high dose group, and both of these parameters were highly statistically significant at the high dose. Based on these data, the developmental NOAEL is 150 mg/kg/day.

Hojo (1995)

This study was conducted according to OECD 414 (1981) and US EPA 83-3 (1984) guideline requirements. Female Japanese White rabbits (3.3–3.8 kg) of 17 weeks of age were acclimatized for 10 days, and then impregnated by artificial insemination with sperm from breeder males of the same strain, followed by 25 units of human chorionic gonadotropin. The day after insemination was considered GD 0; this designation is different than that used in most of the other rabbit studies. Days of gestation have been adjusted for this study by designating the day of insemination as GD 0 to compare with other studies reviewed here. Glyphosate acid (purity: 97.6%, referred to in the report as HR-001) was formulated in 0.5% carboxymethyl cellulose, was stable over the test period and was shown to have an adequate homogeneity. The achieved concentrations were within 5% of the target concentrations. Impregnated does were administered 0, 10, 100 or 300 mg/kg/day by oral gavage on GD 7–19 (18 rabbits per group). The dosing volume was 5 mL/kg body weight, based on the individual body weights on each day of dosing. Animals were examined at least once daily for mortality and clinical signs. Body weights were recorded on GDs 1, 7–19 (daily), 25 and 28. Body weight gains were based on the GD 1 body weight; adjusted weight was not reported, but was calculated herein by subtracting the gravid uterine weight from the body weight on GD 28. Daily food consumption was based on the average consumption over 2-day periods. All surviving animals were sacrificed on GD 28 and the uteri and ovaries were weighed and examined for the numbers of corpora lutea, implantations, resorptions and live and dead fetuses. Uteri without apparent implants were stained to detect possible early resorptions. All fetuses were sexed, weighed and examined for external and internal abnormalities. The skeletons were stained with alizarin red and examined.

The only dose-related clinical sign reported was soft/liquid feces at 300 mg/kg/day. There were no dose-related effects on food consumption, maternal body weight or body weight gain.

Pregnancy outcome and delivery data are presented in Table A5. All of the animals on study were reported to be pregnant. One animal in the 300 mg/kg/day group died on GD 21. In the 10 and 300 mg/kg/day

groups, one doe in each group aborted and one doe in each group had a premature delivery. The authors reported all of these events as abortions (as shown in Table A5).

The total numbers of litters included in the data evaluation were 18, 15, 16 and 14 for the 0, 10, 100 and 300 mg/kg/day groups, respectively. Compared to controls, glyphosate treatment exerted no effect on the numbers of corpora lutea, implantations, pre-implantation loss, post-implantation loss, embryo/fetal deaths, fetal sex ratios or fetal weights.

Table A5 also shows the number and percentage of fetuses and litters in each dose group with external/visceral and skeletal malformations and variations. There was a statistically significant increase in total litters with malformations and variations at 300 mg/kg/day. The increased malformation rate was due to an increase in litters with fetuses showing skeletal malformations, as no external or visceral malformations were noted in fetuses from the high dose group. A change in the number of litters showing defects can be misleading because a litter is counted whether only one or all fetuses are affected. The specific alterations were not available on an individual fetus basis, so it was impossible to determine whether external, visceral or skeletal defects occurred in the same or different fetuses. Even so, the malformations seen were considered to be sporadic in nature rather than related to glyphosate treatment. Further, a dose-response in the number of fetuses showing skeletal malformations was not evident across dose groups. The number of litters with variations was significantly decreased at 300 mg/kg/day, and the incidence of fetuses with skeletal variations was significantly increased at 100 mg/kg/day. Overall, the incidence of fetuses with visceral or skeletal variations did not show a treatment-related change. With regard to malformations of the heart, only one fetus had heart-related defects at 100 mg/kg/day (hypoplasia of the pulmonary artery and ventricular septal defect).

Based on clinical signs at 300 mg/kg/day, the NOAEL for maternal toxicity is considered to be 100 mg/kg/day. The lack of a dose-related increase in fetuses with external, visceral or skeletal defects indicates a lack of biological significance for the total litter finding. Overall, these data support a developmental toxicity NOAEL of ≥ 300 mg/kg/day.

Tasker et al. (1980a)

Although this study was conducted prior to the establishment of GLPs and EPA or OECD study guidelines, it generally adhered to GLP practices and satisfies the general requirements of OECD 414 (1981). Female Dutch belted rabbits of age 7 months were acclimated for at least 30 days prior to being inseminated on GD 0 using semen from only four

proven male rabbits. Glyphosate technical (purity: 98.7%) was formulated in 0.5% aqueous Methocel[®] solution (Dow Chemical Company, Midland, MI). No additional information on formulation was provided. Impregnated does were administered 0, 75, 175, or 350 mg/kg/day by oral gavage on GD 6–27 (16 rabbits per group). The dosing volume was 1 ml/kg body weight. Doses were based on individual body weights on GD 6. Animals were examined once daily for behavior, mortality and clinical signs of toxicity. Body weights were recorded on GDs 0, 6, 12, 18, 24 and 28. Food consumption rates were not recorded. Does that did not survive until the end of the study were necropsied to determine the cause of death. All surviving animals were sacrificed on GD 28. The uteri and ovaries were examined and the numbers of corpora lutea, implantations, resorptions, live and dead fetuses were recorded. The does were further evaluated for gross pathological changes. All fetuses were weighed, sexed internally, examined for external and visceral malformations (via dissection) and prepared for skeletal examination using alizarin red. External malformations were not reported separately from visceral malformations in this study.

Soft stools and diarrhea were noted in all treatment groups, but showed a dose-dependent rise in incidence in does treated with 175 and 350 mg/kg/day glyphosate compared to controls. Animals at 350 mg/kg/day also demonstrated an increase in nasal discharge. Maternal body weight changes were highly variable across groups throughout the study and no significant differences in body weights or body weight gains were noted compared to controls.

Pregnancy outcome and delivery data are shown in Table A6. Abortions occurred in two rabbits from the control group, and in one rabbit in each of the 175 and 350 mg/kg/day treatment groups. The numbers of rabbits that died before the end of study were 0, 1, 2 and 10 in the control, 75, 175 and 350 mg/kg/day glyphosate treatment groups, respectively. Mortality rates were greater than 10% in the intermediate and high dose groups. The causes of maternal death were determined for five of the 13 animals (pneumonia, respiratory disease, enteritis or gastroenteritis), but were not consistent across the groups. No macroscopic findings related to treatment were observed in the does.

Compared to controls, glyphosate treatment exerted no marked effects on the numbers of corpora lutea, implantations, resorptions (early or late), fetal sex ratios or fetal weights. There was also considerable variance around the mean for post-implantation loss. A statistically significant elevation in the number of viable fetuses per doe treated with 75 mg/kg/day was noted, but this result was considered to be a random occurrence because it was not observed in the two higher treatment groups. The total numbers of fetuses with malformations were 0, 3, 2 and 2 in the control, 75, 175 and 350 mg/kg/day dose groups, respectively. External and visceral defects occurred in two fetuses at the high dose

Table A6. Maternal and fetal outcome data for Dutch belted rabbits treated with glyphosate on gestational days 6–27 (Tasker et al., 1980a).

	0 mg/kg/day	75 mg/kg/day	175 mg/kg/day	350 mg/kg/day
Maternal data				
No. animals on study	16	16	16	17
No. non-gravid	2	0	2	0
No. gravid does dead or sacrificed in extremis	0	1	2	10
No. that aborted	2	0	1	1
Embryo/fetal data				
Total No. litters examined†	12	15	11	6
Mean No. corpora lutea	9.0 ± 2.13	10.1 ± 1.64	10.5 ± 3.45	8.5 ± 1.87
Mean No. implantations	5.9 ± 2.39	8.0 ± 1.81	6.1 ± 2.84	7.2 ± 2.93
Mean % pre-implantation loss	NR	NR	NR	NR
Mean No. embryo/fetal deaths	NR	NR	NR	NR
Mean No. viable fetuses/litter	5.3 ± 2.73	7.6 ± 1.84*	5.9 ± 2.77	6.3 ± 2.25
Mean % post-implantation loss‡	16.7 ± 23.0	4.9 ± 8.0	2.5 ± 5.8	18.7 ± 13.5
Mean fetal body weight (g)	33.4 ± 7.27	30.9 ± 4.43	29.9 ± 7.21	29.3 ± 4.82
Total fetuses (litters) with malformations[§]				
External and visceral	0	0	0	2 (1)
Cardiovascular	0	0	0	0
Skeletal	0	3 (3)	2 (2)	0

NR = Not reported.

† Analysis does not include the litters that were aborted.

‡ Calculated from individual animal data in Tasker et al. (1980a).

§ The incidences of variations were not reported in this study.

* $p < 0.05$ ANOVA followed by t-test for multiple comparisons; litter is the statistical unit.

level. Only skeletal malformations were observed in the low- and mid-dose groups, with no defects seen in controls. One fetus at the high-dose level had multiple malformations, including acrania with gastrothoracoschisis, bilateral carpal flexures, fetal anasarca, absent diaphragm, reduced diameter of carotids and associated skeletal changes, while another had a single finding of carpal flexure. Neither the type nor the incidence of these malformations suggests an adverse effect of glyphosate. Although total fetuses and litters with variations were not specifically reported, the types and incidence of fetuses with variations were primarily reduced ossification and there was no indication of a dose-related change. With respect to the heart and cardiovascular system only the fetus with acrania had carotid stenosis.

Based on mortality and clinical signs at 175 and 350 mg/kg/day, the NOAEL for maternal toxicity is considered to be 75 mg/kg/day. The large number of maternal deaths at the high dose makes interpretation of the overall study data difficult. Since no treatment-related increase in developmental toxicity was observed, ≥ 175 mg/kg/day is considered the NOAEL for developmental toxicity. Because the study was limited by having too few fetuses available at the high dose of 350 mg/kg/day for adequate morphological assessment, the NOAEL for developmental toxicity could not be established for doses higher than 175 mg/kg/day.

Suresh (1993)

This study was conducted according to OECD 414 (1981). Female New Zealand White rabbits of at least 6 months of age (≥ 2.5 kg) were acclimatized for at least 10 days, and then mated. The day of mating was considered GD 0. Glyphosate technical (purity 96.8%) was formulated in 0.5% carboxymethyl cellulose and Tween 80. No additional information on formulation was provided. Doses were described as "mg/kg" in the study report, but based on the dosing description it is assumed that these were daily doses (i.e. mg/kg/day). Impregnated does were

administered 0, 20, 100 or 500 mg/kg/day by oral gavage on GD 6–18 (16–20 rabbits per group). The reason for including different numbers of animals per dose group was not reported. The dosing volume was 2 ml/kg body weight. Individual dose volumes were based on animal body weights. Animals were examined twice daily for mortality and clinical signs. Body weights were recorded on GDs 0, 6–18 (daily) and 27. Body weight gain was based on the intervals between body weights (e.g. GDs 0–6, 6–18). Absolute body weight was not reported by the authors, but was calculated here by subtracting the gravid uterine weight from the body weight on GD 28. Food consumption was calculated for GDs 0–6, 6–19, 19–28 and 0–28. All surviving animals were sacrificed on GD 28 and the uteri and ovaries were weighed and examined for the numbers of corpora lutea, implantations, resorptions, and live and dead fetuses. Uteri without apparent implants were stained to detect possible early resorptions. All fetuses were sexed, weighed and examined for external and internal abnormalities. The skeletons were stained with alizarin red and examined.

The major dose-related clinical signs included soft/liquid feces and mucus in the feces; these were observed in 0, 0, 1 and 14 does in the 0, 20, 100 and 500 mg/kg/day groups, respectively. No dose-related effects on maternal food consumption or body weight gain were reported. Maternal body weight, however, was statistically significantly decreased in the 500 mg/kg/day group on GD 0, 6 and 28, indicating that the animals in this group were below the weights of animals in other groups at the beginning of the study.

The pregnancy outcome and delivery data are presented in Table A7. The numbers of non-pregnant animals were 3, 4, 0 and 1 in the 0, 20, 100 and 500 mg/kg/day groups, respectively. Animals that died or were sacrificed *in extremis* were 2, 0, 4 and 8 in the 0, 20, 100 and 500 mg/kg/day groups, respectively. Various findings at gross necropsy were noted in the lungs and trachea for the 100 and 500 mg/kg/day dose groups; these findings suggest possible gavage errors to which the deaths at these doses may be attributed. The number of animals that aborted in each group was not reported.

Table A7. Maternal and fetal outcome data for New Zealand white rabbits treated with glyphosate on gestational days 6–18 (Suresh, 1993)

	0 mg/kg/day	20 mg/kg/day	100 mg/kg/day	500 mg/kg/day
Maternal data				
No. animals on study	26	17	16	15
No. non-gravid	4	4	0	1
No. gravid does dead or sacrificed <i>in extremis</i>	2	0	4	8
No. that aborted	NR	NR	NR	NR
No. with only resorptions	0	0	0	1
Embryo/fetal data				
Total No. litters examined	20	13	12	6†
Mean No. corpora lutea	11 ± 2.8	10 ± 2.4	10 ± 1.9	9 ± 2.0
Mean No. implantations	8 ± 2.0	8 ± 1.5	9 ± 1.8	6 ± 2.4
Mean % pre-implantation loss‡	48	29	20	37
Mean No. embryo/fetal death‡	0.00	1.38	2.00	1.67
Mean No. viable fetuses	6.7	6.1	6.4	5.6
Mean % post-implantation loss‡	13.5 ± 14.3	18.6 ± 13.1	23.4 ± 23.8	23.2 ± 39.0
Mean fetal body weight (g)	32 ± 5.3	35 ± 3.7#	35 ± 2.4#	33 ± 4.9
"Abnormal fetuses" (n, %)	1 (1)	2 (3)	0	0
Total fetuses (litters) with malformations				
External	2 (2)	2 (1)	1 (1)	0 (0)
Visceral	4 (3)	6 (3)	6 (4)	8 (2)*
Cardiovascular	2 (2)	4 (3)	6 (4)	6 (2)
Skeletal	11 (4)	5 (3)	0 (0)	1 (1)
Total fetuses (litters) with minor malformations and variations‡				
External	0	0	1 (1)	0
Visceral	NR (9)	NR (5)	NR (7)	NR (2)
Skeletal	NR (20)	NR (13)	NR (11)	NR (5)

NR = Not reported.

†Only five litters were evaluated for developmental toxicity at 500 mg/kg/day; includes single litter that was aborted at this dose in the analysis.

‡Standard deviation not reported.

Calculated from data provided in Suresh, 1993; values do not exactly match those presented in the study report.

§ Incidence was not reported by individual fetus; rather, the incidence of each type of defect was reported, but more than one may have been seen in the same fetus.

* Significantly higher than control by ANOVA followed by Dunnett's test; litter is the statistical unit.

Significantly different from control by chi-square test.

Table A8. Types and incidence of individual malformations† (Suresh, 1993).

	0 mg/kg/day	20 mg/kg/day	100 mg/kg/day	500 mg/kg/day
No. fetuses examined	133‡	78	77	28
Acephaly, abdominal hernia, external nares absent, shortened upper jaw, tail short & kinky, dorsal displacement of genital tubercle, multiple associated skeletal malformations	3 (1)			
Acrania, open eyelids, kinky tail, arthrogryposis and adactyly (one with microglossia, short upper jaw, thoracic and abdominal hernia, hemimelia, malformed skull, missing cervical centrum and arch; one with cleft palate and oligodactyly)		2 (1)		
Seal-shaped heart	1 (1)			
Cardiomegaly and seal-shaped-heart			1 (1)	
Dilated heart		4 (3)*	4 (2)*	5 (2)*
Dilated ventricle*	1 (1)		1 (1)	1 (1)
Cleft palate	1 (1)			
Forelimb arthrogryposis			1 (1)	
Liver hematoma				1 (1)
Gall bladder absent				1 (1)
Hydronephrosis	1 (1)	1 (1)		
Dilated ureter		1 (1)		
Fused sternebrae		1 (1)		
Malformed sternebrae	1 (1)	1 (1)		
Displaced sternebrae	1 (1)			
Missing ribs	4 (3)			
Bifurcated ribs	2 (2)			
Missing thoracic arch and centrum	3 (3)			
Extra lumbar arch and centrum				1 (1)

†Single fetuses may be represented more than once.

‡One fetus was not examined for skeletal malformations.

*It is unclear from the study report if the dilated ventricles are of the heart or brain. For the purposes of this review, it is assumed that this description relates to the ventricles of the heart.

*Significantly different from control by chi-square test.

The total numbers of litters included in the data evaluation were 20, 13, 12 and 5 for the 0, 20, 100 and 500 mg/kg/day groups, respectively. Compared to controls, glyphosate treatment exerted no effect on the numbers of corpora lutea, implantations or pre-implantation loss. Although there was no effect on pre-implantation loss, it seems high across groups and especially high in the controls (48%). There were no historical control data provided for this endpoint. There was no effect on post-implantation loss, embryo/fetal death or fetal sex ratios. Although fetal body weights in the 20 and 100 mg/kg/day dose groups were reported to be significantly different from control, the weights were increased, the changes were less than 10% of control values and no dose-response across treatment groups was evident. Thus, the fetal body weight differences observed in these two dose groups are biologically inconsequential with respect to adverse effects.

There were no significant treatment-related increases in minor malformations or variations (Table A7). The incidence of visceral malformations appeared to increase with dose, but only 28 fetuses were available for examination in the high-dose group and the incidence in the low, mid and high dose groups was similar.

Major visceral malformations primarily affected the heart, but occurred in single incidences and showed no dose-response (Table A8). The exception was dilated heart, which was reported in 0, 4, 4 and 5 fetuses (0, 3, 2 and 2 litters) in the control, 20, 100 and 500 mg/kg/day dose groups, respectively. The terminology used to describe the heart malformations in this study is difficult to interpret (e.g. dilated heart, seal-shaped heart, cardiomegaly). For example, "dilated heart" was not defined in the study report, and how this malformation might relate to other heart defects (i.e. dilated right ventricle, seal-shaped heart, cardiomegaly) was not reported. Neither the criteria used to diagnose dilated heart nor measurements of the hearts were provided, so it is not possible to directly compare the dilated heart findings to the hearts of the fetuses in other studies. It is possible that the observation of dilated hearts was due to overly stringent inspection compared to criteria used by other laboratories. Only two litters exhibited major visceral malformations in the high dose group: one fetus in one litter and an unknown number in another (individual fetus data were not reported). It should be noted that the high-dose group findings were seen in the presence of extensive maternal toxicity, evidenced by clinical signs and a substantial number of maternal deaths.

This developmental toxicity study in rabbits had several weaknesses including a small number of litters available for examination due to low pregnancy rates and maternal deaths in the mid- and high-dose groups; these weaknesses severely limit the conclusions that can be drawn at these dose levels. It is especially difficult to extract data from the report to confirm the findings. Based on clinical signs and deaths at 500 mg/kg/day, it appears that the high dose in this study significantly exceeded the maximum tolerated dose. Therefore, the NOAEL for maternal toxicity is considered to be 100 mg/kg/day. Since no apparent developmental toxicity was observed at any dose, ≥ 100 mg/kg/day is considered the NOAEL for developmental toxicity. Because the study is limited by having too few fetuses available at the high dose of 500 mg/kg/day for adequate morphological assessment, the NOAEL for developmental toxicity could not be established for doses higher than 100 mg/kg/day.

Bhide & Patil (1989)

This study was conducted according to OECD 414 (1981). It is not clear to what extent this study followed GLP practices, but it appears to be only partially GLP-compliant at most. Female New Zealand white pregnant rabbits of age 24–28 weeks (1.5–2.0 kg) were used; they were acclimatized for six days. The females were mated with "adult vigorous males". The day of mating was considered GD 0. Doses were described as mg/kg doses in the study report, but based on the dosing description it is assumed that these were daily doses. Impregnated does were administered 0, 125, 250 or 500 mg/kg/day glyphosate technical (purity: 95%) by oral gavage on GD 6–18 (15 rabbits per group). The dosing volume was 5 mL/kg body weight; the test material was suspended in 0.1% gum acacia in water. Animals were observed twice daily for clinical signs, general behavior and body weight gain. Body weights were recorded on GDs 0, 6, 12, 18, 23 and 29. Food consumption was measured using the weight day intervals (e.g. GD 0–6, 6–12). The females were "delivered by caesarian section 1 day before expected delivery". The does were sacrificed on GD 29 and the uteri and ovaries examined for the numbers of corpora lutea, uterine weight, implantations, live and dead fetuses. Uteri from non-gravid animals were stained to examine for implantation sites (early resorptions). The does were further evaluated for gross pathological changes. All fetuses were

Table A9. Maternal and fetal outcome data for New Zealand white rabbits treated with glyphosate on gestational days 6-18† (Bhude & Patil, 1989)

	0 mg/kg/day	125 mg/kg/day	250 mg/kg/day	500 mg/kg/day
Maternal data				
No. animals on study	15	15	15	15
No. non-gravid	2	1	1	3
No. gravid does dead or sacrificed <i>in extremis</i>	0	0	0	0
No. that aborted	0	0	0	2
Embryo/fetal data				
Total No. litters examined	13	14	14	12‡
No. litters with no live fetuses	0	0	0	2
Mean No. corpora lutea	10.0 ± 1.69	10.1 ± 1.60	10.3 ± 1.44	9.8 ± 1.57
Mean No. implantations	9.0 ± 1.20	9.3 ± 1.33	9.4 ± 1.12	8.5 ± 1.65
Mean No. early resorptions	1.7 ± 3.22	1.1 ± 2.53	1.0 ± 2.56	1.9 ± 2.43
Mean % pre-implantation loss	21.3 ± 32.4	14.9 ± 24.09	14.7 ± 24.38	13.1 ± 6.34
Mean No. embryo/fetal death	0.07 ± 0.26	0.13 ± 0.35	0.27 ± 0.59	1.4 ± 2.20
Mean No. viable fetuses	7.3 ± 3.10	8.0 ± 2.59	8.0 ± 2.48	5.2 ± 3.03
Mean % post-implantation loss	NR	NR	NR	NR
Mean fetal body weight (gms) *	40.6 ± 16.6	47.1 ± 0.95	47.5 ± 1.38	48.7 ± 1.87
Total fetuses (litters) with malformations‡				
Total fetuses (litters) with malformations‡	3 (3)	6 (6)	10 (10)	20 (14)
External	1 (1)	2 (2)	3 (3)	3 (3)
Visceral	1 (1)	4 (4)	5 (5)	12 (9)
Cardiovascular	0	1 (1)	1 (1)	2 (2)
Skeletal	1 (1)	0	2 (2)	5 (2)

NR = Not reported.

†Body weights, maternal endpoints and some developmental endpoints for all 15 animals in each group appear to be included in the data. It appears that only the gravid animals were included for data on sex ratio and fetal body weight.

‡The two litters that were aborted at this dose were included in the analysis.

*Fetal body weight data are as reported in the study report; it is unclear if all 15 does were included in this calculation.

§The incidences of variations were not reported in this study.

||The total number appears to be the sum of the fetuses and litters with external, visceral and skeletal malformations. Thus, the number of litters in the 500 mg/kg/day dose group is reported as 14 when there were only 12 litters in the group.

weighed and examined for external abnormalities, then processed by a fresh visceral dissection technique to determine sex and to examine for visceral abnormalities, including those of the heart and great vessels. The heads were removed, decalcified, fixed in Bouin's solution and examined separately. The remainder of each skeleton was prepared for the examination of osseous tissue using alizarin red.

The pregnancy outcome and delivery data for this study are shown in Table A9. The authors did not describe any statistical methods and there were no designations of statistical significance in their tables. The description of the results provided in Bhude & Patil (1989) was very limited. The numbers of non-pregnant animals were 2, 1, 1 and 3 in the 0, 100, 250 and 500 groups, respectively. There were no maternal deaths. Two does aborted in the 500 mg/kg/day group and were also included in the "No. Litters examined" endpoint. Data are given in the report for fetuses from 12 individual litters, but it is not clear which litters aborted.

The total number of litters included in the data evaluation for various endpoints was not explained in detail in the report and appear to be different for different endpoints. From the tables in the report, it appears that all 15 animals from each exposure group were evaluated for clinical signs, food consumption, maternal body weight gain, corpora lutea counts, implantations, resorptions and embryo/fetal viability. Consequently, these endpoints would appear to include data from animals that were non-pregnant or which aborted. For sex ratio, fetal body weights, and malformations, it appears that only the gravid animals were included (i.e. 13, 14, 14 and 12 in the 0, 100, 250 and 500 groups, respectively).

There were no dose-related clinical signs reported at any exposure level. Maternal food consumption and body weight gain appear to be reduced from that of controls at 500 mg/kg/day (food consumption, GDs 6-29; body weight gain, GDs 12-29). However, with the inclusion of animals that were non-pregnant or aborted, it is not possible to determine if this is a biologically significant result. There were no differences from control for the number of corpora lutea, implantations or pre-implantation loss. Embryo/fetal deaths were slightly higher and viability was slightly lower than controls. Post-implantation loss was not reported.

The incidences of external, visceral and skeletal malformations as well as total malformations are also shown in Table A9. Data were not reported for individual litters or fetuses, and the numbers for total fetuses and litters appear to be the sum of the number with external, visceral and skeletal defects. As a result, the authors reported 14 litters with malformations in

the high-dose group when only 12 litters were examined. The numbers of fetuses and litters with variations are not reported.

The number of types of malformations reported was low in this study. Several malformations appeared to be increased in the high-dose group, including abnormal tail, missing kidney(s), absent postcaval lung lobe and rudimentary 14th rib. The latter two defects are typically considered variations. The only cardiovascular changes reported as malformations were IV septal defects; these were observed in 0, 1, 1 and 2 fetuses in the 0, 125, 250 and 500 mg/kg/day dose groups. A number of variations were reported, some of which have been included as malformations by other authors; for example, globular heart, small right ventricle, dilated lateral cerebral ventricles and fused thoracic centra. Other variations reported are commonly seen in rabbits (e.g. incomplete septation of lung lobes, irregular palatal rugae, blunt-tipped tail, irregular-shaped liver, globular-shaped kidneys, bilobed vertebral centra, reduced ossification of centra, sternbrae, pubis and skull). Several of these were increased in the high-dose group. In summary, there were a number of changes reported in the high-dose group, but the actual number of fetuses and litters affected is likely to be lower. However, this could not be determined because of the inadequate reporting of data.

This developmental toxicity study in rabbits is limited by the study design (e.g. the number of pregnant does surviving to term in each dose group, especially the high-dose group) and inadequate reporting of data (e.g. the inclusion of inappropriate animals in the calculation of some endpoints, insufficient description of study results). These limitations raise concern about using the results in any evaluation of glyphosate developmental toxicity and NOAELs are not proposed because of these limitations.

Rat developmental toxicity studies

The six rat developmental toxicity studies of glyphosate are summarized below and in Table A10. As in the rabbit studies, we have focused only on the results of the definitive studies. Because the impetus for concern regarding cardiovascular development was the rabbit studies and not the rat studies, these studies were not reviewed in the same level of detail as the rabbit studies. Rather, these studies are addressed in a combined discussion.

Table A10. Maternal and fetal outcome data from the developmental toxicity studies of glyphosate in rats.

Strain (#/group)	Duration of Treatment	Dose (mg/kg/day)	No. gravid females	No. maternal deaths	No. litters examined	Mean % post-implantation loss	Mean No. live fetuses	Mean fetal body wts (gms)	No. malformed fetuses (litters)	Cardiovascular malformations	Maternal toxicity	Ref
Wistar (24)	GD 6-15 ¹	0	22	0	22	9.9 ± 15.5	12.9 ± 2.4	4.86 ± 0.29	1 (1)	None	None	Moxon (2002)
		250	24	0	24	4.0 ± 5.1	12.4 ± 3.4	5.02 ± 0.33	1 (1)	None	None	
		500	23	0	23	7.8 ± 10.8	13.1 ± 2.7	4.95 ± 0.29	1 (1)	None	None	
Sprague-Dawley (25)	GD 6-15	1000	24	0	23	5.8 ± 8.3	12.9 ± 2.9	4.96 ± 0.27	2 (2)	None	None	Wood (1996)
		0	23	0	23	4.9 ± 5.6	14.1 ± 3.3	3.81 ± 0.32	3 (3)	One IV septal defect and persistent truncus arteriosus, 1 retro-esophageal right-sided aortic arch	None	
		100	24	0	24	4.4 ± 4.7	13.8 ± 2.2	3.99 ± 0.47	1 (1)	One IV septal defect	None	
Sprague-Dawley Crj:CD (24)	GD 6-15	500	22	0	22	6.1 ± 7.0	14.0 ± 1.8	3.76 ± 0.29	0	None	None	Hatakenaka (1995)
		1000	25	0	25	5.2 ± 6.8	14.0 ± 3.1	3.79 ± 0.40	0	None	None	
		0	23	0	23	7.0 ± 6.1	13.7 ± 4.1	M: 3.6 ± 0.4 F: 3.3 ± 0.3	2 (1)	None	None	
		30	24	0	24	6.8 ± 7.8	15.0 ± 2.1	M: 3.6 ± 0.2 F: 3.4 ± 0.3	1 (1)	None	None	
		300	24	0	24	7.4 ± 8.0	14.9 ± 2.8	M: 3.5 ± 0.4 F: 3.4 ± 0.4	3 (2)	One right aortic arch, 1 IV septal defect	None	
Sprague-Dawley (25)	GD 6-15	1000	22	0	22	8.4 ± 9.1	15.4 ± 2.1	M: 3.6 ± 0.2 F: 3.4 ± 0.2	5 (2)	One IV septal defect	Loose stool	Brooker et al (1991b) ²
		0	23	0	23	6.1	13.7	3.96	1 (1)	None	None	
		300	23	0	23	7.3	12.7	3.90	2 (2)	None	None	
		1000	25	0	25	5.7	13.2	3.89	1 (1)	One IV septal defect	None	
Wistar	GD 6-15	3500	25	3	22	3.6	13.1	3.71 ³	3 (2)	One IV septal defect	Salivation, loose feces, noisy respiration, wet coats, gasping	Suresh (1991)
		0	30	0	30	8	8.7	3.6 ± 0.4	External/visceral 5 (5) Skeletal 17 (8) ⁴	None	None	
Sprague-Dawley COBS CD rats (25)	GD 6-19	1000	20	0	20	11	7.9	3.7 ± 0.3	External/visceral 0 Skeletal 0 (16) ⁴	None	None	Tasker et al. (1980b) ⁵
		0	22	0	22	4.2 ± 5.7	14.4 ± 1.3	3.5 ± 0.2	3 (3)	None	None	
		300	20	0	20	1.4 ± 3.5	11.9 ± 4.4 ⁶	3.7 ± 0.7	0	None	None	
		1000	21	0	21	3.1 ± 5.6	14.3 ± 2.1	3.6 ± 0.2	0	None	None	
		3500	23	6	16	14.3 ± 24.0 ¹	11.5 ± 4.1 ⁷	3.2 ± 0.3 ⁸	10 (3) ⁹	None	6/25 deaths; various signs of clinical toxicity; decreased weight gain due to weight loss on GD 6-9	

¹Moxon (2002) designated the day of finding sperm as GD1. The exposure period listed here was adjusted using GD 0 as the day of finding sperm.

²Hatakenaka (1995) did not report a combined mean fetal weight, but rather reported the mean fetal weight for males (M) and females (F) separately. Individual animal data were not available to calculate the combined mean fetal weight. Mean post-implantation loss also was not reported but was calculated by the present authors based on data provided in the study report.

³One small IV septal defect was considered a variation by the authors.

⁴Brooker et al. (1991b) did not provide standard deviation values for mean post-implantation loss, mean number of live fetuses, or mean fetal body weights.

⁵Undescended testis and unascended kidneys were considered minor malformations by the authors but are included here.

⁶Several bilobed vertebral centra and delayed ossification of various bones were reported as major malformations, but none fit the author's definition of a major malformation. Individual fetal data were incompletely reported, so it is difficult to determine which type of defects which fetus and litter. The number of fetuses (litters) given here is taken from Table A9 in Suresh (1991).

⁷Post-implantation loss percentages and standard deviations calculated from individual animal data in Tasker et al. (1980b); statistical significance was not calculated.

⁸Includes six fetuses in one litter with a syndrome of bent tail, open eyelids, missing kidneys and ureters, and various skeletal defects and three fetuses in another litter with dwarfism. All malformations were seen in the historical controls.

⁹* $p < 0.01$, Kruskal-Wallis followed by distribution-free Williams' test; litter was the statistical unit.

¹⁰* $p < 0.05$, ANOVA followed by Dunnett's test; statistical unit was not specified.

¹¹** $p < 0.01$, ANOVA followed by Dunnett's test; statistical unit was not specified.

In the rat studies, the day of finding sperm was designated as GD 0,² except in the study by Moxon (2002), which referred to it as GD 1. For the purpose of discussing the timing of exposure and outcome measurements in the rat studies in an integrated fashion, the day of mating and succeeding gestational days have been corrected to GD 0 for Moxon (2002). With the exception of Suresh (1991), all of the studies used a randomized (block) design to assign the impregnated females to treatment groups ($n = 20$ –25 animals/group). In contrast, Suresh (1991) had only one exposure level (1000 mg/kg/day) and it is unclear how the females were assigned to the control and treated groups. Each study included a vehicle control group (0 mg/kg/day). Glyphosate exposure levels ranged from 30 to 3500 mg/kg/day across the studies and were administered as glyphosate technical (i.e. glyphosate acid). The exposure was via oral gavage on GDs 6–15, except in Tasker et al. (1980b), in which animals were exposed on GDs 6–19. Regular observations of the females for mortality, clinical signs and body weight measurements were made in all studies; food consumption was measured in most studies.

In several cases, females were euthanized during the course of the study due to issues that were not associated with glyphosate exposure (e.g. mis-dosing, intubation error). At exposure levels lower than 1000 mg/kg/day, no maternal toxicity was observed over the course of the studies. In Wood (1996), lethargy was reported in two animals on 2 days during treatment; this finding was not considered sufficient evidence of maternal toxicity. Also, in Brooker et al. (1991b), noisy respirations were reported in two animals on a single day. Again, due to the transient nature of the finding, it was not considered evidence of maternal toxicity. At 1000 mg/kg/day and higher, animals in three of the six studies showed signs of lethargy, as well as respiratory and gastrointestinal distress. At 1000 mg/kg/day and lower, there were no maternal deaths. In the two studies that used doses as high as 3500 mg/kg/day (Brooker et al., 1991b; Tasker et al., 1980b), there were three (two considered treatment-related) and six deaths, respectively.

For the most part, exposure levels less than 1000 mg/kg/day did not affect food consumption except during short intervals at the beginning of treatment (Hatakenaka, 1995; Wood, 1996) or post-dosing (Hatakenaka, 1995). At 3500 mg/kg/day, Brooker et al. (1991b) reported a treatment-

related decrease in food consumption during the exposure period (GD 6–15). Tasker et al. (1980b) also tested 3500 mg/kg/day, but did not report food consumption values.

Maternal body weight was not affected in any of the studies at exposure levels lower than 3500 mg/kg/day. At 3500 mg/kg/day, Brooker et al. (1991b) reported that maternal body weight and body weight gain were reduced (GD 6–20); in contrast, Tasker et al. (1980b) did not observe a similar effect at this dose.

Maternal animals were sacrificed on GD 20, except in Moxon (2002) where the animals were sacrificed on GD 21. Standard endpoints of reproductive and developmental toxicity were evaluated (Table A10). There were no dose-related effects on the numbers of corpora lutea, implantations, live and dead fetuses, fetal weight or fetal sex ratio at 1000 mg/kg/day and below. At 3500 mg/kg/day, Brooker et al. (1991b) reported reduced mean fetal weight. At this same dose, Tasker et al. (1980b) reported a statistically significant increased number of resorptions, significantly decreased mean numbers of implantations and viable fetuses per dam, and diminished mean fetal body weights compared to controls. Tasker et al. (1980b) also reported statistically significant decreased mean numbers of implantations and viable fetuses per dam in the 300 mg/kg/day treatment group, but this effect was not observed at 1000 mg/kg/day. Consequently, there was no clear dose-response effect for this parameter.

Glyphosate did not produce adverse effects on structural development (Table A10). Tasker et al. (1980b) reported 10 fetuses with malformations in three litters at 3500 mg/kg/day. Six of these fetuses were in one litter and showed a syndrome of bent tail, open eyelids, missing kidneys and ureters, and various skeletal defects. Three fetuses in another litter were reported to have dwarfism. All these effects were within the historical control range. With respect to specific cardiovascular malformations, three of the six studies reported no effects (Moxon, 2002; Suresh, 1991; Tasker et al., 1980b). The other three studies (Brooker et al., 1991b; Hatakenaka, 1995; Wood, 1996) reported single incidences of specific defects; in two studies, they were observed in the controls as well as in the exposed fetuses. These results indicate that of glyphosate exposure of pregnant rats at doses of up to 3500 mg/kg/day does not produce any evidence of cardiovascular malformations.

²Brooker (1991b) & Suresh (1991) refer to it as Day 0 of Pregnancy.

REVIEW ARTICLE

Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies

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Abstract

Glyphosate, an herbicidal derivative of the amino acid glycine, was introduced to agriculture in the 1970s. Glyphosate targets and blocks a plant metabolic pathway not found in animals, the shikimate pathway, required for the synthesis of aromatic amino acids in plants. After almost forty years of commercial use, and multiple regulatory approvals including toxicology evaluations, literature reviews, and numerous human health risk assessments, the clear and consistent conclusions are that glyphosate is of low toxicological concern, and no concerns exist with respect to glyphosate use and cancer in humans. This manuscript discusses the basis for these conclusions. Most toxicological studies informing regulatory evaluations are of commercial interest and are proprietary in nature. Given the widespread attention to this molecule, the authors gained access to carcinogenicity data submitted to regulatory agencies and present overviews of each study, followed by a weight of evidence evaluation of tumor incidence data. Fourteen carcinogenicity studies (nine rat and five mouse) are evaluated for their individual reliability, and select neoplasms are identified for further evaluation across the data base. The original tumor incidence data from study reports are presented in the online data supplement. 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.

Keywords

amino acid, carcinogenicity, epidemiology, glyphosate, herbicide, mouse, neoplasm, phosphonomethylglycine, Roundup, rat, regulatory, tumor

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Introduction

Glyphosate (Figure 1), an aminophosphonic analog of the natural amino acid glycine, is widely used as an herbicide for the control of annual and perennial grasses and broad-leaved weeds. Glyphosate inhibits 5-enolpyruvate shikimate-3-phosphate synthase (EPSPS), an enzyme of the aromatic acid biosynthesis pathway, which is not present in the animal kingdom. Glyphosate-based herbicide formulations (GBFs) were introduced in 1974 and are formulated with

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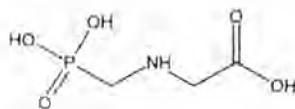


Figure 1. Structure of glyphosate acid.

sodium-, potassium-, ammonium- and isopropyl ammonium-salt forms of the active ingredient. The bulk-manufactured active herbicide glyphosate has the synonyms glyphosate technical acid, technical grade glyphosate and glyphosate acid.

The economic importance of glyphosate for growers is high. It has been estimated that a hypothetical ban of glyphosate would lead to decreases in the production of wheat, fodder, maize and oilseeds, by 4.3–7.1%, with the result of an estimated annual welfare loss of 1.4 billion USD to society in the European Union alone (Schmitz and Harvert 2012). Furthermore, glyphosate plays an important role in integrated pest management strategies, and affords the environmental benefit of substantially reduced soil erosion resulting from no-till and reduced-till agriculture.

The long-term toxicity and carcinogenicity of glyphosate has been investigated by multiple entities including academia, registrants, and regulatory authorities, and the data generated have been evaluated in support of herbicide regulatory approvals in many world regions including the USA (US EPA 1993) and the European Union (EC 2002), and several scheduled reevaluations are currently ongoing in the USA, Canada, Japan and Europe (Germany Rapporteur Member State 2015a), with imminent conclusions.

Studies of appropriate scientific quality are the basis for regulatory decision making. Mandatory testing guidelines (TGs) exist for toxicological studies submitted for regulatory review of active substances for plant protection in many regions of the world. Such TGs have been released, *inter alia*, by the United States Environmental Protection Agency (US EPA 2012), the European Union (EU 2008), the Japanese Ministry of Agriculture, Forestry and Fisheries (JMAFF 2000), and the Organization of Economic Co-operation and Development (OECD 2012b). These TGs set quality standards for each type of study by giving guidance regarding test species, strains, and number of animals to be used, the choice of dosing, exposure duration, and parameters to be measured and observed, as well as for the reporting of results. Due to the lack of effective legal and regulatory provisions for the sharing of vertebrate study data in the past, and to guarantee the safety of technical glyphosate obtained from different processes of synthesis, several manufacturers of glyphosate had to initiate toxicological testing programs of their own. Occasionally, regulatory studies had to be repeated to reflect major changes in the underlying TG. In the case of glyphosate, this has given rise to a multitude of studies for the same toxicological endpoints, leading to the availability of an extraordinarily robust scientific study database that can be considered unique among pesticides, industrial chemicals, and pharmaceuticals. Such a remarkable volume of studies addressing the same endpoints, conducted over the last 40 years by several independent companies and laboratories while toxicology test guidelines have evolved,

warrants investigation for consistency, reliability, and application to their intended purpose: identifying potential human health hazards and setting appropriate endpoints for human health risk assessment. Studies conducted with equivalent test substances using the same TG are readily comparable and can be evaluated by regulators following standardized schemes. Minor differences in the findings reported by such repetitive studies are attributable to statistical chance, natural biological variability, type of basal diet, rate of feed consumption, animal strain differences, choice of dose levels, inter-strain genetic drift over time due to varying vendor breeding practices, changes in animal care and husbandry practices across laboratories over the years, inter-laboratory variations in clinical measurements, and differences between individual pathologist evaluation and interpretation of tissue specimens.

Glyphosate is under significant political pressure due to its widespread use, particularly in association with use on genetically modified crops. One focus area of contention has been the human safety of glyphosate, which has been repeatedly challenged by interest groups via the media, as well as select research publications in the scientific literature (Antoniou et al. 2012, Aris and Leblanc 2011, Aris and Paris 2010, Benachour and Seralini 2009, Gasnier et al. 2010, Paganelli et al. 2010, Romano et al. 2012, Romano et al. 2010). To that end, one specific publication by Seralini et al. (2012, retracted) drew significant criticism from both the toxicology and broader scientific communities (Barale-Thomas 2013, Berry 2013, de Souza and Oda 2013, Grunewald and Bury 2013, Hammond et al. 2013, Langridge 2013, Le Tien and Le Huy 2013, Ollivier 2013, Panchin 2013, Sanders et al. 2013, Schorsch 2013, Tester 2013, Trewavas 2013, Tribe 2013). After a special review of the investigators' raw data by a mutually agreed-upon expert panel, the manuscript was retracted by *Food and Chemical Toxicology* (FCT), for reasons of inconclusive data and unreliable conclusions (Hayes 2014). The Editor of the *International Journal of Toxicology* highlighted this manuscript as an example of possible failure of the peer review process in a well-respected toxicology journal with an editorial board of well-known and respected toxicologists (Brock 2014). The manuscript was later republished without peer-review in an open access journal (Seralini et al. 2014), but will not be addressed in this data evaluation due to the inappropriate study design, insufficient reporting of tumor incidence data, and the lack of a data supplementary to the manuscript.

The chronic/carcinogenicity studies discussed in this paper have been submitted to and evaluated by a variety of agencies over time, including the World Health Organization (WHO/FAO 2004b, WHO/FAO 2014a), the United States Environmental Protection Agency (US EPA 1993), the European Rapporteur Member State Germany for the initial glyphosate Annex I listing (EC 2002) and the recent European reevaluation (Germany Rapporteur Member State 2015a), as well as the ongoing reevaluations in the USA, Canada and Japan. These regulatory bodies, drawing upon internal and/or external expertise have consistently concluded that glyphosate is devoid of carcinogenic risk to humans.

The purpose of this article is to provide the broader scientific community with insight into this large body of carcinogenicity data on glyphosate, originally generated for

regulatory purposes. Each study discussed in this review has been assigned a reliability score in Tables 3–10, following the Klimisch scoring system (Klimisch et al. 1997). In this system, a score of 1 is assigned to studies that are fully reliable based on compliance with Good Laboratory Practice (GLP) and adherence to appropriate study guidelines. A score of 2 is appropriate if some guideline requirements are not met, but if these deficiencies do not negatively affect the validity of the study for its regulatory purpose. Studies with a reliability of 3 employ a test design that is not fit for the scientific purpose of the study, due to significant scientific flaws, or the objective of the study not covering the regulatory endpoints, or both. Such studies can provide supplemental information but do not allow a stand-alone appraisal of a regulatory endpoint. No studies were assigned a reliability of 4, since each report contained sufficient information to judge the validity of the study.

This manuscript presents the robust glyphosate carcinogenicity data generated by industry. Study summaries will focus on carcinogenicity evaluation, to allow third parties the opportunity to independently evaluate the carcinogenicity data presented alongside other relevant data on carcinogenicity, i.e. genotoxicity testing and epidemiology, and facilitate a multidisciplinary carcinogenicity assessment as proposed in the literature, by recognized experts in the fields of toxicology and human health risk assessment (Adami et al. 2011).

Absorption, distribution, metabolism and excretion of glyphosate

A number of absorption, distribution, metabolism, and excretion studies (ADME) have been conducted on glyphosate for evaluation in regulatory submissions (EC 2002, US EPA 1993, WHO/FAO 2004a) and also by academic institutions (Anadon et al. 2009). Glyphosate consistently demonstrates low gastrointestinal absorption (20–40%). Its metabolism is very limited, whereby only small quantities of a single metabolite, aminomethylphosphonic acid (AMPA), are eliminated in feces. AMPA is likely produced by the limited metabolism of glyphosate by the gastrointestinal microflora, rather than via mammalian metabolism. Glyphosate is structurally akin to a phase II metabolite, a glycine-conjugate of methyl phosphonate, and thus avails itself to rapid urinary excretion. Systemic elimination is biphasic, with alpha-phase half-lives in the range of 6–14 h (Anadon et al. 2009, WHO/FAO 2004a).

Toxicological properties of glyphosate

Table 1 contains a short overview of toxicological endpoints of glyphosate that have been published in the List of Endpoints identified for glyphosate by the Rapporteur in the European Union under Regulation 1107/2009 (Germany Rapporteur Member State 2015c). Glyphosate is of low acute toxicity via all routes of exposure. Glyphosate's active ingredient, an organic acid, has an irritating effect on mucosa which is evidenced by eye irritation and effects on oral and gastrointestinal mucosa; final formulated products contain more neutral pH salt forms, as reflected in the tabulated eye irritation data reported in Table 11, on page 109 of the 2004 JMPR Toxicological Evaluation (WHO/FAO 2004a). Glyphosate is not mutagenic, not neurotoxic, and has no effect on pre-natal development and fertility at doses not exceeding the maximum tolerated dose (MTD).

Genotoxicity

Very recently, a review of the vast body of genotoxicity studies on glyphosate and GBFs has been published (Kier and Kirkland 2013), including an online data supplement presenting detailed data from 66 separate *in vitro* and *in vivo* genotoxicity assays. The authors incorporated these studies and published genotoxicity data into a weight-of-evidence analysis. The vast majority (over 98%) of the available bacterial reversion and *in vitro* mammalian micronucleus and chromosomal aberration assays were negative. Negative results for *in vitro* gene mutation and a large majority of negative results for clastogenic effect assays in mammalian cells support the conclusion that glyphosate is not genotoxic for these endpoints in mammalian test systems. DNA damage effects are reported in some instances for glyphosate at high or toxic dose levels. The compelling weight of evidence is that glyphosate and typical GBFs are negative in core assays, indicating that the reported high-dose effects are secondary to toxicity and are not due to DNA-reactive mechanisms. Mixed results were observed for micronucleus assays in non-mammalian systems and DNA damage assays of GBFs. These effects of GBFs may also be associated with surfactants present in the formulated products. Kier and Kirkland conclude that glyphosate and its typical formulations do not present significant genotoxic risk under normal conditions of human or environmental exposures.

Epidemiology

Available epidemiological studies of glyphosate and cancer endpoints were recently reviewed (Mink et al. 2012). Seven cohort studies and fourteen case-control studies examining a potential association between glyphosate and one or more cancer outcomes were subjected to a qualitative analysis. The review found no consistent pattern of positive associations between total cancer (in adults or children) or any site-specific cancer, and exposure to glyphosate. A recent review article (Alavanja et al. 2013) cites one epidemiology study associating glyphosate use with non-Hodgkin's lymphoma (NHL), and accepts the study findings *prima facie*. However, Alavanja et al. (2013) did not highlight six other published epidemiology studies which evaluated glyphosate use and NHL, noting that any association between NHL and glyphosate use was null or not statistically significant. All seven studies were scrutinized by Mink et al. (2012). NHL is not a specific disease, as mentioned in both the epidemiology review publications above, but is rather multiple presentations of lymphoma which are simplistically classified as not being Hodgkin's lymphoma (HL). This dichotomous classification of HL/NHL was rejected by the World Health Organization in 2001, whereby 43 different lymphomas of various etiologies were precisely characterized (Berry 2010). The Bradford Hill criteria are often applied in efforts to determine whether an association between a health effect and human exposure may be deemed causal. However, an important premise often overlooked from Sir Austin Bradford Hill's famous speech of 1965, is that before applying these criteria, the observations should "reveal an association between two variables, perfectly clear-cut and beyond what we care to attribute to the play of chance" (Bradford Hill 1965). This predicate of the association being "perfectly clear-cut"

Table 1. Summary of toxicological endpoints for glyphosate (Germany Rapporteur Member State 2015c).

Endpoint	Value	Remark
Oral absorption	ca 20%	Rat, <i>in vivo</i> Human, <i>in vitro</i> , 0.015 g glyphosate/l.
Dermal absorption	< 1%	
Rat LD50 oral	> 2000 mg/kg bw	4-h exposure
Rat LD50 dermal	> 2000 mg/kg bw	
Rat LC50 inhalation	> 5 mg/L	
Skin irritation	Not irritating	
Eye irritation	Acid: moderately to severely irritating Salts: slight or non-irritating	
Skin sensitization	Not sensitizing (LLNA, Magnusson-Kligman, and Buchler test)	
Genotoxicity	Not genotoxic (<i>in vitro</i> and <i>in vivo</i>)	
Chronic toxicity	BW gain, liver (organ weight ↑, clinical chemistry, histology); salivary glands (organ weight ↑, histology); stomach mucosa and bladder epithelium (histology); eye (cataracts), caecum (disilemon, organ weight ↑) NOAEL = 100 mg/kg bw/day (2-yr rat)	Critical study used for ADI setting
Reproductive toxicity	Reduced pup weight at parentally toxic doses NOAEL = 300 mg/kg bw/day	
Developmental toxicity	Post-implantation loss, fetal BW & ossification ↓; effects confined to maternally toxic doses Rat NOAEL: 300 mg/kg bw/day Rabbit NOAEL: 50 mg/kg bw/day	
Delayed neurotoxicity	No relevant effects, NOAEL = 2000 mg/kg bw/day	
Acceptable Daily Intake (ADI)	0.5 mg/kg bw/day Based on developmental toxicity in rabbits	Safety factor 100
Acceptable Operator Exposure Level (AOEL)	0.1 mg/kg bw/day Based on maternal toxicity in rabbit teratogenicity study	Safety factor 100 Corrected for oral absorption of 20%

was recently highlighted as requiring statistical significance, wherein the confidence interval of a relative risk ratio is bracketed above 1.0, as well as concluding that the association may not be attributable to bias, confounding or sampling error (Woodside and Davis 2013). According to Bradford Hill, should an epidemiology study be considered to demonstrate a “perfectly clear-cut” association between glyphosate exposure and a human health outcome, only then should the Bradford Hill criteria be investigated to determine whether there is causality. To date, no such “perfectly clear-cut” association between glyphosate exposure and any cancer exists. However, investigative toxicology is an important discipline to evaluate chemicals before any human exposure occurs, and these data may inform subsequent considerations of whether associations are attributable to causality. One Bradford Hill criterion in establishing disease causality is *plausibility*, based on known disease etiologies. In the case of lymphoma, there are numerous etiologies for the numerous and different lymphoma diseases, and as such, each lymphoma type should be investigated for a plausible mechanism to determine whether causality may be attributed an appropriately qualified association. Another Bradford Hill criterion is identification of a biological gradient, or dose-response, which is a key consideration in the following data evaluation.

Chronic toxicity studies

Several one-year chronic studies have been undertaken in dogs and one in rats, in addition to the many chronic/carcinogenicity studies with one-year interim sacrifice groups. Current Test Guidelines (OECD, EPA, EU and JMAFF) for long-term studies clearly state that the highest dose tested should either be at the maximum tolerated dose (MTD), conventionally interpreted as a dose causing non-lethal toxicity, often noted

as reduced body weight gain of 10% or more (IUPAC 1997). For test substances with low toxicity, a top dose not exceeding 1000 mg/kg bw/day may apply, except when human exposure indicates the need for a higher dose level to be used (OECD 2012a). All human exposure estimates are well below 1 mg/kg bw/day (see Discussion section), so that 1000 mg/kg bw/day is a practical limit dose for glyphosate in carcinogenicity studies. In the original pre-guideline chronic/carcinogenicity study, rats were dosed well below the MTD (Monsanto 1981), but in many subsequent studies, they were dosed well in excess of today's standard practice of not exceeding the dose limit.

Dog chronic studies

Five one-year oral toxicity studies have been conducted in Beagle dogs (Table 2). Studies in dogs are not designed to detect neoplastic effects; these studies are therefore not discussed in detail. Nonetheless, the histopathological investigations that are part of one-year dog studies according to OECD TG 452 did not identify (pre) neoplastic lesions related to the administration of glyphosate.

Treatment-related effects in dog studies with glyphosate were restricted to non-specific findings like small retardations in body weight gain and soft stools, which are common findings in this test species. The lowest relevant NOAEL (i.e. highest NOAEL below the lowest LOAEL) in dogs on a daily treatment regimen for one year was 500 mg/kg bw/day. These studies demonstrate that glyphosate is of very low toxicity following repeat exposures in dogs.

Rat chronic studies

The chronic toxicity potential of glyphosate acid was assessed in a 12-month feeding study (conducted in 1995 and 1996) in

Table 2 Summary of one-year toxicity studies with glyphosate.

Authors:	Monsanto (1985)
Reliability/Justification	2 Study performed according to GLP and OECD guideline requirements, with the following deviation: MTD not reached by highest dose
Substance:	Glyphosate (96.1% pure)
Species/Strain:	Dog/Beagle, groups of 6 ♂ and 6 ♀
Administration route:	Oral, capsule
Doses:	0, 20, 100, 500 mg/kg bw/day
Duration:	1 year
Findings:	≥ 500 mg/kg bw/day, NOAEL (♂ + ♀) no treatment-related effects
Authors:	Chemimova (1990)
Reliability/Justification	1 Study performed according to GLP and OECD guideline requirements, with no deviations
Substance:	Glyphosate (98.6–99.5% pure)
Species/Strain:	Dog/Beagle, groups of 4 ♂ and 4 ♀
Administration route:	Oral, capsule
Doses:	0, 30, 300, 1000 mg/kg bw/day
Duration:	1 year
Findings:	300 mg/kg bw/day: NOAEL (♂ + ♀) 1000 mg/kg bw/day: soft, liquid stools (attributable to capsule administration); equivocal impact on body weight gain
Authors:	Nufarm (2007)
Reliability/Justification	2 Study performed according to GLP and OECD guideline requirements, with the following deviation: MTD not reached by highest dose
Substance:	Glyphosate (95.7% pure)
Species/Strain:	Dog/Beagle, groups of 4 ♂ and 4 ♀
Administration route:	Oral, capsule
Doses:	0, 30, 125, 500 mg/kg bw/day
Duration:	1 year
Findings:	≥ 500 mg/kg bw/day: NOAEL (♂ + ♀) No treatment-related effects
Authors:	Arysta Life Sciences (1997c)
Reliability/Justification	2 Study performed according to GLP and OECD guideline requirements, with the following deviation: MTD not reached by highest dose
Substance:	Glyphosate (94.6% pure)
Species/Strain:	Dog/Beagle, groups of 4 ♂ and 4 ♀
Administration route:	Oral, diet
Concentration:	0, 1600, 8000, 50 000 ppm diet (♂ about 34.1, 182, 1203 mg/kg bw/day; ♀ about 37.1, 184, 1259 mg/kg bw/day)
Duration:	1 year
Findings:	182/184 mg/kg bw/day: NOAEL (♂/♀) At high dose: loose stool, non-statistically significant retarded body weight gain, decreased urinary pH, slight and non-statistically significant focal pneumonia (♀), minor clinical chemistry changes of Cl ⁻ , albumin I, P ₁ (♀)
Authors:	Syngenta (1996a)
Reliability/Justification	1 Study performed according to GLP and OECD guideline requirements, with no deviations
Substance:	Glyphosate (95.6% pure)
Species/Strain:	Dog/Beagle, groups of 4 ♂ and 4 ♀
Administration route:	Oral, diet
Concentration:	0, 3000, 15 000, 30 000 ppm diet (♂ about 90.9, 440, 907 mg/kg bw/day; ♀ about 92.1, 448, 926 mg/kg bw/day)
Duration:	1 year
Findings:	15 000 ppm diet: NOAEL (♀) ≥ 30 000 ppm diet: NOAEL (♂); No treatment-related effects 30 000 ppm diet: slight body weight reduction (♀)
Authors:	Syngenta (1996b)
Reliability/Justification	1 Study performed according to GLP and OECD guideline requirements, with no deviations.
Substance:	Glyphosate (95.6% pure)
Species/Strain:	Rat/Wistar Alpk: AP,SD, groups of 24 ♂ and 24 ♀
Administration route:	Oral, diet
Concentration:	0, 2000, 8000, 20 000 ppm diet (♂ about 141, 560, 1409 mg/kg bw/day; ♀ about 167, 671, 1664 mg/kg bw/day)
Duration:	1 year
Findings:	8000 ppm diet: NOAEL (♂ + ♀) 20 000 ppm diet, parotid salivary glands (local basophilia of the acinar cells considered non-adverse adaptive response, ♂: 13/24, ♀: 15/24), body weight reduction

24 male and female Wistar rats per group, dosed at 0, 2000, 8000 and 20 000 ppm (Syngenta 1996). The mean achieved dose levels were 0, 141, 560 and 1409 mg/kg bw/day for males, and 0, 167, 671 and 1664 mg/kg bw/day for females. Spasmodic significant reductions in bodyweight were evident in animals receiving 20 000 ppm glyphosate acid, together with a marginal reduction in bodyweight in rats receiving 8000 ppm, but food consumption relative to controls was lower for these dose groups, suggesting reduced palatability of the diets containing

these doses of glyphosate. There were no toxicologically significant or treatment-related effects on hematology, blood and urine clinical chemistry, or organ weights (Table 2).

The treatment-related pathological finding, that is increased incidence of mild focal basophilia, and a hypertrophy of the acinar cells of the parotid salivary gland in both sexes which had received 20 000 ppm glyphosate acid, is considered an adaptive response due to oral irritation from the ingestion of glyphosate, an organic acid, in the diet. This was verified by

mode of action investigations and studies with dietary administration of citric acid, a non-toxic organic acid with irritation properties and pH dilution curve similar to those of glyphosate (Saltmiras et al. 2011), which elicited the same response in the acinar cells of the parotid salivary glands.

In conclusion, the 12-month NOAEL in rats for glyphosate acid, as determined from this study, is 8000 ppm (corresponding to 560 mg/kg bw/day in males and 671 mg/kg bw/day in females). This study does not cover neoplastic endpoints. These were addressed in a subsequent study by the same sponsor (Syngenta 2001). Consistent with the findings observed in dogs, this study demonstrates that glyphosate is of very low toxicological concern following long-term daily exposures.

Similarly, most of the following 2-year rat carcinogenicity studies included additional groups for 1-year interim sacrifice to evaluate chronic toxicity. These studies did not elucidate significant toxicological concerns for chronic dietary exposures to glyphosate in rats in multiple expert reviews by governmental agencies and several technical branches of the World Health Organization including the Joint Meeting on Pesticide Residues Toxicological Evaluations (WHO/FAO 2004a).

Carcinogenicity studies

Chronic/carcinogenicity tests are designed to simulate lifetime exposures to an individual chemical and represent the most robust *in vivo* assay to evaluate the effects of chronic exposure including carcinogenicity. These models are biological systems with natural background variability due to tumor formation as a natural consequence of aging. Glyphosate was found to have no carcinogenic potential, which is reflected in the data showing only background noise of spontaneous tumors across the wide range of doses. Normal biological variability should display various tumor types across all dose groups without an apparent dose-response. The study summaries discuss "select neoplasms", identified by the authors as having an elevated incidence above concurrent controls across one or more dose groups, most of which lacked statistical significance and/or dose-response within an individual study. These tumors are then evaluated in the context of the whole data set, to provide a robust weight of evidence overview for the doses spanning several orders of magnitude. While not all studies have select neoplasms identified in the individual study summary tables, select neoplasms for all studies are reported in Tables 20–23. Summary tables of the select neoplasms footnote the strain tested for each dose, to allow consideration of strain differences in spontaneous tumor susceptibility (Tables 20–23). In addition, complete tumor incidence summary tables have been extracted from the original eight rat (the published rat study, Study 9, is not included) and five mouse study reports or study files, and posted in their original format, as a comprehensive online data supplement to this manuscript.

Rat carcinogenicity

A total of nine chronic/carcinogenicity studies in the rat, including one peer-reviewed published study, were available for review. This duplication of large-scale studies in the same animal model using the same test substance is not consistent with today's broader appreciation for animal welfare and the reduction of unnecessary animal testing. However, these

studies offer the opportunity for a critical discussion of findings in individual studies in the context of the larger body of data. Wistar and Sprague Dawley were the strains used for the bioassays in rats. Seven studies were conducted under conditions of GLP, and two studies were not under GLP (Study 1, conducted before the introduction of GLP; Study 9, non-GLP). Most studies in rats were designed as combined chronic toxicity/carcinogenicity studies, with interim sacrifices after 12 months of treatment for the assessment of non-neoplastic chronic toxicity. Statistical methods are noted in the manuscript tables where statistical significance was attained. Statistical differences in neoplasm incidence summary tables are reported in the online data supplements. Chronic endpoints and NOAEL values are captured in each study summary table; however, the following study reviews focus on carcinogenicity.

Study 1 (Monsanto 1981)

An early study into the long-term effects of orally administered glyphosate in the rat was conducted between 1978 and 1980 (Monsanto 1981), prior to the adoption of international test guidelines and GLP standards (Tables 3–6). Nonetheless, the test protocol was broadly compliant with OECD TG 453 (1981). However, an MTD was not reached and the high dose was well below an acceptable dose limit of 1000 mg/kg bw/day. Therefore, this study is rated Klimisch 3 for reliability, and is considered inadequate for carcinogenicity evaluation from a regulatory perspective.

Groups of 50 male and 50 female Sprague Dawley rats were administered glyphosate acid in the diet, at concentrations of 0, 30, 100 and 300 ppm, for up to least 26 months. The mean doses achieved were 0 (control), 3, 10, and 31 mg/kg bw/day for the males, and 0 (control), 3, 11, and 34 mg/kg bw/day for the females. Study results are summarized in Table 3.

In general, the incidences of all neoplasms observed in the treated and control animals were similar, or occurred at low incidence, such that a treatment-related association could not be made. The most common tumors found were common spontaneous neoplasms, as reported in the literature relating to rat (Johnson and Gad 2008), in the pituitary glands of both control and treated animals (Table 4). In the females, mammary gland tumors were the next most common neoplasm across control and dose groups (see data Supplementary Study 1 to be found online at <http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423>).

Table 3. Study 1–26-month feeding study of glyphosate in rats (Monsanto 1981).

Study owner:	Monsanto (1981)
Reliability/Justification:	3 Study not performed under GLP. High-dose well below MTD. Does not conform to modern testing standards.
Substance:	Glyphosate (98.7% pure)
Species/Strain:	Rat/Sprague-Dawley, groups of 50 ♂ and 50 ♀
Administration route:	Diet
Concentration:	0, 30, 100, 300 ppm diet (♂ about 0, 3, 10, 31 mg/kg bw/day; ♀ about 0, 3, 11, 34 mg/kg bw/day)
Duration:	26 months
Findings:	≥ 300 ppm diet, NOAEL (♂ + ♀) No treatment-related effects
Select neoplasms:	Pituitary adenoma, Testes interstitial cell

Table 4. Study 1 – Pituitary tumor findings.

Tumors	Dose group (mg/kg bw/day)							
	Males				Females			
	0	3.05	10.3	31.49	0	3.37	11.22	34.02
Pituitary tumors	Number of animals/total number examined (% per group)							
Adenomas - B	16/48 (33)	19/49 (39)	20/48 (42)	18/47 (38)	34/48 (70)	29/48 (60)	31/50 (62)	26/49 (53)
Carcinomas - M	3/48 (6)	2/49 (4)	3/48 (6)	1/47 (2)	8/48 (17)	7/48 (14)	5/48 (10)	12/49 (24)
Combined	19/48 (40)	21/49 (43)	23/48 (48)	19/47 (40)	42/48 (88)	36/48 (75)	36/50 (72)	38/49 (78)

B benign, M malignant

The incidence of interstitial cell tumors of the testes in male rats in both the scheduled terminal sacrifice animals, as well as for all animals, suggested a possible treatment-related finding, and was presented along with contemporary historical control data for comparison (Tables 5 and 6). It was noted that at 12 months, the incidence of interstitial tumors was near zero; however, in animals aged 24–29 months at necropsy, the incidence increased to approximately 10%. The historical control data for chronic toxicity and carcinogenicity from 5 studies terminated at 24–29 months showed background levels of interstitial cell tumors comparable to those found at the highest dose in the study. Furthermore, the reported incidences in all dose groups reflect the normal range of interstitial cell tumors in rat testes, reported in the Registry of Industrial Toxicology Animal Data (Nulte et al. 2011). The incidence of interstitial cell hyperplasia did not provide evidence of a pre-neoplastic lesion. The investigators noted that at terminal sacrifice, the incidence of interstitial cell tumor was 15.4% (4/26), while the range in control animals from 5 contemporary studies (historical controls) was 6.2% (4/65) to 27.3% (3/11), with an overall mean value of 9.6% (16/166). When all animals on test are included, the incidence for the high-dose males was 12% (6/50), compared to a contemporary historical control range of 3.4% (4/116) to 6.7% (5/75), with a mean of 4.5% (24/535). The concurrent control incidence of interstitial cell tumors (0%) was not representative of the normal background incidence noted in contemporary historical control data. Therefore, the data suggest that the incidence in treated rats is within the normal biological variation observed for interstitial cell tumors at this site in this strain of rat. When evaluated in the context of the full data set for male rats (Table 20), a dose-response is clearly absent for the 25 doses evaluated in rats, ranging from 3 to 1290 mg/kg bw/day, which demonstrates that this tumor is clearly not a consequence of glyphosate exposure.

In conclusion, glyphosate was not considered carcinogenic in Sprague Dawley rats following continuous dietary exposure of up to 300 ppm, corresponding to 31 and 34 mg/kg bw/day in males and females, respectively, which is consistent with evaluations by the US EPA (US EPA 1993), the original Annex I listing in Europe (EC 2002), and WHO/FAO (WHO/FAO 2004a).

Based on the low doses tested in Study 1, Monsanto was obliged to conduct a second chronic/carcinogenicity study in rats (Study 2, discussed below) in accordance with OECD TG 453 (1981), which had been developed and instituted after this initial study was conducted.

Study 2 (Monsanto 1990)

In response to evolving regulatory requirements, this study was conducted in accordance with the contemporary version of OECD TG 453 (Monsanto 1990). The chronic toxicity and carcinogenic potential of glyphosate were assessed in a 24-month feeding study in 50 male and 50 female Sprague Dawley rats, dosed with 0, 2000, 8000 and 20 000 ppm (equivalent to mean achieved dose levels of 0, 89, 362 and 940 mg/kg bw/day for males and 0, 113, 457 and 1183 mg/kg bw/day for females (Table 7). In addition, 10 rats per sex per dose were included for interim sacrifice after 12 months. Observations covered clinical signs, ophthalmic examinations, body weight, food consumption, hematology, clinical chemistry and urinalysis, as well as organ weights, necropsy, and histopathological examination. This study was rated Klimisch 3 for reliability.

Treatment-related findings in this study were significantly reduced body weight in high-dose females, as well as increased liver weight in high-dose males and females, and a slight increase in incidence of cataract lens changes in high-dose males, which was not statistically significant for eye lesions confirmed by histopathology (Table 7). The body weight changes confirm that the MTD was achieved in the highest dose group. Benign thyroid C-cell adenomas were statistically higher than controls in the mid-dose terminally sacrificed males, but when pooled with unscheduled deaths, no statistically significant increase was noted. Benign pancreas islet cell adenomas were not statistically higher for the unscheduled or scheduled deaths, but when combined, were statistically higher than controls in the low and high dose males. In both cases, the benign tumors did not exhibit a dose-response, and did not progress to carcinomas, and thus the US EPA concluded that these tumors were not related to the administration

Table 5. Study 1 - Interstitial cell tumor findings in the testes.

Tumors	Dose (mg/kg bw/day)			
	0	3.05	10.3	31.49
Interstitial cell tumor - B	Number of animals/total number examined (% per group)			
Terminal sacrifice	0/15 (0)	2/26 (7.7)	1/16 (6.3)	4/26 (15.4)
All Animals	0/50 (0)	3/50 (6)	1/50 (2)	6/50 (12)
Interstitial cell hyperplasia	Number of animals (% per group)			
Terminal sacrifice	1/15 (6.7)	1/26 (3.8)	0/16 (0)	0/26 (0)
All Animals	1/50 (2)	1/50 (2)	1/50 (2)	0/50 (0)

B benign, M malignant

Table 6. Study 1 – Summary of the contemporary historical control data for interstitial cell tumors in the testes of rats in chronic toxicity studies.

	Study 1	Study 2	Study 3	Study 4	Study 5	Range
	Number of control animals/total number examined (% per study)					
Terminal sacrifice	4/65 (6.2)	3/11 (27.3)	3/26 (11.5)	3/24 (12.5)	3/40 (7.5)	6.2–27.3%
All animals	4/116 (3.4)	5/75 (6.7)	4/113 (3.5)	6/113 (5.3)	5/118 (4.2)	3.4–6.7%

of glyphosate (US EPA 1993). These neoplasms, in addition to skin keratoacanthoma in males, a common rat tumor, were selected for further weight of evidence evaluation (Tables 20 and 21). No evidence of a glyphosate-induced carcinogenic effect was noted in either sex (see data Supplementary Study 2 to be found online at <http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423>).

In conclusion, glyphosate was not carcinogenic in Sprague Dawley rats following continuous dietary exposure of up to 20 000 ppm for 24 months, corresponding to 940 and 1183 mg/kg bw/day in males and females, respectively, which is consistent with evaluations by the US EPA (US EPA 1993), European Authorities (EC 2002), and WHO/FAO (WHO/FAO 2004a).

Study 3 (Cheminova 1993a)

The chronic toxicity and carcinogenic potential of glyphosate technical acid were assessed in a 104-week feeding study in

male and female Sprague Dawley rats (Cheminova 1993a). The study was conducted between 1990 and 1992. Groups of 50 rats per sex received daily dietary doses of 0, 10, 100, 300, or 1000 mg/kg bw/day of glyphosate technical acid for 24 months (Table 8). Five additional groups of 35 rats per sex, receiving daily dietary doses of 0, 10, 100, 300 or 1000 mg/kg bw/day, were included for interim sacrifice at the 12th month for evaluation of chronic toxicity. The dietary glyphosate levels were adjusted weekly to ensure that animals were receiving the intended dose levels at all times. This study was rated Klimisch 1 for reliability.

At 1000 mg/kg bw/day, female mean liver weights were decreased, while males and females had statistically significant reductions in body weight throughout the study, confirming that the MTD was achieved (Table 8). Neoplasms were noted in control and treated groups, but dose-responses were not evident, and no statistically significant increases versus controls were noted for any tumor type ($p < 0.05$). No treatment-related neoplastic lesions were observed at termination.

Table 7. Study 2 – Two-year feeding study of glyphosate in rats (Monsanto 1990).

Study owner:	Monsanto (1990)			
Reliability/Justification:	1 Study performed according to GLP and OECD guideline requirements, with no deviations.			
Substance:	Glyphosate (96.5% pure)			
Species/Strain:	Rat/Sprague-Dawley, groups of 50 ♂ and 50 ♀ (10 rats per sex per dose were included for interim sacrifice after 12 months).			
Administration route:	Diet			
Concentration:	0, 2000, 8000, 20 000 ppm diet (♂ about 0, 89, 362, 940 mg/kg bw/day; ♀ about 0, 133, 457, 1183 mg/kg bw/day)			
Duration:	2 years			
Findings:	8000 ppm diet: NOAEL (♂+♀) 20 000 ppm diet: cataracts (♂), > 20% reduced cumulative body weight gain through months 18–20 (♀), 13% increased liver weight (♂), local effects: inflammation of gastric mucosa			
Select neoplasms:	Pancreatic islet cell adenoma, skin keratoacanthoma (males), thyroid C cell adenoma			
Tumor		Dose (mg/kg bw/day)		
Males	0	89	362	940
Findings for dead and moribund sacrificed animals				
Pancreas: Islet cell adenoma – B	1/34 (3%)	4/28 (14%)	2/33 (6%)	4/32 (13%)
Skin: Keratoacanthoma – B	0/36	1/31 (3%)	2/33 (6%)	1/32 (3%)
Thyroid: C cell adenoma – B	0/36	2/29 (7%)	1/31 (3%)	1/33 (3%)
Thyroid: C cell carcinoma – M	0/36	1/29 (3%)	2/31 (6%)	1/33 (3%)
Findings for animals sacrificed at termination				
Pancreas: Islet cell adenoma – B	0/14	4/19 (21%)	3/17 (6%)	3/17 (6%)
Skin: Keratoacanthoma – B	0/13	2/19 (11%)	2/17 (12%)	2/17 (12%)
Thyroid: C cell adenoma – B	0/14	2/19 (11%)	*7/17 (41%)	4/17 (24%)
Thyroid: C cell carcinoma – M	0/14	0/19	0/17	0/17
Females	0	113	457	1183
Findings for dead and moribund sacrificed animals				
Pancreas: Islet cell adenoma – B	3/28 (11%)	0/28	3/33 (9%)	0/31
Thyroid: C cell adenoma – B	0/28	0/28	1/33 (3%)	2/32 (6%)
Thyroid: C cell carcinoma – M	0/28	0/28	1/33 (3%)	0/32
Findings for animals sacrificed at termination				
Pancreas: Islet cell adenoma – B	2/22 (9%)	1/22 (5%)	1/17 (6%)	0/18
Thyroid: C cell adenoma – B	2/22 (9%)	2/22 (9%)	5/17 (29%)	4/18 (22%)
Thyroid: C cell carcinoma – M	0/22	0/22	0/17	0/18

B benign, M malignant

*Statistically higher than controls ($p < 0.05$, Fisher's Exact Test with the Bonferroni Inequality)

Table 8. Study 3 – Two-year feeding study of glyphosate in rats (Cheminova 1993a).

Study owner:	Cheminova (1993a)
Reliability/Justification:	1 Study performed according to GLP and OECD guideline requirements, with no deviations.
Substance:	Glyphosate (98.7–98.9% pure)
Species/Strain:	Rat/Sprague-Dawley, groups of 50 ♂ and 50 ♀ (additional groups of 35 ♂ and 35 ♀ per dose were included for 1-year interim sacrifice)
Administration route:	Diet
Achieved dose:	♂ + ♀: 0, 10, 100, 300, 1000 mg/kg bw/day (weekly adjustment of dietary concentration for the first 13 weeks and 4-weekly thereafter)
Duration:	2 years
Findings:	300 mg/kg bw/day: NOAEL (♂ + ♀) 1000 mg/kg bw/day: body weights ↓, urinary pH ↓, salivary glands (histopathology, organ weight ↑); evidence of weak liver toxicity (alkaline phosphatase ↑, ♀; organ weight ↑)
Select neoplasms:	No neoplasms from this study were identified for further consideration.

and no select neoplasms were identified in this study for further consideration (see data Supplementary Study 3 to be found online at <http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423>). Glyphosate was not considered carcinogenic in male and female Sprague-Dawley rats following 104 weeks of continuous dietary exposure of up to 1000 mg/kg bw/day, the limit dose, which is consistent with evaluations by the European Authorities (EC 2002, Germany Rapporteur Member State 2015b) and WHO/FAO (WHO/FAO 2004a).

Study 4 (Feinchemie Schwebda 1996)

A 2-year bioassay in the Wistar rat used dietary glyphosate levels of 0, 100, 1000, and 10 000 ppm (Feinchemie Schwebda 1996). Groups of 50 rats per sex were fed for 24 months. The mean achieved dose levels were 0, 7.4,

73.9, and 740.6 mg/kg bw/day (Table 9). This study was rated Klimisch 1 for reliability.

In addition, one vehicle control with ten rats per sex and one high dose (10 000 ppm) group with 20 rats per sex were included for interim sacrifice after one year of treatment, to study non-neoplastic histopathological changes. The mean achieved dose level in the treated group was 764.8 mg/kg bw/day. Observations covered clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, as well as organ weights, necropsy, and histopathological examination.

There were no treatment-related deaths or clinical signs in any of the dose-groups. Moreover, there were no treatment-related effects on body weight gain or food consumption noted. This suggests that the MTD may not have been reached by the applied dosing regimen.

There was some background variation in the incidences of benign tumors (e.g. reduced tumor incidence in low and mid-dose males, increased tumor incidence in mid-dose females), which was considered incidental in absence of a dose-response relationship (see data Supplementary Study 4 to be found online at <http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423>).

The different liver tumors observed in the dead and moribund sacrificed and terminally sacrificed rats included hepatocellular adenoma, intrahepatic bile duct adenomas, cholangiocarcinoma, hepatocellular carcinoma, histiocytic sarcoma, fibrosarcoma, and lymphosarcoma. Among these, hepatocellular adenomas and carcinomas occurred more frequently, as often observed in aging rats (Thoolen et al. 2010). These tumors appeared to be incidental and not compound-related, as their frequency of occurrence was not dependent on dose. Hepatocellular adenomas and carcinomas were considered select neoplasms (Table 9), based on increased incidence above controls for total animals, albeit non-dose

Table 9. Study 4 – Two-year feeding study of glyphosate in rats (Feinchemie Schwebda 1996).

Study owner:	Feinchemie Schwebda (1996)			
Reliability/Justification:	1 Study performed according to GLP and OECD guideline requirements, with no deviations.			
Substance:	Glyphosate (96.0–96.8% pure)			
Species/Strain:	Rat/Wistar, groups of 50 ♂ and 50 ♀			
Administration route:	Diet			
Concentration:	0, 100, 1000, 10 000 ppm diet (♂ about 0, 6.3, 59.4, 595 mg/kg bw/day; ♀ about 0, 8.6, 88.5, 886 mg/kg bw/day)			
Duration:	2 years			
Findings:	10 000 ppm diet: ≥ NOAEL (♂ + ♀) Only mild effects on clinical chemistry (liver enzymes), without histopathological change.			
Select neoplasms:	Hepatocellular adenoma, hepatocellular carcinoma			
Tumor Males		Dose (mg/kg bw/day)		
	0	7.4	73.9	741
Findings for dead and moribund sacrificed animals				
Hepatocellular adenoma – B	9/30 (30%)	9/30 (30%)	6/32 (19%)	6/21 (29%)
Hepatocellular carcinoma – M	12/30 (40%)	12/30 (40%)	9/32 (28%)	5/21 (24%)
Findings for animals sacrificed at termination				
Hepatocellular adenoma – B	15/20 (75%)	13/20 (65%)	4/16 (25%)	15/20 (75%)
Hepatocellular carcinoma – M	9/20 (45%)	16/20 (80%)	9/16 (56%)	19/29 (66%)
Females		Dose (mg/kg bw/day)		
	0	7.4	73.9	741
Findings for dead and moribund sacrificed animals				
Hepatocellular adenoma – B	2/26 (8%)	8/23 (35%)	3/17 (18%)	5/29 (17%)
Hepatocellular carcinoma – M	4/26 (15%)	4/23 (17%)	2/17 (12%)	5/29 (17%)
Findings for animals sacrificed at termination				
Hepatocellular adenoma – B	16/24 (67%)	10/25 (40%)	16/32 (50%)	8/21 (38%)
Hepatocellular carcinoma – M	6/24 (25%)	11/25 (44%)	12/32 (38%)	4/21 (19%)

B benign, M malignant

responsive, for adenoma in mid-dose females, carcinoma in low- and high-dose males, and carcinoma in low- and mid-dose females. These liver neoplasms are considered in the weight of evidence evaluation (Tables 20 and 21).

The study report concluded that glyphosate technical acid was not carcinogenic in Wistar rats following continuous dietary exposure of up to 595 and 886 mg/kg bw/day in males and females, respectively, for 24 months, which is consistent with evaluations by the European Authorities (EC 2002, Germany Rapporteur Member State 2015b).

Study 5 (Excel 1997)

A 2-year feeding study in the Sprague Dawley rats (Excel 1997) featured dietary concentrations of 0, 3000, 15 000, and 25 000 ppm glyphosate technical acid. Groups of 50 rats per sex were fed for 24 months, and mean dose levels of 0, 150, 780 and 1290 mg/kg bw/day (males) and 0, 210, 1060 and 1740 mg/kg bw/day (females) were achieved (Table 10).

In addition, 20 rats/sex/group were included for interim sacrifice at week-52, to study non-neoplastic histopathological changes with a different high-dose level of 30 000 ppm. The dietary doses correspond to 180, 920 and 1920 mg/kg bw/day (males) and 240, 1130 and 2540 mg/kg bw/day (females), for 3000, 15 000 and 30 000 ppm, respectively. Thus, a limit dose above 1000 mg/kg bw/day was achieved.

The study report notes that glyphosate technical acid was not carcinogenic in Sprague Dawley rats following continuous dietary exposure to up to 1290 mg/kg bw/day, and 1740 mg/kg bw/day for males and females, respectively, for 24 months. However, this study was rated Klimisch 3 for reliability (Germany Rapporteur Member State 2015b), and therefore, is considered unreliable for carcinogenicity evaluation based on lower than expected background tumor incidences (see data Supplementary Study 5 to be found online at <http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423>). In addition, the test substance was not adequately characterized, and several deviations from the OECD Test Guideline 453 were noted.

Study 6 (Arysta Life Sciences 1997b)

A combined chronic toxicity/carcinogenicity study in Sprague Dawley rats (Arysta Life Sciences 1997b) was conducted between December 1994 and December 1996. The rats were fed 0, 3000, 10 000, and 30 000 ppm glyphosate for two years (equivalent to 0, 104, 354 and 1127 mg/kg bw/day for males and 0, 115, 393 and 1247 mg/kg bw/day for females (Table 11). Thus, a limit dose was achieved, and the MTD was noted at the high dose in males and females with decreased body weight, increased cecum weight, distention of the cecum, loose stool and skin lesions. In addition, 30 rats/sex/group were included for interim sacrifice at 26, 52 and 78 weeks, to study non-neoplastic histopathological changes. Observations covered clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, as well as organ weights, necropsy, and histopathological examination. This study was rated Klimisch 1 for reliability.

Non-statistically significant increases versus controls ($p < 0.05$) were noted for pituitary adenomas, skin keratoacanthoma in high-dose males, and mammary gland fibroadenoma in low and mid-dose females (Table 11). These neoplasms were considered for the weight of evidence evaluation (Tables 20 and 21), and the full tumor summary data are available online (see data Supplementary Study 6 to be found online at <http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423>). As mentioned under Study 1, pituitary and mammary tumors are common spontaneous neoplasms in aging rats (Johnson and Gad 2008), and skin keratoacanthoma is noted as one of the most common spontaneous benign neoplasms in male Sprague Dawley rats (Chandra et al. 1992). The study report concluded that glyphosate was not carcinogenic in Sprague Dawley rats following continuous dietary exposure to up to 30 000 ppm for 24 months, corresponding to 1127 mg/kg bw/day and 1247 mg/kg bw/day for males and females, respectively, which is consistent with the recent evaluation in Europe under the Annex I Renewal of glyphosate (Germany Rapporteur Member State 2015b).

Table 10. Study 5 – Two-year feeding study of glyphosate in rats (Excel 1997).

Study owner:	Excel (1997)		
Reliability/Justification:	3 Test substance not characterized and other deviations from OECD 453, lower than expected background tumor incidence		
Substance:	Glyphosate (no purity reported)		
Species/Strain:	Rat/Sprague-Dawley, groups of 50 ♂ and 50 ♀, additional groups of 20 rats per sex and group were included for interim sacrifice after 52 weeks		
Administration route:	Diet		
Concentration:	2-year group: 0, 3000, 15 000, 25 000 ppm diet (♂ about 0, 150, 780, 1290 mg/kg bw/day; ♀ about 0, 210, 1060, 1740 mg/kg bw/day) 1-year group: 0, 3000, 15 000, 30 000 ppm diet (♂ about 0, 180, 920, 1920 mg/kg bw/day; ♀ about 0, 240, 1130, 2540 mg/kg bw/day)		
Duration:	2 years		
Findings:	≥ 25 000 ppm diet: NOAEL (♂ + ♀) Only mild toxic effects, such as clinical chemistry of questionable relevance in aged rats, without correlating histopathological organ changes.		
Select neoplasms:	No neoplasms from this study were identified for further consideration. Low background tumor incidence indicates low study reliability with no relevant increases in the incidence of tumors.		
Males	Dose (mg/kg bw/day)		
	0	150	740.6
Mortality	16/50 (32%)	17/50 (34%)	18/50 (36%)
Females	Dose (mg/kg bw/day)		
	0	1060	1740
Mortality	19/50 (38%)	20/50 (40%)	25/50 (50%)

Table 11 Study 6 – Two-year feeding study of glyphosate in rats (Arysta Life Sciences 1997b)

Study owner:	Arysta Life Sciences (1997b)			
Reliability/Justification:	1 Study performed according to GLP and OECD guideline requirements, with no deviations.			
Substance:	Glyphosate (94.6–97.6% pure)			
Species/Strain:	Rat/Sprague-Dawley, groups of 50 ♂ and 50 ♀; satellite groups of 30 ♂ and 30 ♀ for interim investigations			
Administration route:	Diet			
Concentration:	0, 3000, 10 000, 30 000 ppm diet (♂ about 0, 104, 354, 1127 mg/kg bw/day; ♀ about 0, 115, 393, 1247 mg/kg bw/day)			
Duration:	2 years			
Findings:	3000 ppm diet: NOAEL (♂+♀) 10 000 ppm diet: cecum weight ↓, distension of cecum, loose stool, follicular hyperkeratosis and/or folliculitis/follicular abscess of the skin, body weight ↓			
Select neoplasms:	Pituitary adenoma, skin keratoacanthoma (males), mammary gland fibroadenoma (females)			
Tumor	Dose (mg/kg bw/day)			
Males	0	104	354	1127
Findings for dead and moribund sacrificed animals (Table 25–10)				
Pituitary anterior adenoma – B	22/32 (69%)	21/30 (70%)	*14/32 (44%)	18/21 (86%)
Skin keratoacanthoma – B	2/32 (6%)	1/30 (3%)	0/32	1/21 (5%)
Findings for animals sacrificed at termination (after 104 weeks, Table 25–8)				
Lung adenoma – B	0/18	2/20 (10%)	1/18 (6%)	3/29 (10%)
Pituitary anterior adenoma – B	13/18 (72%)	14/20 (70%)	13/18 (72%)	21/29 (72%)
Pituitary adenoma in intermediate part – B	0/18	1/20 (5%)	0/18	0/29 (0%)
Skin keratoacanthoma – B	1/18 (6%)	2/20 (10%)	0/18	6/29 (21%)
Tumor	Dose (mg/kg bw/day)			
Females	0	115	393	1247
Findings for dead and moribund sacrificed animals				
Pituitary anterior adenoma – B	34/35 (97%)	29/31 (94%)	28/33 (82%)	31/36 (86%)
Thyroid follicular adenoma – B	0/35	2/31 (6%)	0/32	0/36
Mammary gland fibroadenoma – B	13/35 (37%)	14/31 (45%)	12/34 (35%)	20/36 (56%)
Findings for animals sacrificed at termination				
Pituitary anterior adenoma – B	12/15 (80%)	19/19 (100%)	12/16 (75%)	13/14 (93%)
Mammary gland fibroadenoma – B	10/15 (67%)	13/19 (68%)	12/16 (75%)	10/14 (71%)

B benign, M malignant

*Statistically lower than controls ($p < 0.05$).

Study 7 (Syngenta 2001)

The same rat model that was used in the previously discussed 12-month chronic rat study (Syngenta 1996b) was also employed in a 2-year feeding study (Syngenta 2001). A group of 52 male and 52 female Wistar rats received 0, 2000, 6000 or 20 000 ppm via feed (Table 12). The mean achieved dose levels were 0, 121, 361 and 1214 mg/kg bw/day for males, and 0, 145, 437 and 1498 mg/kg bw/day for females. Thus, a limit dose was achieved. In addition, three satellite groups with 12 rats per sex each were included for interim sacrifice after 12 months of treatment, to investigate potential non-neoplastic histopathological changes. Observations covered clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, as well as organ weights, necropsy, and histopathological examination. This study was rated Klimisch 1 for reliability.

Treatment-related findings in this study were found in the liver and kidney, and were confined to animals (predominantly males) fed 20 000 ppm glyphosate acid. There were a number of changes in males and females fed 20 000 ppm glyphosate acid, notably renal papillary necrosis, prostatitis, periodontal inflammation, urinary acidosis, and hematuria, which may be attributed to the acidity of the test substance. Slight increases in proliferative cholangitis and hepatitis were noted in males at 20 000 ppm. Despite the findings at 20 000 ppm, survival was better in males fed 20 000 ppm than in the controls and lower dose groups. This improved survival was associated with a decreased severity of renal glomerular nephropathy and a 5% reduction in body weight (see data Supplementary Study 7 to be found online at [\[informahealthcare.com/doi/abs/10.1093/oxfordjournals.oxford.000323\]\(http://informahealthcare.com/doi/abs/10.1093/oxfordjournals.oxford.000323\), for neoplastic and non-neoplastic findings\).](http://</p>
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A small increase in the incidence of hepatocellular adenoma was observed in males fed 20 000 ppm glyphosate acid. While not statistically significant using the Fisher's exact test, the difference was statistically significant for total male rats using the Peto Test for trend. However, there was no evidence of pre-neoplastic foci, no evidence of progression to adenocarcinoma, and no dose-response. In addition, the incidence was within the laboratory's historical control range for tumors of this type in the liver (Table 12). Therefore, the increased incidence was considered not to be related to treatment, yet these were considered select neoplasms (Table 12) and evaluated in context of the complete data set (Tables 20 and 21).

The study report concluded that glyphosate acid was not carcinogenic in the Wistar rats following continuous dietary exposure to up to 20 000 ppm for 24 months, at 1214 and 1498 mg/kg bw/day in males and females, respectively, which is consistent with the WHO/FAO review (WHO/FAO 2004a) and the recent evaluation in Europe under the Annex I Renewal of glyphosate (Germany Rapporteur Member State 2015b).

Study 8 (Nufarm 2009b)

The most recent study in this series of regulatory studies investigating the potential carcinogenicity of glyphosate in rats was conducted from September 2005 through March 2008 (Nufarm 2009b). The study was conducted by feeding dietary concentrations of 0, 1500, 5000 and 15 000 ppm glyphosate to groups of 51 Wistar rats per sex. To ensure that a received limit dose of 1000 mg/kg bw/day overall was achieved, the highest dose level was progressively increased to 24 000 ppm

Table 12. Study 7 – Two-year feeding study of glyphosate in rats (Syngenta 2001).

Study owner:	Syngenta (2001)			
Reliability/Justification:	1 Study performed according to GLP and OECD guideline requirements, with no deviations.			
Substance:	Glyphosate (97.6% pure)			
Species/Strain:	Rat/Wistar Alpk. APSD, groups of 52 ♂ and 52 ♀ (additional 12 animals per sex and dose for 1-year interim sacrifice)			
Administration route:	Diet			
Concentration:	0, 2000, 6000, 20 000 ppm diet (♂ about 0, 121, 361, 1214 mg/kg bw/day; ♀ about 0, 145, 437, 1498 mg/kg bw/day)			
Duration:	2 years			
Findings:	6000 ppm diet: NOAEL (♂ + ♀) 20 000 ppm diet: Kidney and liver findings. Increased survival due to reduction in CPN, prostatitis, periodontal inflammation			
Select neoplasms:	Hepatocellular adenoma (males), not a statistically significant increase for the high dose using the Fisher's exact test, but statistically significant using Peto trend analysis			
		Dose (mg/kg bw/day)		
Males	0	121	361	1214
Liver				
Hepatocyte fat vacuolation	6	7	11	11
Hepatitis	3	4	2	5
Kidney				
		Dose (mg/kg bw/day)		
Females	0	145	437	1498
Liver				
Hepatocyte fat vacuolation	7	5	6	6
Hepatitis	6	5	4	4
Tumors:		Dose (mg/kg bw/day)		
Males	0	121	361	1214
Findings for dead and moribund sacrificed animals				
*Hepatocellular adenoma – B	0/37	2/36 (6%)	0/35	3/26 (12%)
Hepatocellular carcinoma – M	0/37	0/36	0/35	0/26
Findings for animals sacrificed at termination				
*Hepatocellular adenoma – B	0/16	0/17	0/18	2/26 (8%)
Hepatocellular carcinoma – M	0/16	0/17	0/18	0/26

B benign, M malignant

*Historical Control Range: 0–11.5% total males with hepatocellular adenoma, 26 studies, 1984–2003

Mean dose levels of 86/105, 285/349, and 1077/1382 mg glyphosate/kg bw/day (males/females) were achieved (Table 13). This study was rated Klimisch 1 for reliability.

Non-neoplastic findings included transient liver enzyme activity for mid-dose males and high-dose males and females, and equivocal nephrocalcinosis depositions at the high-dose. Histopathology noted a statistically significant increase in

adipose infiltration of the bone marrow in high-dose males compared to controls, suggestive of myeloid hypoplasia, which may be considered a stress response (Everds et al. 2013).

Skin keratoacanthoma in males and mammary gland adenocarcinoma in females (Table 13) were considered for evaluation in the context of the weight of evidence for rat tumor incidence (Tables 20 and 21), wherein dose-

Table 13. Study 8 – Two-year feeding study of glyphosate in rats (Nufarm 2009b).

Study owner:	Nufarm (2009a)			
Reliability/Justification:	1 Study performed according to GLP and OECD guideline requirements, with no deviations			
Substance:	Glyphosate (95.7% pure)			
Species/Strain:	Rat/Wistar, groups of 51 ♂ and 51 ♀			
Administration route:	Diet			
Concentration:	0, 3000, 10 000, 15 000 ppm diet, the top dose was progressively increased to reach 24 000 ppm diet by Week-40 (♂ about 0, 84, 285, 1077 mg/kg bw/day; ♀ about 0, 105, 349, 1382 mg/kg bw/day)			
Duration:	2 years			
Findings:	≥ 1077/1382 mg/kg bw/day: NOAEL (♂/♀) Transient liver enzyme activity for mid-dose males and high-dose males and females; equivocal nephrocalcinosis depositions at the high-dose males and females; increased adipose infiltration of the bone marrow in high-dose males			
Select neoplasms:	Skin keratoacanthoma (males), mammary gland adenocarcinoma			
		Dose (mg/kg bw/day)		
Tumor				
Males	0	84	285	1077
Findings for all animals				
Skin keratoacanthoma – B	2/51 (4%)	3/51 (6%)	0/51	6/51 (12%)
		Dose (mg/kg bw/day)		
Females	0	105	349	1382
Findings for all animals				
Mammary gland adenocarcinoma – M	2/51 (4%)	3/51 (6%)	1/51 (2%)	6/51 (12%)

B benign, M malignant

responses were not evident. Tumor incidence summary data have been tabulated (see data Supplementary Study 8 to be found online at <http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423>). Microscopic evaluation of tissues did not reveal any indications of neoplastic lesions caused by glyphosate treatment. The study report concluded that glyphosate acid was not carcinogenic in Wistar rats following continuous dietary exposure to up to 24 000 ppm for 24 months, at 1077 and 1382 mg/kg bw/day in males and females, respectively, which is consistent with the recent evaluation in Europe under the Annex I Renewal of glyphosate (Germany Rapporteur Member State 2015b).

Study 9 Publication (Chruscielska et al. 2000a)

A two-year combined chronic toxicity and carcinogenicity study in Wistar rats was published by academic researchers from Warsaw, Poland. The study was conducted as a drinking-water study in Wistar-RIZ rats according to OECD TG 453. The test material was a 13.85% aqueous formulation of glyphosate as its ammonium salt (equivalent to 12.6% glyphosate acid). However, the ammonium salt of glyphosate tested is not commercially available, and the concentration of active ingredient suggests that a glyphosate-formulated product was tested; this is supported by a concurrent genotoxicity publication by the same lead author (Chruscielska et al. 2000b), previously reviewed by Kier and Kirkland (Kier and Kirkland 2013), in which a glyphosate formulation, Perzocyd, was tested. Deficiencies noted with respect to OECD TG 453 include insufficient dosing to elicit toxic effects, inadequate test material characterization, no reporting of water/feed consumption, body weights and diet composition, and no individual animal data. Although the manuscript reporting deficiencies may have been included in the study, they were not reported in the manuscript, and could warrant a Klimisch reliability score of 4 (not assignable), but the low doses employed in this study justify a Klimisch reliability score of 3.

The test material was administered in water at glyphosate salt concentrations of 0, 300, 900, and 2700 mg/L. Each dose group consisted of 85 animals per sex. Ten animals per sex and dose were sacrificed after 6, 12, and 18 months of exposure, for evaluation of general toxicity. The remaining 55 animals per sex and dose were scheduled for sacrifice after 2 years of exposure.

Water consumption was claimed to have been measured, but these data have not been reported. To estimate the glyphosate doses received via drinking water, the assumed default water consumptions were 50 and 57 mL/kg bw/day by male and female rats, respectively (Gold et al. 1984). Using these standard figures and the glyphosate content of the tested formulation (12.6%), daily doses are estimated at 0, 1.9, 5.7, and 17 mg of glyphosate/kg bw/day for males and 0, 2.2, 6.5, and 19 mg of glyphosate/kg bw/day for females. As this study appears to have tested a formulated product, data were not included in the weight of evidence review (Tables 20 and 21), but given the very low glyphosate doses and reported low tumor incidence, these were of no consequence to the overall data review.

Exposure to glyphosate ammonium salt had no effect on body weight, appearance and behavior, and hematological parameters, which is consistent with glyphosate chronic toxicity data regulatory reviews. Even though there seems to be a trend towards higher 2-year mortality in treated females

(Table 14), this difference had no statistical significance according to the authors. There were sporadic alterations of clinical-chemical and urinalysis parameters, but not in a consistent fashion over time and without dose-dependence. These alterations were not interpreted as treatment-related. There was no effect of glyphosate on the incidence of neoplastic lesions (Table 14). Thus, the NOAEL for chronic toxicity and carcinogenicity in this study was greater than or equal to 17 and 19 mg glyphosate/kg bw/day, in males and females, respectively.

Due to the lack of systemic effects in the highest dose group, the MTD was not reached by this study. Judging from other rat studies reviewed here, the MTD is likely to be greater than 1000 mg/kg bw/day. Thus, the top glyphosate dose of an estimated 19 mg/kg bw/day in this study is too low to satisfy regulatory validity criteria for a carcinogenicity study.

Mouse carcinogenicity

There are a total of five carcinogenicity studies with glyphosate in mice, that have been submitted to support glyphosate Annex I renewal in the European Union. All but the oldest study (Study 10) were considered reliable without restriction, and were performed under conditions of GLP following OECD TGs. Most studies were conducted in the CD-1 strain. Each study was sponsored by a different manufacturer. In each case, technical grade glyphosate was administered via diet for at least 18 months. Select neoplasms, mostly lymphoreticular, liver and lung, are summarized for all mouse chronic studies in Tables 22 and 23. These neoplasms are widely recognized as occurring spontaneously in aging mice (Gad et al. 2008, Son and Gopinath 2004). Lymphomas have been recognized for many years as one of the most common, if not the most common category of spontaneous neoplastic lesions in aging mice (Brayton et al. 2012, Gad et al. 2008, Son and Gopinath 2004). The subclassification of malignant lymphomas is not a typical diagnostic feature in rodent studies, likely due to either expense and/or feasibility. It is, however, important to recognize that lymphomas are not a single type of neoplasm, rather they are a grouping of different neoplasms arising from different pathogeneses, and should be considered as different diseases (Bradley et al. 2012). As is the case for NHL in humans, these different immune system neoplasms are clustered together based on manifestation in lymphocytes, despite their very different etiologies; for example, the most common subset of NHL lymphomas clustered together as “diffuse large B cell lymphomas”, have for many years been considered multiple clinical-pathologic entities (Armitage 1997), and therefore may be considered attributable to different modes of action. Chronic endpoints and NOAEL values are captured in each study summary table; however, the following study reviews focus on carcinogenicity.

Study 10 (Monsanto 1983)

The first chronic-carcinogenicity mouse study with glyphosate was conducted between March 1980 and March 1982 (Monsanto 1983), prior to the institution of GLP (Table 15). The study design was essentially in compliance with OECD TG 451 for carcinogenicity studies, adopted in 1981, when

Table 14. Publication, Study 9 – Two-year drinking water study in rats with 13.85% glyphosate ammonium salt (Chrascielska et al. 2000a).

Authors:	Chrascielska et al. (2000a)							
Reliability/Justification:	3 Study not performed according to GLP, but according to OECD TG 453, with the following deficiencies: Reporting deficits (water and feed consumption, body weight, diet composition, individual animal data, substance composition, purity, and stability) Highest dose did not elicit toxicity.							
Substance:	Ammonium salt of glyphosate, 13.85% solution							
Species/Strain:	Rat/Wistar-RLZ outbred, 85 ♂ and 85 ♀ per dose group, 10 ♂ and 10 ♀ each were sacrificed after 6, 12, and 18 months of exposure.							
Administration route:	Drinking water							
Concentration:	0, 300, 900, and 2700 mg/l. Estimated glyphosate intake: ♂: 0, 1.9, 5.7, and 17 mg/kg bw/day; ♀: 0, 2.2, 6.5, and 19 mg/kg bw/day, based on assumed water consumptions of 50/57 ml/kg bw/day (♂/♀), (Gold, et al 1984)							
Duration:	2 years							
Findings:	17/19 mg glyphosate/kg bw/day: NOAEL (♂/♀) No treatment-related effects							
Tumors reported for 85 rats/sex/dose:	No increase in the incidence of tumors attributable to glyphosate administration							
	Estimated dose (mg/kg bw/day)							
	0	1.9/2.2		5.7/6.5		17/19		
	♂	♀	♂	♀	♂	♀	♂	♀
Two-year mortality	42%	38%	42%	45%	54%	53%	44%	60%
Lungs								
Lymphoma	2	–	2	–	1	–	3	1
Histiocytoma	–	–	–	–	–	–	–	1
Adenocarcinoma	1	–	–	–	–	–	–	–
Histiocytoma, malignant	–	1	–	–	1	–	–	–
Spleen, leukemia	0	–	2	–	0	–	1	–
Kidneys, Fibrous histiocytoma	–	–	–	–	–	–	1	–
Pituitary gland								
Adenoma	4	10	4	6	2	8	0	3
Adenoma, malignant (assumed to be carcinoma)	0	1	0	3	1	2	1	5
Carcinoma	0	–	0	–	1	–	0	–
Thyroid								
Adenoma	1	1	1	2	0	0	3	3
Carcinoma	0	–	1	–	0	–	0	–
Uterus, cervix carcinoma	–	0	–	0	–	0	–	1
Uterus, body, histiocytoma	–	3	–	1	–	0	–	1
Mammary gland								
Fibroma	–	0	–	0	–	0	–	0
Fibroadenoma	–	3	–	2	–	3	–	3
Adrenal medulla, adenoma	1	2	2	2	1	2	0	2
Thymus, lymphoma	0	–	0	–	0	–	1	–
Testis, Leydigoma	–	–	3	–	6	–	1	–
Subcutaneous tissue								
Fibroma	0	–	1	–	1	–	3	–
Lipoma	–	–	–	–	–	–	–	1
Cystadenoma	–	1	–	–	–	–	–	–
Lymph nodes								
Lymphoma	0	–	0	–	0	–	1	–
Lymphoma, malignant	–	1	–	–	–	–	–	–
Skin, carcinoma	2	–	–	–	–	–	–	–
Prostate, adenoma	1	–	–	–	–	–	–	–

the study was already ongoing. Groups of 50 male and female CD-1 mice received glyphosate at dietary levels of 1000, 5000, and 30 000 ppm, over a period of nearly two years. The mean achieved doses were 157/190, 814/955, and 4841/5874 mg/kg bw/day in males and females, respectively, exceeding the limit dose. Based on this study predating both GLP and OECD TG 451, a reliability score of Klimisch 2 has been assigned.

In addition to post-mortem pathological examinations after terminal sacrifice, hematological investigations were performed on 10 mice per sex and dose at months 12 and 18, and on 12 male animals/group, as well as all surviving females at scheduled termination.

Two non-neoplastic histological changes affecting the liver and urinary bladder were assumed to be treatment-related. There was a higher incidence of centrilobular hepatocyte

hypertrophy in high-dose males, and a more frequent occurrence of slight-to-mild bladder epithelial hyperplasia in the mid and high dose; however, a clear dose-response was lacking. Tumor incidences, which did not significantly increase with dose, were mostly bronchiolar-alveolar, hepatocellular, or lymphoreticular, all of which are commonly noted spontaneously occurring tumors in aging mice (Table 15). Lymphoreticular tumors combined for males and females totaled 7, 12, 10 and 12 for control, low, mid- and high-dose groups respectively, and were not considered as being related to test substance.

A more frequent occurrence of slight-to-mild bladder epithelial hyperplasia was observed in the mid and high-dose groups; however, clear dose-response was lacking (Table 15) and no urinary bladder neoplasms were noted at these doses (see data Supplementary Study 10 to be found online at <http://>

Table 15. Study 10 - Two-year feeding study with glyphosate in mice (Monsanto 1983).

Study owner:	Monsanto (1983)			
Reliability/Justification	2 Study was performed prior to institution of GLP and OECD guideline requirements			
Substance:	Glyphosate (99.7% pure)			
Species/Strain:	Mouse/CD-1, groups of 50 ♂ and 50 ♀			
Administration route:	Diet			
Concentration:	0, 1000, 5000, 10 000 ppm diet (♂ about 0, 157, 814, 4841 mg/kg bw/day; ♀ about 0, 190, 955, 5874 mg/kg bw/day)			
Duration:	24 months			
Findings:	1000 ppm diet: NOAEL (♂ + ♀) 5000 ppm diet: body weight ↓, histological changes in liver and urinary bladder (slight to mild epithelial hyperplasia in males at mid and high doses)			
Select neoplasms ¹	Lymphoreticular neoplasms, bronchiolar-alveolar adenocarcinoma			
	Dose (mg/kg bw/day)			
Males	0	157	814	4841
Lymphoreticular system				
Lymphoblastic lymphosarcoma with leukemia - M	1/48 (2%)	4/49 (8%)	3/50 (6%)	2/49 (4%)
Lymphoblastic lymphosarcoma without leukemia - M	0/48	1/49 (2%)	0/50 (0%)	0/49
Composite lymphosarcoma - M	1/48 (2%)	0/49	1/50 (2%)	0/49
Histiocytic sarcoma - M	0/48	1/49 (2%)	0/50	0/49
Total lymphoreticular neoplasms*	2/48 (4%)	6/49 (12%)	4/50 (8%)	2/49 (4%)
Females	0	190	955	5873
Lymphoreticular system				
Lymphoblastic lymphosarcoma with leukemia - M	1/50 (2%)	4/48 (8%)	5/49 (10%)	1/49 (2%)
Lymphoblastic lymphosarcoma without leukemia - M	0/50 (0%)	1/48 (2%)	0/49 (0%)	3/49 (6%)
Composite lymphosarcoma - M	3/50 (8%)	1/48 (2%)	1/49 (2%)	6/49 (12%)
Histiocytic sarcoma - M	0/50 (0%)	0/48 (0%)	0/49 (0%)	0/49 (0%)
* Total lymphoreticular neoplasms	3/50 (10%)	6/48 (13%)	6/49 (12%)	10/49 (20%)

*Sum of lymphoblastic lymphosarcoma, composite lymphosarcoma, and histiocytic sarcoma.
M malignant

informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423). Benign renal tubule adenomas were noted in mid- and high-dose males at incidences of 1/50 and 3/50 respectively. These neoplasms were not observed in females, lacked statistical significance, and were considered spontaneous and unrelated to glyphosate administration by the study pathologists; this neoplasm, while not seen in the concurrent control group, had previously been noted in control male CD-1 mice of comparable age by the author of the study. As an additional measure of diligence, a Pathology Working Group was convened, and it concluded that the absence of any pre-neoplastic kidney lesion in all male animals provided sufficient evidence that this finding was spurious and not related to glyphosate administration. This is reflected in the US EPA review of glyphosate (US EPA 1993). This neoplasm was not observed in the other four mouse carcinogenicity studies discussed.

The author of the study also reported a trend towards a non-statistically significant increased occurrence of lymphoreticular neoplasia in treated female mice (Table 15). However, these consisted of three different categories of lymphoreticular neoplasms. Regulatory reviews confirmed that there is no apparent dose-dependence for these endpoints (EC 2002, US EPA 1993, WHO/FAO 2004a). Summary tables of incidence of neoplastic findings are available (see data Supplementary Study 10 to be found online at <http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423>).

Glyphosate was reported as not carcinogenic in CD-1 mice up to doses well in excess of the limit dose for carcinogenicity testing, which is consistent with evaluations by the US EPA (US EPA 1993), European Commission (EC 2002), recent EU Annex I Renewal evaluation by the Rapporteur (Germany Rapporteur Member State 2015b), and WHO/FAO (WHO/FAO 2004a).

Study 11 (Chemnova 1993b)

Another carcinogenicity bioassay in mice was conducted between December 1989 and December 1991 (Table 16) (Chemnova 1993b). In this assay, 50 male and 50 female CD-1 mice per dose group received glyphosate via their diet over a period of approximately two years. This treatment period is 6 months longer than the 18 months stipulated for mice by OECD TG 451 (1981 version). The dietary levels were adjusted regularly to achieve constant dose levels of 0, 100, 300 and 1000 mg/kg bw/day, achieving the limit dose. This study was rated Kiimisch 1 for reliability.

Slight non-statistically significant increases in bronchiolar-alveolar adenomas were noted for all male dose groups above controls in a non-dose-responsive manner. Bronchiolar-alveolar neoplasms are evaluated in the context of the full data set (Tables 22 and 23), demonstrating a lack of dose-response across doses ranging from approximately 15 mg/kg bw/day to 5000 mg/kg bw/day. Although the number of pituitary adenomas were low and considered incidental, they were conservatively included in the select neoplasms, based on being slightly higher in high dose females than concurrent controls (Table 16). The data summary of all histological findings, including tumor incidence, is available (see data Supplementary Study 11 to be found online at <http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423>).

There were no statistically significant increases in the occurrence of any tumor type in this study. The observed variations did not show a dose relationship, and were within the range of historical control data. Glyphosate was determined to be not carcinogenic to CD-1 mice at up to 1000 mg/kg bw/day, which is consistent with evaluations by the European Commission (EC 2002) and WHO/FAO (WHO/FAO 2004a).

Table 16. Study 11 – Two-year feeding study with glyphosate in mice (Cheminova 1993b).

Study owner:	Cheminova (1993b)			
Reliability/Justification:	1 Study performed according to GLP and OECD guideline requirements			
Substance:	Glyphosate (98.6% pure)			
Species/Strain:	Mouse/CD-1, groups of 50 ♂ and 50 ♀			
Administration route:	Diet			
Concentration:	♂ + ♀: 0, 100, 300, 1000 mg/kg bw/day (regular adjustment of dietary concentration)			
Duration:	24 months			
Findings:	≥ 1000 mg/kg bw/day: NOAEL (♂+♀) no treatment-related effects			
Select neoplasms:	Bronchiolar-alveolar adenoma, bronchiolar-alveolar carcinoma, pituitary adenoma (females)			
		Dose (mg/kg bw/day)		
Males	0	10	300	1000
Bronchiolar-alveolar adenoma – B	9/50 (18%)	15/50 (30%)	11/50 (22%)	13/50 (26%)
Bronchiolar-alveolar carcinoma – M	10/50 (20%)	7/50 (14%)	8/50 (16%)	9/50 (18%)
		Dose (mg/kg bw/day)		
Females	0	100	300	1000
Bronchiolar-alveolar adenoma – B	7/50 (14%)	3/50 (6%)	3/50 (6%)	6/50 (12%)
Bronchiolar-alveolar carcinoma – M	3/50 (6%)	2/50 (4%)	1/50 (2%)	5/50 (10%)
Pituitary adenoma – B	1/41 (2%)	0/32	0/23	3/43 (6%)

B benign, M malignant

Study 12 (Arysta Life Sciences 1997a)

An 18-month feeding study in ICR-CD-1 mice, conducted between February 1995 and September 1996, investigated higher doses by admixing 1600, 8000, or 40 000 ppm glyphosate into the diet fed to groups of 50 male and 50 female mice per dose (Arysta Life Sciences 1997a). The calculated test substance intake was 165/153, 838/787, and 4348/4116 mg/kg bw/day (males/females, Table 17), exceeding the limit dose. This study was rated Klimisch 1 for reliability.

Histopathological examinations did not show statistically significant increases for any type of neoplastic lesion in all treatment groups of both sexes (see data Supplementary Study 12 to be found online at <http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423>). Select neoplasms evaluated across the data set with some non-

statistically significant increases above concurrent controls included lymphoma and lung tumors, all of which lacked a clear dose-response. Glyphosate was considered not carcinogenic in CD-1 mice up to doses well in excess of the limit dose for carcinogenicity testing, which is consistent with the recent evaluation in Europe under the Annex 1 Renewal of glyphosate (Germany Rapporteur Member State 2015b).

Study 13 (Feinchemie Schwebda 2001)

An 18-month feeding study in Swiss albino mice (Feinchemie Schwebda 2001), conducted between December 1997 and June 1999, featured treatment groups, each with 50 animals per sex, receiving 100, 1000, and 10 000 ppm technical grade glyphosate

Table 17. Study 12 – Two-year feeding study with glyphosate in mice (Arysta Life Sciences 1997a).

Study owner:	Arysta Life Sciences (1997b)			
Reliability/Justification:	1 Study performed according to GLP and OECD guideline requirements, with no deviations.			
Substance:	Glyphosate (94.6–97.6% pure)			
Species/Strain:	Mouse/CD-1, groups of 50 ♂ and 50 ♀			
Administration route:	Diet			
Concentration:	♂: 1600, 8000, or 40 000 ppm diet (♂ about 0, 165, 838, 4348 mg/kg bw/day; ♀ about 0, 153, 787, 4116 mg/kg bw/day)			
Duration:	18 months			
Findings:	8000/1600 ppm diet: NOAEL (♂/♀) 8000 ppm diet (♀): retarded growth 40 000 ppm diet: pale-colored skin ♂, loose stool, retarded growth, reduced food consumption and food efficiency, cecum distension and increased absolute and relative cecum weight, without histopathological findings of increased incidence of anal prolapse, consistent with histopathological erosion/ulcer of the anus			
Select neoplasms:	Lung adenoma, lung adenocarcinoma, lymphoma			
		Dose (mg/kg bw/day)		
Males	0	165	838	4348
Lung adenoma – B	8/50 (16%)	14/50 (28%)	13/50 (26%)	11/50 (11%)
Lung adenocarcinoma – M	1/50 (2%)	1/50 (2%)	6/50 (12%)	4/50 (8%)
Lymphoma – M	2/50 (4%)	2/50 (4%)	0/50	6/50 (12%)
		Dose (mg/kg bw/day)		
Females	0	153	787	4116
Lung adenoma – B	8/50 (16%)	5/50 (10%)	12/50 (24%)	5/50 (10%)
Lung adenocarcinoma – M	1/50 (2%)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Lymphoma – M	6/50 (12%)	4/50 (8%)	8/50 (16%)	7/50 (14%)

B benign, M malignant

Table 18. Study 13–18-Month feeding study with glyphosate in mice (Feinchemie Schwedda 2001).

Study owner:	Feinchemie Schwedda (2001)				
Reliability/Justification	2 Study performed according to GLP and OECD guideline requirements, with no deviations, but possible viral infection may have confounded interpretation of results				
Substance:	Glyphosate (>95% pure)				
Species/Strain	Mouse/Swiss albino, groups of 50 ♂ and 50 ♀				
Administration route:	Diet				
Concentration:	0, 100, 1000, 10 000 ppm diet (♂ about 0, 14.5, 150, 1454 mg/kg bw/day, ♀ about 0, 15.0, 151, 1467 mg/kg bw/day)				
Duration:	18 months				
Findings:	1000 ppm diet: NOAEL (♂ + ♀) 10 000 ppm diet (♂ + ♀): increased mortality Bronchiolar/alveolar adenoma, lymphoma				
Select neoplasms:	Bronchiolar/alveolar adenoma, lymphoma				
	Historical controls		Dose (mg/kg bw/day)		
		0	14.5	150	1454
Males					
Mortality	†11/50–27/50	22/50 (6)	20/50 (6)	22/50 (8)	27/50 (8)
Findings for dead and moribund sacrificed animals					
Lymphoma – M	*20/75	26.7% [0–44]	9/22 (41.0%)*	*13/22 (59.0%)*	13/27 (48.0%)*
Findings in animals sacrificed at termination					
Lymphoma – M	26/175	14.9% [8–24]	1/28 (3.6%)	3/30 (10.0%)	3/28 (10.7%)
Total animals					
Lymphoma – M	46/250	18.4% [6–30]	10/50 (20.0%)	15/50 (30.0%)	16/50 (32.0%)*
			Dose (mg/kg bw/day)		
			15.0	151	1467
Females					
Mortality	12/50–20/50	16/50 (7)	16/50 (7)	20/50 (2)	20/50 (3)
Findings for dead and moribund sacrificed animals					
Bronchiolar/alveolar adenoma – B	–	0/16	0/16	1/20 (5%)	2/20 (10%)
Lymphoma – M	49/77	63.6% [0–100]	9/16 (56.0%)	10/16 (63.0%)	13/20 (65.0%)*
Findings in animals sacrificed at termination					
Bronchiolar/alveolar adenoma – B	–	1/34 (3%)	0/0	1/1 (100%)	1/30 (3%)
Lymphoma – M	50/175	28.9% [20–43]	9/34 (26.5%)	10/30 (29.4%)*	6/30 (20.0%)*
Total animals					
Bronchiolar/alveolar adenoma – B	–	1/50 (2%)	0/16	2/21 (10%)	3/50 (6%)
Lymphoma – M	99/250	39.6% [14–58]	18/50 (36.0%)	20/50 (40.0%)	19/50 (38.0%)*

B benign, M malignant.

†Nine studies, performed by the same laboratory in the timeframe encompassing the study summarized here.

* (Number of animals killed in extremis)

*Five studies, conducted in the same laboratory between 1996 and 1999.

*Statistically higher than concurrent controls ($p < 0.05$).

in the diet. Control mice received a plain diet. The calculated test substance intake was 14.5/15.0, 150/151, 1454/1467 mg/kg bw/day (males/females, Table 18), exceeding the limit dose, as reflected in elevated mortality in the high dose groups. This study was rated Klimisch 2 for reliability, based on speculation of a viral infection within the colony, discussed below.

Based on the slightly higher mortality and lower survival rates in the high dose groups, the NOAEL was considered 1000 ppm (151 mg/kg bw/day). There were no treatment-related effects on clinical signs, behavior, eyes, body weight, body weight gain, food consumption, and differential white blood cell counts in both sexes. Gross pathology, organ weight data, and histopathological examination demonstrated no treatment-related effects. An increase in the number of malignant lymphomas, the most common spontaneously occurring tumor category in the mouse, was statistically significant in the high-dose groups compared to controls (Table 18). The Germany Rapporteur Member State concluded that the malignant lymphoma increase in high-dose males was inconclusive but unrelated to treatment in the context of similar higher dosed studies (Germany Rapporteur Member State 2015h), and considered this endpoint irrelevant to carcinogenic risk in humans (Germany Rapporteur Member State

2015a). Whether or not a viral component (Taddesse-Heath et al. 2000) may have contributed to this endpoint, the finding was considered incidental background variation based on historical control data, and in agreement with the study director. As in Study 11, bronchiolar-alveolar adenoma was also considered a select neoplasm for evaluation in the broader data set (Tables 22 and 23), and as previously discussed, demonstrates a lack of dose-response across doses ranging from approximately 15 mg/kg bw/day to 5000 mg/kg bw/day. Summary tables of all histopathological neoplastic findings are available (see data Supplementary Study 13 to be found online at <http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423>).

Technical grade glyphosate was reported as not carcinogenic in Swiss albino mice, following continuous dietary exposure of up to 1460 mg/kg bw/day (average for both sexes) for 18 months. The NOAEL for general chronic toxicity was 151 mg/kg bw/day for both sexes combined.

Study 14 (Nufarm 2009a)

The most recent mouse carcinogenicity assay was conducted between October 2005 and November 2007 (Nufarm 2009a).

Table 19. Study 14–18-Month feeding study with glyphosate in mice (Nufarm 2009a).

Study owner:	Nufarm (2009b)			
Reliability/Justification:	1 Study performed according to GLP and OECD guideline requirements, with no deviations			
Substance:	Glyphosate (94.6–97.6% pure)			
Species/Strain:	mouse/CD-1, groups of 51 ♂ and 51 ♀			
Administration route:	Diet			
Concentration:	0, 500, 1500, and 5000 ppm diet (♂ about 0, 0, 71–4, 234, 810 mg/kg bw/day; ♀ about 0, 97.9–300, 1081 mg/kg bw/day)			
Duration:	18 months			
Findings:	≥ 5000 ppm diet: NOAEL (♂/♀) No treatment-related effects			
Select neoplasms:	Bronchiolar-alveolar adenoma, Bronchiolar-alveolar adenocarcinoma, hepatocellular adenoma (males), hepatocellular carcinoma (males), lymphoma, pituitary adenoma (females)			
		Dose (mg/kg bw/day)		
Males	0	157	814	4841
Bronchiolar-alveolar adenoma – B	9/51 (18%)	7/51 (14%)	9/51 (18%)	4/51 (8%)
Bronchiolar-alveolar adenocarcinoma – M	5/51 (10%)	5/51 (10%)	7/51 (14%)	11/51 (22%)
Hepatocellular adenoma – B	1/51 (2%)	1/51 (2%)	4/51 (8%)	2/51 (4%)
Hepatocellular carcinoma – M	6/51 (12%)	11/51 (22%)	7/51 (14%)	4/51 (8%)
Lymphoma – M	0/51	1/50 (2%)	2/51 (4%)	5/51 (10%)
		Dose (mg/kg bw/day)		
Females	0	190	955	5873
Bronchiolar-alveolar adenoma – B	2/51 (4%)	4/51 (8%)	2/51 (4%)	2/51 (4%)
Bronchiolar-alveolar adenocarcinoma – M	5/51 (10%)	2/51 (4%)	2/51 (4%)	3/51 (6%)
Lymphoma – M	11/51 (22%)	8/51 (16%)	10/51 (20%)	11/51 (22%)
Pituitary adenoma – B	0/51	1/50 (2%)	0/51	2/51 (4%)

B benign, M malignant

Groups of 51 CD-1 mice per sex received daily dietary doses of 0, 500, 1500, and 5000 ppm technical grade glyphosate (equivalent to an average intake of 85, 267 and 946 mg/kg bw/day, Table 19). The MTD was apparently not reached in the high-dose group, which is more indicative of low general toxicity of the test substance rather than a flaw in the study design. The NOAEL for chronic toxicity was 810 mg/kg bw/day for male mice and 1081 mg/kg bw/day for female mice, the highest dosage tested. Despite not quite achieving a limit dose in males, this study was arguably rated Klimisch 1 for reliability.

Several increases in common spontaneous mouse neoplasms in male mice were noted. Non-dose-response increases were noted for hepatocellular adenoma and carcinoma in males, and dose-responses were noted for bronchiolar-alveolar adenocarcinoma and malignant lymphoma in males, but not females. Pituitary adenoma incidences were low, and considered incidental in low and high-dose females, although they were slightly higher than controls (Table 19). These neoplasms were all evaluated in context of the broader data set (Tables 22 and 23). The summary of neoplastic findings is available (see data Supplementary Study 14 to be found online at <http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423>).

Glyphosate was considered not carcinogenic in the CD-1 mice, following continuous average dietary exposure for males and females, to quantities up to 945.6 mg/kg bw/day for 18 months, which is consistent with the recent evaluation in Europe under the Annex 1 Renewal of glyphosate (Germany Rapporteur Member State 2015b).

Discussion

An extraordinarily large volume of animal data has been compiled to evaluate the carcinogenic potential of glyphosate.

The expected normal biological variability for spontaneous tumor formation is reflected across this extensive data set (Tables 20–23). However, no specific neoplasm stands out as a consequence of glyphosate exposures. While some individual studies may note an increase in a specific neoplasm at the high dose, the pooled data fail to identify any consistent pattern of neoplasm formation, demonstrating that the effect is not reproducible and not treatment-related. The lack of a dose-response across the several orders of magnitude suggests that no individual tumor of single etiology is attributable to glyphosate administration.

Glyphosate has undergone repeated and extensive review by the United States Environmental Protection Agency (US EPA 1993), the European Union (EC 2002, Germany Rapporteur Member State 2015b) and the World Health Organization/Food and Agriculture Organization of the United Nations (WHO/FAO 2004b, WHO/FAO 2004a). With regard to potential carcinogenic effects of glyphosate, the unanimous outcome of these reviews has been that the data provide sufficient evidence to conclude that glyphosate should not be considered a carcinogen. Genotoxicity studies with glyphosate, conducted under conditions stipulated by internationally accepted testing guidelines and GLP, as reviewed in 2000 (Williams et al. 2000) and recently updated (Kier and Kirkland 2013), indicate that glyphosate clearly does not exhibit the properties of a DNA-reactive genotoxic carcinogen. This lack of mutagenicity rules out an important concern for carcinogenicity.

Mink et al. published a review of the available epidemiological studies that investigated possible associations between glyphosate and cancer diagnosed in humans (Mink et al. 2012). No evidence was found for a statistically significant positive association between cancer and exposure to glyphosate. While one Agricultural Health Study (AHS) publication mentions a "suggested association" between glyphosate use and multiple myeloma (De Roos et al. 2005), a later summary of AHS

Table 20. Summary of select neoplasms in male rats (Studies 1–8).

Select neoplasm	Tumor incidence/number of animals examined, by dose (mg/kg bw/day)											
	Controls – 0 [% range for studies]	^a 3	^a 7.4	^a 10	^a 10	^a 31	^a 73.9	^a 86	^a 89	^a 100	^a 104	^a 121
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	1/75	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	^a 1/51	5/58	1/17	10/74	^a 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	20/50	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

Select neoplasm	Tumor incidence/number of animals examined, by dose (mg/kg bw/day)													
	^a 150	^b 285	^c 300	^c 354	^c 361	^b 362	^a 740.6	^e 780	^b 940	^a 1000	^b 1077	^a 1127	^a 1214	^a 1290
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	^a 0/51	2/21	5/79	^a 1/63	8/58	1/50	NF	7/60	8/49	^a 3/51	6/78	^a 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	2/78	1/63	NF

^aStudy 1 (Monsanto) (CD) SD rats, rated unreliable for carcinogenicity evaluation.
^bStudy 2 (Monsanto) (CD) SD rats, including interim sacrifice groups.
^cStudy 3 (Chemnova) SD rats.
^dStudy 4 (Feinchemie Schwedda) Wistar rats.
^eStudy 5 (Excel) SD rats, rated unreliable for carcinogenicity evaluation.
^fStudy 6 (Arysta Life Sciences) Crj:CD SD rats, including interim sacrifice groups.
^gStudy 7 (Syngenta) Alpk:AP,SD Wistar rats, including interim sacrifice groups.
^hStudy 8 (Nufarm) Wistar Han Crj:WI rats.
^aRecorded as parafollicular adenoma.
 NF not found/not reported.

Table 21. Summary of select neoplasms in female rats (Studies 1–8).

Select neoplasm	Tumor incidence/number of animals examined, by dose (mg/kg bw/day)											
	Controls – 0 [% range for studies]	^a 3	^a 7.4	^a 10	^a 11	^a 34	^a 73.9	^a 100	^a 105	^b 113	^a 115	^a 145
Pancreas islet cell adenoma	11/397 [0–9]	1/50	0/23	2/27	1/50	0/49	0/16	2/29	0/51	1/60	2/79	0/63
Pituitary adenoma	246/397 [14–78]	29/48	13/33	19/28	31/50	26/49	7/23	19/29	23/51	48/60	54/79	44/63
Pituitary carcinoma	16/155 [2–17]	7/48	NF	5/28	5/50	12/49	NF	5/28	NF	0/60	NF	NF
Thyroid C cell adenoma	25/302 [3%–16%]	3/49	0/24	1/27	6/50	3/47	1/17	1/29	^a 1/51	2/60	7/78	^a 0/63
Hepatocellular adenoma	22/302 [0–36]	NF	18/48	1/50	NF	NF	19/49	3/50	0/51	2/60	1/79	0/64
Hepatocellular carcinoma	14/210 [0–20]	0/50	15/48	0/50	0/50	2/50	14/49	0/50	0/51	0/60	NF	NF
Mammary gland fibroadenoma	113/384 [6–58]	16/46	NF	12/28	20/48	16/44	NF	17/29	9/51	^a 24/54	30/79	4/63
Mammary gland adenocarcinoma	40/334 [2–22]	6/46	0/30	NF	5/48	8/44	0/33	NF	3/51	10/54	8/79	0/63

Select neoplasm	Tumor incidence/number of animals examined, by dose (mg/kg bw/day)													
	^a 210	^a 300	^b 349	^c 393	^a 437	^a 457	^a 740.6	^a 1000	^a 1060	^b 1183	^a 1247	^b 1382	^a 1498	^a 1740
Pancreas islet cell adenoma	NF	2/29	0/51	1/78	1/64	4/60	1/49	1/49	NF	0/59	1/78	0/51	0/64	NF
Pituitary adenoma	NF	25/30	16/51	47/77	46/63	46/60	6/50	34/49	NF	34/59	52/78	32/51	49/64	NF
Pituitary carcinoma	NF	2/30	NF	NF	NF	0/60	NF	7/49	NF	1/59	NF	NF	NF	NF
Thyroid C cell adenoma	NF	2/29	^a 1/50	8/76	^a 0/64	6/60	1/47	7/49	NF	6/60	4/78	^a 0/51	^a 2/64	NF
Hepatocellular adenoma	NF	1/50	1/51	0/78	1/64	6/60	13/50	2/50	NF	1/60	0/78	1/51	0/64	NF
Hepatocellular carcinoma	NF	0/50	1/51	NF	NF	1/60	9/50	0/50	NF	2/60	NF	0/51	NF	NF
Mammary gland fibroadenoma	1/22	19/30	7/51	27/77	6/64	^a 27/59	NF	20/50	5/22	^a 28/57	30/78	5/51	5/64	5/50
Mammary gland adenocarcinoma	0/22	NF	1/51	11/77	0/64	^a 14/59	0/48	NF	0/22	9/57	8/78	6/51	2/64	0/50

^aStudy 1 (Monsanto) (CD) SD rats, rated unreliable for carcinogenicity evaluation.
^bStudy 2 (Monsanto) (CD) SD rats, including interim sacrifice groups.
^cStudy 3 (Chemnova) SD rats.
^dStudy 4 (Feinchemie Schwedda) Wistar rats.
^eStudy 5 (Excel) SD rats, rated unreliable for carcinogenicity evaluation.
^fStudy 6 (Arysta Life Sciences) Crj:CD SD rats, including interim sacrifice groups.
^gStudy 7 (Syngenta) Alpk:AP,SD Wistar rats, including interim sacrifice groups.
^hStudy 8 (Nufarm) Wistar Han Crj:WI rats.
^aRecorded as adenoma/adenofibroma/fibroma.
^bRecorded as carcinoma/adenocarcinoma.
 NF not found/not reported.

Table 22. Summary of select neoplasms in male mice (Studies 10–14).

Select neoplasm	Tumor incidence/number of animals examined, by dose (mg/kg bw/day)							
	Controls – 0 [% range for studies]	^a 14.5	^a 85	^b 100	^d 150	^e 157	^e 165	^e 267
Bronchiolar-alveolar adenoma	31/249 [10–18]	2/22	^b 7/51	15/50	0/22	9/50	^b 14/50	^d 9/51
Bronchiolar-alveolar adenocarcinoma	10/149 [2–10]	NF	^b 5/51	NF	NF	3/50	^b 1/50	^d 7/51
Bronchiolar-alveolar carcinoma	10/100 [0–20]	0/22	NF	7/50	0/22	NF	NF	NF
Hepatocellular adenoma	27/250 [0–28]	5/25	1/51	12/50	3/28	0/50	15/50	4/51
Hepatocellular carcinoma	15/250 [0–16]	0/25	11/51	5/50	0/28	0/50	1/50	7/51
Malignant lymphoma	16/205 [0–100]	15/50	1/51	2/4	16/50	^e 5/50	2/50	2/51
Myeloid leukemia	3/101 [0–6]	1/50	1/51	NF	1/50	NF	NF	0/51

Select neoplasm	Tumor incidence/number of animals examined, by dose (mg/kg bw/day)							
	^b 300	^a 814	^a 838	^a 946	^b 1000	^d 1454	^e 1348	^e 4841
Bronchiolar-alveolar adenoma	11/50	9/50	^b 13/50	^b 4/51	13/50	1/50	^b 11/50	9/50
Bronchiolar-alveolar adenocarcinoma	NF	2/50	^b 6/50	^b 11/51	NF	NF	^b 4/50	1/50
Bronchiolar-alveolar carcinoma	8/50	NF	NF	NF	9/50	1/50	NF	NF
Hepatocellular adenoma	11/50	1/50	15/50	2/51	9/50	3/50	7/50	0/50
Hepatocellular carcinoma	6/50	0/50	3/50	4/51	7/50	2/50	1/50	2/50
Malignant lymphoma	1/1	^a 4/50	0/50	5/51	6/8	19/50	6/50	^b 2/50
Myeloid leukemia	NF	NF	NF	0/51	NF	1/50	NF	NF

^aStudy 10 (Monsanto) CD-1 mice.^bStudy 11 (Chemnova) CD-1 mice.^cStudy 12 (Arysta Life Science) CD-1 mice.^dStudy 13 (Feinchemie Schwabed) Swiss albino mice.^eStudy 14 (Nufarm) CD-1 mice.^fRecorded as lung rather than bronchiolar-alveolar.^gRecorded as sum of malignant lymphoblastic lymphosarcoma with leukemia, lymphoblastic lymphosarcoma without leukemia and composite lymphosarcoma.^hRecorded as lymphoblastic lymphosarcoma with leukemia.

NF not found/not reported.

results note that there were no associations between glyphosate use and a number of cancers, including lymphohematopoietic cancers, leukemia, NHL, and multiple myeloma (Weichenthal et al. 2010). A subsequent reanalysis of AHS data obtained under the Freedom of Information Act notes no suggestion of an association between glyphosate use and multiple myeloma, with a relative risk of 1.1 and 95% and a confidence interval of 0.5–2.9 (Sorahan 2012). A recent review paper (Alavanja et al.

2013) cites another epidemiology study claiming an association between glyphosate use and NHL (Eriksson et al. 2008), but this research is strongly criticized in the recent Reevaluation Assessment Report for glyphosate Annex 1 Renewal in Europe (Germany Rapporteur Member State 2015b), highlighting potential referral bias, selection bias, uncontrolled confounding, limited data usage contrary to claims of including all new cases (living cases only, rather than living

Table 23. Summary of select neoplasms in female mice (Studies 10–14).

Select neoplasm	Tumor incidence/number of animals examined, by dose (mg/kg bw/day)							
	Controls – 0 [% range for studies]	^d 15.0	^a 85	^b 100	^d 151	^e 153	^e 190	^e 267
Bronchiolar-alveolar adenoma	28/250 [2–20]	0/16	^b 4/51	3/49	2/21	^b 5/50	9/50	^b 2/51
Bronchiolar-alveolar adenocarcinoma	2/99 [2]	NF	^b 2/51	NF	NF	^b 2/50	3/50	^b 2/51
Bronchiolar-alveolar carcinoma	9/151 [2–10]	0/16	NF	2/49	0/20	NF	NF	NF
Malignant lymphoma	54/215 [10–100]	20/50	8/51	12/15	19/50	4/50	^b 6/50	10/51
Myeloid leukemia	2/156 [0–4]	1/50	0/51	NF	2/50	0/50	NF	1/51
Pituitary adenoma	1/232 [0–2]	0/16	1/51	0/32	0/17	1/50	0/21	0/51

Select neoplasm	Tumor incidence/number of animals examined, by dose (mg/kg bw/day)							
	^b 300	^a 787	^a 946	^a 955	^b 1000	^d 1467	^e 1116	^e 5874
Bronchiolar-alveolar adenoma	3/50	^b 12/50	^b 2/51	10/49	6/50	3/50	^b 5/50	1/50
Bronchiolar-alveolar adenocarcinoma	NF	^b 3/50	^b 3/51	4/49	NF	NF	^b 1/50	4/50
Bronchiolar-alveolar carcinoma	1/50	NF	NF	NF	5/50	0/50	NF	NF
Malignant lymphoma	9/12	8/50	11/51	^b 6/50	13/14	25/50	7/50	^b 10/50
Myeloid leukemia	NF	0/50	0/51	NF	NF	1/50	1/50	NF
Pituitary adenoma	0/23	0/50	2/51	0/44	3/50	1/48	0/50	0/37

^aStudy 10 (Monsanto) CD-1 mice.^bStudy 11 (Chemnova) CD-1 mice.^cStudy 12 (Arysta Life Science) CD-1 mice.^dStudy 13 (Feinchemie Schwabed) Swiss albino mice.^eStudy 14 (Nufarm) CD-1 mice.^fRecorded as lung rather than bronchiolar-alveolar.^gRecorded as sum of lymphoblastic lymphosarcoma with leukemia, lymphoblastic lymphosarcoma without leukemia and composite lymphosarcoma.^h2 animals in anterior lobe, 1 animal in intermediate lobe.

NF not found/not reported.

plus dead), and questionable definition/interpretation of dose-response. It is important to note that the Eriksson et al. study did detect statistically significant positive associations for small lymphocytic lymphoma/chronic lymphocytic leukemia and “unspecified NHL”, while the following lymphomas were not statistically significantly associated with glyphosate use: B-cell lymphomas, grade I-III follicular lymphoma, diffuse large B-cell lymphoma, other specified B-cell lymphomas, unspecified B cell lymphomas, and T-cell lymphomas (Eriksson et al. 2008). As previously discussed, statistically significant associations need to be evaluated further for study bias, confounders and sampling error, before expending resources and energy on further evaluation of potential causality.

Epidemiological investigations face the difficulty of reliably determining the magnitude of exposure to the chemical in question, while ruling out confounders like co-exposure to other chemicals, and environmental and lifestyle factors. In contrast, carcinogenicity studies in experimental animals, when conducted according to appropriate testing guidelines, are designed in a fashion that allows a direct association between observed effects and substance exposure, yet the relevance of observed findings to humans is an important consideration. This manuscript collectively presents the scientific community with carcinogenicity results from a remarkably large body of data from fourteen long-term carcinogenicity studies on glyphosate.

Glyphosate is of very low acute toxicity with an oral LD₅₀ in the rat in excess of 5000 mg/kg of body weight. The sub-chronic NOAEL is 400 mg/kg bw/day, and is based on effects that do not impair long-term survival (WHO/FAO 2004b, WHO/FAO 2004a). This allows administration of very high glyphosate doses to rodents for a prolonged time. Dietary levels of up to 30 000 and 40 000 milligrams of glyphosate per kilogram of diet have been administered to rats and mice, respectively, in chronic feeding studies covering their expected lifespan without apparent effects on longevity.

One of the most critical aspects of designing a carcinogenicity study is the choice of dose levels, especially the top dose, at either the limit dose or MTD. The relevant OECD TGs 451 and 453 for carcinogenicity studies propose a body

weight depression of approximately 10% as evidence for systemic toxicity. This is equivalent to the concept of the MTD, which is discussed in a supporting OECD guidance document (OECD 2012b). For chemicals which are well tolerated by the experimental animal, where no dose-limiting toxicity is observed, the respective OECD guidance suggests 1000 mg/kg bw/day as the highest dose level (OECD 2012a). Many of the carcinogenicity studies performed in rats and mice with glyphosate have been conducted with the high dose group receiving levels of glyphosate at, or in excess of the limit dose because of its very low toxicity following repeat exposure. Following this extensive testing, even at very high exposure levels, there was no evidence of a carcinogenic effect related to glyphosate treatment. The select neoplasms highlighted in Tables 20–23 show normal biological background levels of spontaneous neoplasms, with lack of dose-response across the data sets. The combined studies clearly indicate that glyphosate’s carcinogenic potential is extremely low or non-existent in animal models up to very high doses.

By way of comparison, the worst-case calculated human dietary exposure to glyphosate, the Theoretical Maximum Daily Intake (TMDI) is 0.14 mg/kg bw/day (EFSA 2012). Systemic exposure of operators, as assessed for the EU reapproval of glyphosate, is predicted to be between 0.0034 (German BBA model, tractor-mounted ground-boom sprayer) and 0.226 mg/kg bw/day (UK POEM, hand-held-spraying to low targets, data not shown). The model estimates are supported by human biomonitoring data in farmers showing systemic exposures of 0.004 and 0.0001 mg/kg/day for worst-case and mean acute doses, respectively (Acquavella et al. 2004). The high doses in chronic rodent studies at which no evidence of carcinogenicity is demonstrated are at least hundreds of thousands fold greater than peak human systemic exposure levels. Clearly, there is no scientific basis for concern of carcinogenic risk to humans resulting from glyphosate exposure.

With over 40 years of scientific research on glyphosate, no compelling evidence exists for a mechanism for glyphosate to cause cancer. Mammalian metabolism does not activate glyphosate to a toxic metabolite (Anadon et al. 2009, WHO/FAO 2004a). The lack of glyphosate DNA reactivity supports the

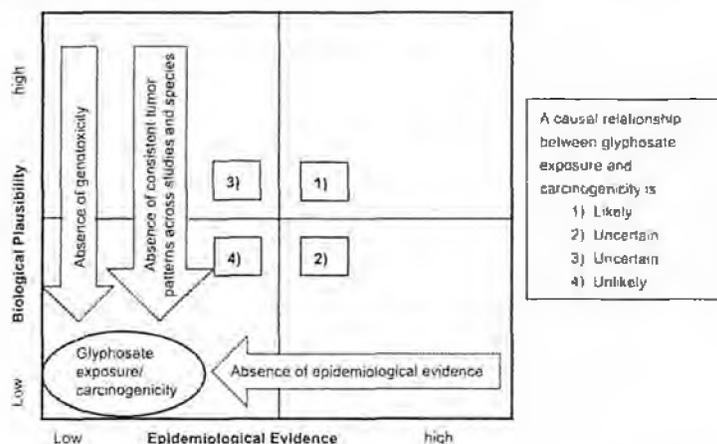


Figure 2. Likelihood of glyphosate carcinogenicity based on experimental and epidemiological data, a causal inference grid as proposed by Adami et al. (2011) to utilize both toxicological and epidemiological data.

lack of potential for an initiation event for carcinogenesis (Kier and Kirkland 2013). Clearly, there is a lack of potential for glyphosate to induce hormonal oncogenesis, based on both the tumor incidence data presented and the unequivocal evidence that glyphosate is not an endocrine disruptor (Bailey et al. 2013, Levine et al. 2012, Salmiras and Tobia 2012, Webb et al. 2013, Williams et al. 2012).

The absence of test substance-related neoplastic findings in a total of 14 rodent cancer bioassays with glyphosate is in stark contrast to the recent dramatic media reports, internet postings, and YouTube videos of rat tumors, hypothesized to be caused by treatment with maize containing glyphosate residue or drinking water spiked with a glyphosate formulation (Seralini et al. 2014). Such reports, under the scrutiny of the global scientific community, demand greater data transparency and accountability within the peer review process.

The absence of a glyphosate-related mechanism for carcinogenesis, the huge volume of genotoxicity data studies indicating no likely mutagenic or DNA-reactive potential (Kier and Kirkland 2013), combined with the lack of epidemiological evidence for glyphosate-induced cancer (Mink et al. 2012), and the lack of carcinogenicity in multiple rodent carcinogenicity assays, are depicted in a causal inference grid in Figure 2, as put forth by Adami et al. (Adami et al. 2011). The overwhelming weight of the available evidence, demonstrating a lack of both biological plausibility and epidemiological effects, draws a compelling conclusion that glyphosate's carcinogenic potential is extremely low or non-existent.

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Declaration of interest

The employment affiliation of the authors is as shown on the cover page. Volker Mostert was an employee of the consulting group, Dr. Knecht Consult GmbH, involved in the preparation of the recent glyphosate Annex I Renewal dossier for the Glyphosate Task Force (GTF; a consortium of European glyphosate registrants <http://www.glyphosatetaskforce.org/>). Helmut Greim was funded as an independent consultant for his expert contributions to this manuscript. David Salmiras and Christian Strupp are employed by member companies of the GTF, Monsanto and ADAMA Agricoltura B.V. (formerly Feinchemie Schwebda GmbH) respectively. David Salmiras is also Chair of the Toxicology Technical Working Group of the GTF. Christian Strupp is an expert member of the Toxicology Technical Working Group of the GTF. Monsanto Company was the original producer and marketer of glyphosate formulations. The authors had sole responsibility for the writing and content of the paper and the interpretations and opinions expressed in the paper are those of the authors and may not necessarily be those of the member companies of the Glyphosate Task Force.

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Supplementary material available online

Data Supplementary Study 1–14.

REVIEW ARTICLE

Review of genotoxicity biomonitoring studies of glyphosate-based formulations

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Abstract

Human and environmental genotoxicity biomonitoring studies involving exposure to glyphosate-based formulations (GBFs) were reviewed to complement an earlier review of experimental genotoxicity studies of glyphosate and GBFs. The environmental and most of the human biomonitoring studies were not informative because there was either a very low frequency of GBF exposure or exposure to a large number of pesticides without analysis of specific pesticide effects. One pesticide sprayer biomonitoring study indicated there was not a statistically significant relationship between frequency of GBF exposure reported for the last spraying season and oxidative DNA damage. There were three studies of human populations in regions of GBF aerial spraying. One study found increases for the cytokinesis-block micronucleus endpoint but these increases did not show statistically significant associations with self-reported spray exposure and were not consistent with application rates. A second study found increases for the blood cell comet endpoint at high exposures causing toxicity. However, a follow-up to this study 2 years after spraying did not indicate chromosomal effects. The results of the biomonitoring studies do not contradict an earlier conclusion derived from experimental genotoxicity studies that typical GBFs do not appear to present significant genotoxic risk under normal conditions of human or environmental exposures.

Abbreviations: BC, blood cells; BM, blood monocyte cells; BNMN, binucleated cells with micronuclei; CBMN, cytokinesis-block micronucleus; CA, chromosomal aberrations; GBF, glyphosate-based formulation; MN, micronucleus; MOMN, mononuclear cells with micronuclei; SCE, sister chromatid exchange; 8-OHdG, 8-hydroxydeoxyguanosine

Keywords

biomonitoring, formulation, genotoxicity, glyphosate, mutagenicity

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Introduction

Glyphosate is the active ingredient of very extensively used herbicide formulations and, accordingly, glyphosate and glyphosate-based formulations (GBFs) have been extensively studied for their toxic properties. One of these toxic properties is genotoxicity and there has been a recent extensive review of glyphosate and GBF experimental genotoxicity studies (Kier and Kirkland 2013). This review concluded that there was a strong weight of evidence that glyphosate and GBFs are predominantly negative in well-conducted core bacterial reversion and *in vivo* mammalian micronucleus and chromosomal aberration assays. Although some positive results for glyphosate and GBFs were reported in DNA damage assays and for the micronucleus endpoint for GBFs in non-mammalian studies, the positive results were associated with high dose levels and/or toxic effects. The preponderance of negative results in core assays supports the conclusion that reports of DNA damage or non-mammalian micronucleus effects are likely to be secondary to cytotoxicity rather than indicative of DNA-reactive mechanisms. This conclusion is consistent with and supported by a recent review of 14 experimental rodent carcinogenicity studies of glyphosate that indicated a weight of evidence that there was no carcinogenic effect related to glyphosate treatment (Greim et al. 2015).

The earlier Kier and Kirkland (2013) review focused on experimental studies and did not consider reports of human

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or environmental biomonitoring studies where there was GBF exposure. This review complements the earlier review by identifying and considering a number of human and environmental biomonitoring studies where exposure to GBFs was indicated and one or more genotoxicity endpoints were employed. Such studies can provide perspective on potential for effects on humans or other organisms with actual environmental or occupational exposures. However, they are also much more complicated to interpret and derive definitive conclusions from than experimental studies because of confounding exposures to other agents, complexity of applying methodology to subject populations and limits on availability of endpoints and sample sizes.

Identification of published studies

The published studies for review consideration were identified by literature searches for published reports containing references to glyphosate or GBFs (e.g., Roundup™ formulation) that also contained searchable terms which indicated that human or environmental genotoxicity studies were performed (e.g., alkaline single cell gel electrophoresis (comet) or micronucleus endpoints). Emphasis was placed on publications in peer-reviewed journals. Abstracts or other sources with incomplete information were not considered. Reviews without original data were not considered for evaluation; however, these reviews were examined to determine if there were any cited publications that had not been detected in the literature searches.

General methodology

Populations

Table 1 summarizes the identified genotoxicity biomonitoring studies involving GBF exposure. Most of these studies are cross-sectional studies in which genotoxicity biomarkers in an exposed population were compared to an unexposed referent population. A few studies are longitudinal studies where sampling was made before and after exposures (Lebailly et al. 2003, Bolognesi et al. 2009). For cross-sectional studies, a suitable sample size and a carefully matched referent population are important (Albertini et al. 2000, Collins et al. 2014). Although sample size should ideally be defined in reference to a pre-determined desired sensitivity, this does not appear to have been rigorously considered in the identified studies. A few of the studies had quite small (e.g., < 25) exposed and referent population sizes (e.g., Gregio D'Arce and Colus 2000, Vlastos et al. 2006, Paz-y-Minu et al. 2007, Bortoli et al. 2009).

Careful matching of exposed and referent populations for cross-sectional studies requires consideration of the specific endpoint and confounding factors that might affect the endpoint. Recommendations of major endpoint specific factors include gender and age for the CBMN endpoint (Battershill et al. 2008, Fenech et al. 2011), age for the buccal micronucleus (MN) endpoint (Bonassi et al. 2011), and gender, age and smoking status for the comet endpoint in blood cells (Collins et al. 2014). For genotoxicity endpoints, a large number of other factors may also be considered as possible confounding variables such as diet (Bonassi et al. 2011, Fenech et al. 2011, Collins et al. 2014), sleep (Kahan et al. 2010, Tenorio et al. 2013), disease status (Albertini et al. 2000, Battershill et al. 2008, Fenech et al. 2011), and seasonal variation (Albertini et al. 2000, Moller 2005, Verschaeve et al. 2007).

Many of the human biomonitoring studies had similar gender, age and usually smoking and alcohol consumption distributions for their exposed and referent populations. Although many of the studies indicated that information on lifestyle or other factors was collected (e.g., medical history and treatments, X-ray exposures and diet), most of the studies did not present comprehensive detailed data on these confounding factors. Some of the studies had moderate to fairly large differences in gender distribution (Bolognesi et al. 2002, 2004, Pastor et al. 2003, Simonelli et al. 2008, Benedetti et al. 2013, Koureas et al. 2014). One factor recommended for recording of the blood cell comet endpoint in human biomonitoring studies is exercise (Collins et al. 2014); however, the cross-sectional studies employing the comet endpoint did not appear to explicitly consider this as a confounding variable.

Exposures

Human exposures were usually characterized by self-reporting of the types of pesticides used as determined by survey of the exposed population or by more general use information. Additionally, the use of personal protective equipment may have been indicated. In most cases pesticides were characterized only by the active ingredient and not as a specific formulation. In some cases the extent of individual pesticide use was described as a frequency of use and/or amount of use but in most cases there were exposures to multiple pesticides. There are only a few biomonitoring studies where some assessment of the specific effects of exposures to GBFs can be inferred from the circumstances or exposure data presented. The identified studies only rarely attempted to estimate actual amount of exposure to specific pesticides or to evaluate exposure by chemical monitoring. No cases of chemical monitoring of exposure to glyphosate or GBFs were encountered in the genotoxicity biomonitoring studies. Uncertainty in extent and amount of exposure and dose is a major limitation in interpretation of the genotoxicity biomonitoring studies of pesticide exposure.

Endpoints

The most common endpoints employed in the biomonitoring studies were the CBMN assay on cultured lymphocytes (six human studies), the micronucleus assay on buccal cells (six human studies) and the comet assay on blood cells (five human studies and one environmental study). Other endpoints included measurement of sister chromatid exchange (SCE) in cultured lymphocytes (three human studies), chromosomal aberration in cultured lymphocytes (three human studies), erythrocyte micronucleus assays (two environmental studies), and bacterial reversion (Ames test strains) on urine (one human study). Two human studies measured DNA alterations (bulky adducts and oxidative DNA damage).

The CBMN assays generally used similar standardized methodologies for culture, including addition of cytochalasin B at 44 h after phytohemagglutinin stimulation. The studies used whole blood rather than isolated leukocytes for culture and scored 1000 or 2000 binucleated cells per subject for micronuclei. Referent population frequencies of binucleated cells with micronuclei (BNMN) ranged from about 1.8 to 9 per 1000 which seems reasonably close to a mean of 6.5 per

Table 1. Studies of human and environmental populations with reported GBF exposure.

Exposed population ^a	Endpoint ^b	Pesticide/GBF exposures	Exposed group result ^c	References
<i>Human studies</i>				
Agricultural workers (20): R (16)	Lymphocyte CA ^{NC}	19 pesticides reported used including GBF	No statistically significant increase in CA	Gregio D'Arce and Colus (2000)
Greenhouse farmers (104): R (44)	Lymphocyte SCE ^{NC}	9 pesticides or pesticide classes reported as used. GBF used by 99/104 farmers	Statistically significant increases in SCE/ chromosome and high SCE frequency cells	Shaham et al. (2001)
Floriculturists (107): R (61)	Lymphocyte CBMN	> 30 pesticides reported used. GBF use reported in 57/107 workers	Statistically significant increase in BNMN	Bolognesi et al. (2002)
Hungarian agricultural workers (84): R (65)	Lymphocyte CBMN Buccal MN	14 pesticides reported used. GBF use frequency reported as 16.1%	No statistically significant increases in BNMN or buccal cell MN frequencies	Pastor et al. (2003)
Fruit growers (12 in one season for urine and comet; 17 in second season for urine only): NR	BM comet ^{NC} Ames test on urine	Samples collected before and after captan spraying. GBF use reported in 2/29 growers 1 day before captan spraying and in 1/19 grower on the day of captan spraying	No statistically significant effects on comet % DNA damage or tail moment; correlation between predicted captan exposure and response in Salmonella strain TA102	Lehailly et al. (2003)
Floriculturists (51): R (24)	Lymphocyte CBMN	25 pesticides reported used. GBF use reported in 21/51 workers with average of 106.5 kg/year applied	No statistically significant increase in BNMN	Bolognesi et al. (2004)
Workers exposed to pesticides (33): R (33)	Lymphocyte SCE Lymphocyte CBMN Lymphocyte CA	> 30 pesticides reported used including GBF	Statistically significant increases in BNMN and SCE but not CA	Costa et al. (2006)
Farmers (11): R (11)	Lymphocyte CBMN ^{NC}	17 pesticides reported used. GBF use reported in 3/11 farmers	Statistically significant increase in MN frequency but not in frequency of BNMN; statistically significant increases in small MN	Vlastos et al. (2006)
Fruit farmers (29): NR	BC DNA adducts (³² P-postlabelling)	GBF use reported in 1 of 29 fruit farmers. Sampling on morning of and morning after spraying	No statistically significant effects comparing relative adduct levels at different sampling times	Andre et al. (2007)
Individuals at or near GBF aerial spraying (24): R (21)	BC comet ^{NC}	GBF aerially sprayed within 3 km. Blood samples collected two weeks to two months after spraying	Statistically significant increase in comet tail length and appearance of high damage comets	Paz-y-Mino et al. (2007)
Workers exposed to pesticides (54): R (30)	BC comet	13 pesticides reported used including GBF	Statistically significant increase in damaged cells	Simontello et al. (2008)
Humans in 3 areas where GBF was sprayed (60, 64 and 28): R (region of no pesticide exposure, 60).	Lymphocyte CBMN	Samples collected before, within 5 days and 4 months after GBF spraying in 3 regions. Pesticide use reported by 76.6%, 61.7% and 28.6% of subjects in GBF sprayed regions	Statistically significant increase in BNMN sampled within 5 days of GBF spraying in 3 regions; statistically significant decrease in 4 month sample compared to < 5 day sample in 1 region.	Bolognesi et al. (2009)
Agricultural workers (29): R (37)	Buccal MN	10 pesticides reported used including GBF	Statistically significant increase in MN cell frequency	Bortoli et al. (2009)
Agricultural workers (70): R (70)	Lymphocyte SCE Buccal MN	25 pesticides reported used including GBF	Statistically significant increases in SCE/ metaphase and MN cell frequency	Martinez-Valenzuela et al. (2009)
Subjects in areas with GBF aerial spraying up to 2 years previously (92): R (90)	Lymphocyte CA ^{NC}	Aerial GBF spraying for illicit crop control up to two years before sampling	Normal karyotypes and percentage of chromosomal fragility within normal parameters	Paz-y-Mino et al. (2011)
Agricultural workers (81): R (46)	BC comet Buccal MN ^{NC}	25 pesticides reported used including GBF	Statistically significant increases in damaged comets and MN cell frequency	Benedetti et al. (2013)

(Continued)

Table 1. (Continued)

Exposed population ^a	Endpoint ^b	Pesticide/GBF exposures	Exposed group result ^c	References
Children living in areas of pesticide application (125); R (325)	Buccal MN ^{NC}	> 30 pesticides reported used including GBF	Statistically significant increase in MN cell frequency	Gomez-Arango et al. (2013)
Agricultural workers (41); R (32)	BC comet ^{NC} Buccal MN ^{NC}	Exposure of up to 7 different pesticides with 56.7% of workers exposed to a single pesticide (fenprophathrin, carbofuran or GBF)	Statistically significant increase in MN cell frequency and in comet endpoints (% DNA in tail and tail moment)	Khayat et al. (2013)
Pesticide sprayers (80); R (206)	BC 8-OHdG	> 30 pesticides used including GBF	Statistically significant increases in 8-OHdG; no statistically significant increase with frequency of GBF applications in last spraying season	Koureas et al. (2014)
<i>Environmental Studies</i>				
Meadow vales living on golf courses (22 in 2001, comet only; 61 in 2002, comet and MN); R (0 in 2001; 8 in 2002)	BC comet ^{NC} Erythrocyte MN ^{NC}	Numerous pesticides reported used including GBF	Comet tail length and moment statistically correlated with total pesticide exposure in 2001 but not 2002; no statistically significant pesticide effects on polychromatic erythrocyte MN frequencies	Knopper et al. (2005)
Fish from dams (various species; 3 per species)	Erythrocyte MN	Wide GBF use reported in adjacent lands along with other pesticides	Higher MN frequencies than normal or expected from other reports but no negative concurrent controls used	Salvagni et al. (2011)

^aDescription of exposed population with number of exposed individuals in (), R with () indicates number of individuals in non-exposed referent population. NR indicates no concurrent referent population studied.

^bGenotoxicity endpoint(s) measured. See abbreviations for endpoint abbreviations. ^{NC} after SCE, CBMN or comet endpoints indicates that slides were not indicated as coded before scoring.

^cResults reported for exposed group compared to referent group.

thousand with an inter-quartile range of 3–12 per thousand observed for a large number of normal subjects from many laboratories (Fenech et al. 2011).

The buccal micronucleus (buccal MN) assays generally followed recommendations for number of cells scored with 1000–3000 cells scored per subject. There is a recommendation for the use of DNA-specific staining for this assay such as Foulgen-Fast Green (Thomas et al. 2009). Two of the laboratories used relatively non-specific Giemsa staining (Benedetti et al. 2013, Bortoli et al. 2009). The mean frequencies of micronucleated cells in referent populations ranged from about 0.37 per thousand to 1.78 per thousand. This range seems reasonably close to a mean of 0.74 micronucleated cells per thousand for a large number of healthy subjects not knowingly exposed to genotoxic substances or radiation (Bonassi et al. 2011). The study with the highest mean frequency of micronucleated cells in a referent population (1.78 per thousand) employed the relatively non-specific Giemsa stain (Bortoli et al. 2009).

The comet studies generally used similar standard methodology for cell lysis, alkaline treatment, and staining of DNA. One study used isolated leukocytes (Lebailly et al. 2003) but the other studies used whole blood. It should be noted that whole blood contains a high percentage of short-lived neutrophils and thus may be more suitable for recent exposures to genotoxic agents (Collins et al. 2014). Recent guidance for comet assay methodology suggests that the most useful comet measurement is the percentage of DNA in the comet

tail (Anderson et al. 2013, Azqueta and Collins 2013, Collins et al. 2014). Only one of the six comet studies reported measurement of percentage of DNA in the comet tail (Khayat et al. 2013).

Most of the endpoints employed in the biomonitoring studies involve visual scoring for endpoints or visual selection of comets for image analysis. There are consistent and numerous recommendations that slides for scoring for these endpoints should be coded so that the scorer is not aware of the treatment conditions, individual or groups to which the slides belong (e.g., OECD 479, 1986, OECD 474, 1997, Albertini et al. 2000, Tice et al. 2000, Hartmann et al. 2003, Fenech 2007, Thomas et al. 2009, OECD 475, 2014, OECD 489, 2014). However, a number of the biomonitoring studies for these endpoints, as indicated in Table 1, did not include an explicit statement in the methodology that slides were coded for analysis. It is possible that the methodology used actually did involve coding of slides but that this was not mentioned in the publication. If this is the case then clear indication of coding slides for analysis should be encouraged in the methodology sections of such publications. Alternately, it is possible that coding was not used and that the scorers may have been aware of the groups to which the slides belonged. This would be a significant deviation from recommended practice and coding of slides and reporting this in the methodology should be encouraged for all biomonitoring study endpoints where visual scoring or selection of objects is involved.

Results for human biomonitoring studies

Studies with low GBF exposure incidence

Table 2 summarizes conclusions about the studies relevant to GBF effects. For some of the human biomonitoring studies, the indicated frequency or incidence of pesticide exposure to GBF in the pesticide exposed population was very low (Pastor et al. 2003, Lebailly et al. 2003, Vlastos et al. 2006, Andre et al. 2007). The incidence of GBF exposure reported for these studies was too low to allow any reasonable conclusions about any relationships between GBF exposure and genotoxicity endpoint effects or lack of effects.

Studies with exposure to multiple pesticides

A number of human monitoring studies in Table 1 and as summarized in Table 2 indicated exposure to a list of multiple

pesticides including GBF but did not indicate the frequency or extent of exposure to any specific pesticides (Gregio D'Arce and Colus 2000, Costa et al. 2006, Simonello et al. 2008, Bortoli et al. 2009, Martinez-Valenzuela et al. 2009, Benedetti et al. 2013, Gomez-Arroyo et al. 2013). One of the studies did not find statistically significant increases for the lymphocyte CA endpoint in agricultural workers (Gregio D'Arce and Colus 2000). The other six studies reported statistically significant increases for genotoxic endpoints for pesticide exposed populations compared to referent populations. An interesting observation of the Costa et al. (2006) study is that two endpoints (lymphocyte CBMN and SCE) had statistically significant increases in the exposed population but the chromosomal aberration endpoint did not. This suggests the possibility of different sensitivity to genotoxic effects of the endpoints which could possibly reflect different

Table 2. Summary GBF exposure conclusions from human genotoxicity biomonitoring studies.

Study reference	GBF conclusions and comments*
<i>Reported low GBF exposure incidence</i>	
Pastor et al. (2003)	Not informative because of low reported incidence of GBF exposure
Lebailly et al. (2003)	Not informative because of low reported incidence of GBF exposure. Longitudinal study focusing on captan exposure
Vlastos et al. (2006)	Not informative because of low reported incidence of GBF exposure
Andre et al. (2007)	Not informative because of low reported incidence of GBF exposure. Longitudinal study with no referent population
<i>Multiple pesticide exposures and unknown extent of GBF exposure</i>	
Gregio D'Arce and Colus (2000)	Not informative because of exposures to multiple pesticides and unknown extent of GBF exposure. Negative result for CA endpoint indicates no positive effects from GBF exposure but extent of GBF exposure is not known
Costa et al. (2006)	Not informative because of exposures to multiple pesticides and unknown extent of GBF exposure. Negative results for CA endpoint indicates no positive effects from GBF exposure but extent of GBF exposure is not known
Simonello et al. (2008)	Not informative because of exposures to multiple pesticides and unknown extent of GBF exposure
Bortoli et al. (2009)	Not informative because of exposures to multiple pesticides and unknown extent of GBF exposure
Martinez-Valenzuela et al. (2009)	Not informative because of exposures to multiple pesticides and unknown extent of GBF exposure
Benedetti et al. (2013)	Not informative because of exposures to multiple pesticides and unknown extent of GBF exposure
Gomez-Arroyo et al. (2013)	Not informative because of exposures to multiple pesticides and unknown extent of GBF exposure
<i>Multiple pesticide exposures and reported significant extent of GBF exposure</i>	
Shaham et al. (2001)	Not informative because significant exposures to multiple pesticides were reported including GBF. Positive SCE effects not ascribed to GBF exposure
Bolognesi et al. (2002)	Not informative because significant exposures to multiple pesticides were reported including GBF. Positive CBMN effects not ascribed to GBF exposure
Khayat et al. (2013)	Not informative because significant exposures to multiple pesticides were reported including GBF. Positive buccal MN and BC comet effects not ascribed to GBF exposure. Use of only one pesticide (including GBF) reported for a large proportion of the population but no separate endpoint analysis of single pesticide exposure indicated
<i>Informative for GBF exposure effects</i>	
Bolognesi et al. (2004)	Some limited evidence for lack of effects of GBF exposure on lymphocyte CBMN endpoint. No statistically significant increases in BNMN frequency of exposed population with significant proportion (21/51) reporting exposure to GBF. Difference in gender distribution between exposed and referent populations. Small sample size of population exposed to GBF
Paz-y-Mino et al. (2007)	Evidence for BC comet effects for population in region of GBF aerial spraying. Small exposed and referent populations with differences in gender distribution. Samples collected and processed at different times after spraying. No indication of coding of slides for scoring. Significant clinical signs of toxicity and much higher than normal rates of application reported for exposed population. Comet effects may be secondary to toxicity
Bolognesi et al. (2009)	Inconclusive for lymphocyte CBMN effects for populations in regions of aerial GBF spraying. Statistically significant increases in BNMN frequencies were observed immediately after GBF spraying but statistically significant correlations were not observed with self-reported exposure to spray and results were not consistent with GBF application rates
Paz-y-Mino et al. (2011)	Some evidence of lack of chromosomal effects in a population exposed earlier to GBF aerial spraying. Publication indicates no chromosomal effects but contains no details on methodology or detailed chromosomal aberration data
Kuurens et al. (2014)	Some evidence of lack of oxidative DNA damage from GBF exposure. Univariate analysis indicated lack of statistically significant correlation between reported GBF exposure frequency and 8-OHdG in blood DNA. Exposures are reported from last spraying season and relationship between exposure and sampling is not clear

*See abbreviations for endpoint abbreviations.

mechanisms and sensitivities to those mechanisms. Some support for this possibility is also provided by the negative lymphocyte CA result of Greggio D'Arce and Colus (2000), but this study did not measure other endpoints. None of these studies presented any detailed information on individual pesticide exposure or ascribed observed genotoxic effects to any specific pesticide. The fact that there were exposures to multiple pesticides, ranging from 10 to more than 30, in these studies and an unknown extent or frequency of exposure to GBFs does not allow any conclusions about genotoxic biomarker effects or lack of effects related to GBF exposure. It should be noted that positive results in genotoxicity biomonitoring studies involving multiple pesticide exposures have been frequently observed regardless of whether these exposures included GBF (Bolognesi et al. 2003, Bull et al. 2006).

Another set of human biomonitoring studies involved exposures to multiple pesticides but indicated frequency of exposure to specific pesticides that included a significant proportion of the exposed population using GBF (Shaham et al. 2001, Bolognesi et al. 2002, 2004, Khayat et al. 2013). One of these studies reported no statistically significant increase in BNMN frequency compared to a referent population for the CBMN endpoint in a population of 51 floriculturists of whom 21 reported GBF use (Bolognesi et al. 2004). Although the authors suggested trends for an increase in BNMN frequency with pesticide use and exposure time and a trend toward higher proportion of centromere-containing MN with pesticide exposure and in a subgroup using benzimidazole compounds, the statistically negative result for BNMN frequency might be taken as some evidence indicating lack of detectable effect for this endpoint in the appreciable portion of floriculturists exposed to GBF.

Three other studies with multi-pesticide exposure including significant frequency of GBF use in the exposed populations reported positive genotoxic effects for the lymphocyte SCE endpoint (Shaham et al. 2001), the CBMN endpoint (Bolognesi et al. 2002), and the blood cell comet and buccal MN endpoints (Khayat et al. 2013). Two of these studies presented data on frequency of pesticide or pesticide class use and for both of these studies most participants used multiple pesticides and GBF use, while frequent, was not dominant compared to numerous other pesticides (Shaham et al. 2001, Bolognesi et al. 2002). Neither of these studies analyzed or attributed genotoxicity marker effects to specific pesticides and, given the multiplicity of pesticide exposures, there is no basis to conclude that GBF exposure was responsible for the effects observed. The Khayat et al. (2013) study reported that an appreciable percentage (56.7%) of the exposed population were exposed to only one pesticide and the single pesticide exposures were to GBF, fenprothrin, or carbofuran. How many workers were exposed to each pesticide was not indicated. It should be noted that the Khayat et al. (2013) data table reporting multiplicity of pesticide exposures appeared to only present data for 30 workers but there were 41 workers in the exposed population. Despite the apparent occurrence of single pesticide exposures in a large portion of the exposed group, the study did not indicate a pesticide-specific analysis of genotoxic marker effects. In the absence of such analysis the genotoxic marker effects observed cannot be attributed to any specific pesticide, including GBF.

Studies assessing GBF exposure effects

As indicated in Tables 1 and 2, there were four studies where specific information on GBF exposure effects was presented. Three published studies focused on populations believed to be exposed to GBFs by their presence at or near aerial GBF spraying operations (Paz-y-Mino et al. 2007, 2011, Bolognesi et al. 2009).

One of these studies reported induction of blood cell comet effects on a Northern Ecuadorian population living within 3 km of areas sprayed with GBF for illicit crop eradication (Paz-y-Mino et al. 2007). The sprayed material was reported to be Roundup Ultra, a GBF containing 43.9% glyphosate, polyethoxylated tallowamine surfactant, and a proprietary component, Cosmolux 411E. The populations studied were relatively small (24 exposed individuals and 21 non-exposed individuals) and the referent population had a higher proportion of males (4/21 vs. 1/24 in the exposed group). Blood sampling was reported to have been at 2 weeks to 2 months after spray exposure and samples were indicated to have been processed immediately. Specific methods for collection, storage, and transport of blood samples were not described for either the exposed population or referent group but it was noted that referent group samples were not processed concomitantly with the exposed group samples. Time between collection and assay and storage conditions and variation in sampling time between exposed and referent sample collection have been cited as potentially important variables for human biomonitoring studies using the comet endpoint (Collins et al. 2014). Inclusion of reference standards is advised when samples are processed at different times (Azqueta and Collins 2013) but this was not indicated in Paz-y-Mino et al. (2007) publication. The Paz-y-Mino publication also did not indicate that slides were coded for scoring for comet effects. As noted above there are numerous recommendations for coding of slides scored in the comet assay unless the scoring is fully automated (Tice et al. 2000, Hartmann et al. 2003, Collins et al. 2014, OECD 489, 2014).

The Paz-y-Mino et al. (2007) study reported increases in damaged cell categories and statistically significant increases in DNA migration (tail length) in the presumably exposed population. Interpretation of the results of this study should consider numerous reported signs of toxicity in the exposed population and the reported application rate of 23.4 liters/ha which was stated to be more than 20 times the maximum recommended application rate. Some of the reported exposed group health effects described by Paz-y-Mino et al. (2007) appear to be consistent with severe exposures noted in clinical reports of acute poisoning incidents (often self-administered) with GBFs and other pesticide formulations rather than typical bystander exposures (Menkes et al. 1991). Given the considerably favorable general toxicology profile of glyphosate as reported by the WHO/FAO Joint Meeting on Pesticide Residues (WHO/FAO 2004) and in Williams et al. (2000), factors related to either high surfactant exposure, unusual GBF components in this formulation or other undocumented variables appear to be confounding factors in this study. It is possible that the reported comet effects, if indeed resultant from GBF exposure, could well have been secondary to the clinical toxicity reported in this study population.

Subsequent to the original Paz-y-Mino et al. (2007) study, a baseline study was conducted on residents on the northeastern Ecuadorian border near where there had been aerial applications of GBF (Paz-y-Mino et al. 2011). Apparently, samples were collected about 2 years after the last aerial spraying. The exposed population used for genomic and chromosome analysis (92 individuals) and the referent sample population (90 individuals) were much larger than those of the previous Paz-y-Mino et al. (2007) study and the proportion of males in the exposed population was much higher. Publication details on sample collection, storage, transportation, and methodology for chromosomal aberration analysis are very limited and typical data for the chromosomal aberration endpoint were not presented. Thus, there is some uncertainty that the endpoint used was the typical chromosomal aberration endpoint. Nevertheless, the publication indicated that none of the exposed population had any type of chromosomal alteration and the percentage of chromosomal fragility was within normal parameters.

Another publication (Bolognesi et al. 2009) reported results for a lymphocyte CBMN study of individuals in three areas of Colombia treated with GBF by aerial spraying for illicit crop eradication (Putumayo and Nariño regions) or sugar cane maturation (Valle del Cauca region). Other populations were from an area using manual eradication for illicit crops and pesticides including GBF for agriculture (Boyaca region) and a region where agricultural practices do not include pesticide application (Santa Marta region). Although the title of the publication contains the term "agricultural workers", it appears that only some of the total population studied had agriculture as an occupation. The percent of subjects listing agriculture as an occupation varied from 7.1% in Valle del Cauca to 60% or more in Putumayo and Nariño. Although percentage of subjects reporting current use of pesticides is reported for the various regions and there was a reference to higher prevalence of use of genotoxic pesticides in Putumayo and Nariño no detailed information on the pesticides used or frequency of use was presented in the publication.

The human lymphocyte culture and scoring methodology employed in the Bolognesi et al. (2009) study appear to be generally consistent with commonly used and recommended practices for this assay. There is a question as to how long the blood samples used in the study were stored prior to initiating cultures. The publication only indicated that blood samples were kept at room temperature and cultures were initiated at a central laboratory within 24 h of collection. There may have been differences in the time between sampling and culture initiation for different sets of samples. Also, the populations in the aerially sprayed regions had a second sampling within 5 days after the first sampling and this second sampling time was not used for the other regions. It appears that collection and processing of samples may have occurred for different times for the aerially sprayed regions and the other regions.

The publication reported a small statistically significant increase in the frequency of BNMN in samples collected from people living in three regions within 5 days after spraying of GBFs compared with values for samples collected just before spraying. The publication also indicated a statistically significant increase of micronucleated mononuclear cells (MOMN) in the immediate post-spraying samples for two regions (Nariño and Valle del Cauca). In the samples taken 4 months

after spraying, a statistically significant decrease in BNMN frequency compared to immediate post-spraying frequency was observed for one of the spraying regions (Nariño) but the other sprayed regions did not exhibit a statistically significant difference in BNMN frequency between the immediate post-spraying and 4 month samples.

Although the increases in BNMN frequencies in the post-spraying samples of the three regions suggest an effect from GBF exposure, more detailed consideration of exposure factors raises significant questions about this conclusion. The populations in each of the sprayed regions self-reported exposure to the spray (e.g., being in sprayed fields after spraying or observing spray drops in the air or on skin). For all three sprayed regions, there was no statistically significant difference in BNMN frequency between those self-reporting spraying exposure and those self-reporting no spraying exposure. The largest percentage post-spraying increase in BNMN frequency was reported for Valle del Cauca but only 1 of 26 people from this population self-reported spray exposure. Also, it was noted that GBF spraying in Valle del Cauca was at a rate significantly lower (1 kg acid equivalents glyphosate/ha) than that in Nariño and Putumayo (3.69 kg acid equivalents glyphosate/ha). The lack of clear correlation between self-reported exposure and BNMN increases after regional GBF spraying led to some caution in interpretation by the authors. The Bolognesi et al. (2009) publication suggested that results indicated low genotoxic risk from the GBF aerial spraying for illicit crop eradication. Another possible conclusion that appears to be supported by the self-reported exposure information is that this study does not clearly demonstrate an association between GBF exposure and CBMN endpoint effects.

Koureas et al. (2014) published a study examining effects of pesticide exposure on a measure of oxidative DNA damage, 8-hydroxydeoxyguanosine (8-OHdG) in blood DNA, which addressed whether GBF exposure appeared to affect this endpoint. The publication indicated that the exposed population had recently applied pesticides with no longer than 7 days between the last application and sampling. Several of the analyses were based on self-reported frequency of exposure to specific pesticides during the last spraying season and the timing relationship between specific pesticide applications and blood sampling is not clear. Statistically significant increases in 8-OHdG DNA levels were observed in blood samples collected from pesticide applicators compared to a non-exposed referent population. A univariate analysis was conducted to determine if specific high/low pesticide exposure classifications based on seasonal application frequencies were statistically associated with increased 8-OHdG levels in blood DNA. This analysis found statistically significant associations with 8-OHdG levels for herbicide exposure frequency and specifically for glufosinate herbicide exposure. Other statistically significant specific pesticide frequency exposure correlations were observed for neonicotinoids. A statistically significant exposure frequency correlation was not observed for GBF exposure. While certainly of limited power, this analysis provides some evidence that GBF exposures in pesticide applicators were not associated with oxidative DNA damage.

The human genotoxicity biomonitoring studies that specifically address GBF effects appear to have some evidence for

lack of persistent genotoxic effects, especially under normal conditions of exposure. One study suggests lack of DNA oxidation effects with GBF application and a study employing CBMN does not show statistically significant effects correlating with self-reported exposure to GBF spraying. One study reported effects on the blood cell comet endpoint following exposures to very high levels of GBF spraying which apparently were sufficient to elicit significant clinical signs of toxicity. However, a subsequent study conducted 2 years after GBF spraying using much larger populations did not detect chromosomal alterations or an increase in chromosomal fragility indicating that the comet effects did not appear to be manifested as persistent genotoxic effects. It should be noted that there is growing appreciation that comet endpoint effects in biomonitoring studies may result from indirect (i.e., non DNA-reactive) mechanisms such as inhibition of DNA repair, perturbation of cytokinesis, and oxidative stress (Collins et al. 2014). It seems very likely that the observed blood cell comet effects, if indeed associated with GBF exposure, were secondary to toxicity from very high GBF exposures and that these effects do not indicate DNA-reactive genotoxicity or a genotoxic risk from normal GBF exposures.

Results for environmental biomonitoring studies

There are two publications related to environmental biomonitoring for genotoxic endpoints. One study using blood cell comet and erythrocyte MN endpoints was conducted on samples from meadow voles living on or near golf courses where pesticides had been applied (Knopper et al. 2005). Different comet sample processing methodology (use or non-use of dimethylsulfoxide in lysis buffer) was used for the two different seasons and statistically significant differences in the average comet tail moment between the two seasons were ascribed to this different methodology. Although some suggestions of effects were reported, GBF was only one of a number of applied pesticides and the effects observed were considered by the authors as possibly attributable to exposure to Daconit® fungicide.

A second publication reported results for the erythrocyte MN assay applied to fish collected from several dams in Brazil (Salvagni et al. 2011). GBF was one of a number of pesticides reported to be used in the area of the dams. This study reported what were considered to be high numbers of micronuclei in cells but there were no concurrent negative controls. In the absence of these controls, the results might not be interpreted as conclusively indicating effects of pesticide exposure.

Conclusions

Two environmental genotoxicity biomonitoring studies conducted on a mammalian species and fish species were not informative about possible environmental genotoxic effects of GBFs. Both studies involved exposures or potential exposures to multiple pesticides without characterizing the relative extent of GBF exposure.

There have been a fairly large number of human genotoxicity biomonitoring studies where some exposure to GBFs was reported. Several of these studies were not informative about effects of GBF exposure because there was exposure to multiple pesticides and reported GBF exposure frequencies were low or very low. Another set of human biomonitoring studies

were also not informative about possible genotoxic effects of GBF exposure because these studies listed exposure to large numbers of pesticides (10 to more than 30) in the exposed population without indicating the frequency or extent of exposure to any of the pesticides. Although positive genotoxic endpoint effects were observed in most of these studies no conclusions can be made regarding which pesticide exposures were responsible for the effects.

A third set of human genotoxicity biomonitoring studies involved exposures to multiple pesticides but did indicate significant frequency of GBF exposure in the populations. One of these studies did not find statistically significant effects for the lymphocyte CBMN endpoint in the exposed population compared to a referent population. This study offers some limited evidence for lack of significant, detectable effects on this endpoint for human exposure to any of the pesticides with significant exposure frequencies, including GBF, but the population sizes exposed were low. Three other studies reported positive genotoxic endpoint effects but the exposure data and endpoint data presented did not permit attribution of these effects to any specific pesticide exposure.

Finally, there are data from four human genotoxicity biomonitoring studies that provide information on GBF exposure effects. A study of oxidative effects on blood DNA indicated that observed increases in oxidative DNA damage did not statistically correlate with last season frequency of GBF application. These results provide limited evidence for this indirect genotoxic mechanism not operating at a significant level in humans using GBFs. Three studies involved measurement of genotoxic endpoints in human populations living in regions where GBFs were applied by aerial spraying. One study used a longitudinal design involving populations in regions of aerial GBF applications where samples were taken before, within 5 days and 4 months after GBF spraying. Statistically significant post-spraying increases for the CBMN endpoint were observed in these populations. However, the increases were not significantly correlated with self-reported exposure to the sprays or with the spraying application rate. Application of well-respected criteria for relating epidemiology cause and effect (Bradford-Hill 1965) to these results does not permit a conclusion that the observed effects were clearly related to GBF spray exposure. Two other studies were made of humans in GBF aerial spraying regions. A cross-sectional study found increases for the blood cell comet endpoint in the exposed population compared to a referent population. The exposures in this study appeared to be very excessive in terms of GBF application rate and significant signs of toxicity were observed in the exposed population. It seems possible that effects for this endpoint, if induced by GBF spraying exposure, may well have been indirect mechanism effects secondary to toxicity. A follow-up study of larger sample size from the sprayed regions conducted 2 years after spraying did not indicate any effects on chromosomal alteration or fragility endpoints. These latter results suggest that no persistent genotoxic effects were induced in the sprayed population and are consistent with the possibility that earlier reported comet effects may well have been secondary to toxic effects rather than resulting from a DNA-reactive mechanism.

The overall conclusion from the human biomonitoring studies is that none of the reported positive results for

studies involving exposure to multiple pesticides present evidence specifically relating GBF exposure to these results. There is some limited evidence for lack of oxidative DNA damage from normal human GBF exposure. The studies of populations in regions where GBF spraying occurred do not provide clear evidence correlating exposure to chromosomal effects such as aberrations or induction of micronuclei. The single study result of DNA damage comet effects in a population presumably exposed to GBF aerial spraying might well have been due to abnormally high toxic exposures to the GBFs rather than a DNA-reactive mechanism and does not indicate genotoxic risk to humans under normal exposure conditions.

An earlier review of a very extensive number of experimental genotoxicity studies of glyphosate and GBFs concluded that there is a convincing weight of evidence supporting the lack of genotoxic potential for both glyphosate and typical GBFs in core gene mutation and chromosomal effect endpoints and that observations of DNA damage effects were likely to be secondary to toxicity (Kier and Kirkland 2013). This earlier review concludes that the lack of genotoxic hazard potential evidenced by core gene mutation and chromosomal effect studies, coupled with the very low human and environmental species systemic exposure potential, indicate that glyphosate and typical GBFs present negligible genotoxicity risk. A subsequent review of experimental rodent carcinogenicity studies did not indicate that glyphosate was associated with carcinogenicity (Greim et al. 2015) which supports the conclusion that glyphosate does not have DNA-reactive genotoxic properties. A review of human and environment genotoxicity biomonitoring studies does not indicate any significant evidence to contradict these conclusions.

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REVIEW ARTICLE

Review of genotoxicity studies of glyphosate and glyphosate-based formulations

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Abstract

An earlier review of the toxicity of glyphosate and the original Roundup™-branded formulation concluded that neither glyphosate nor the formulation poses a risk for the production of heritable/somatic mutations in humans. The present review of subsequent genotoxicity publications and regulatory studies of glyphosate and glyphosate-based formulations (GBFs) incorporates all of the findings into a weight of evidence for genotoxicity. An overwhelming preponderance of negative results in well-conducted bacterial reversion and *in vivo* mammalian micronucleus and chromosomal aberration assays indicates that glyphosate and typical GBFs are not genotoxic in these core assays. Negative results for *in vitro* gene mutation and a majority of negative results for chromosomal effect assays in mammalian cells add to the weight of evidence that glyphosate is not typically genotoxic for these endpoints in mammalian systems. Mixed results were observed for micronucleus assays of GBFs in non-mammalian systems. Reports of positive results for DNA damage endpoints indicate that glyphosate and GBFs tend to elicit DNA damage effects at high or toxic dose levels, but the data suggest that this is due to cytotoxicity rather than DNA interaction with GBF activity perhaps associated with the surfactants present in many GBFs. Glyphosate and typical GBFs do not appear to present significant genotoxic risk under normal conditions of human or environmental exposures.

Keywords

Formulation, genotoxicity, glyphosate, mutagenicity, Roundup™

History

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Introduction

Glyphosate is an active ingredient (a.i.) in very widely used herbicide formulations. Accordingly, the toxicity of glyphosate and glyphosate-based formulations (GBFs) has been extensively studied. An earlier extensive review of glyphosate and glyphosate formulation safety and risk assessment included descriptions and analyses of genetic toxicology studies of glyphosate and Roundup™-branded and other

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Abbreviations

a.e.,	acid equivalents
a.i.,	active ingredient
CB MN,	cytokinesis block micronucleus
GBF,	glyphosate-based formulation
i.p.,	intraperitoneal
MN,	micronucleus
MN PCE,	micronucleated polychromatic erythrocyte
NCE,	nonochromatic erythrocyte
PCE,	polychromatic erythrocyte
p.o.,	oral administration
SCE,	sister chromatid exchange
SCGE	single cell gel electrophoresis (Comet assay)
OECD,	Organization for Economic Co-operation and Development
S9,	9000×g liver homogenate supernatant
UDS,	unscheduled DNA synthesis

glyphosate formulations (Williams et al., 2000). These studies included a wide variety of test systems and endpoints. Subsequent to this review a number of genotoxicity studies of glyphosate and GBFs have been published in the literature. Additionally, there are large number of genetic toxicology studies of glyphosate and GBFs sponsored by companies that were not included in the previous review. The number and diversity of these studies warrant careful examination and integration of their findings with previous results to produce an updated assessment of the overall genotoxicity profile for glyphosate and a genotoxicity profile that is typical of the GBFs.

Identification and analysis of published studies

The published studies for review consideration were identified by literature searches for published reports containing references to glyphosate that also contained searchable terms which indicated that genotoxicity studies were performed. Details of search procedures are provided in the "online supplementary material". Each identified publication was evaluated to verify that it contained original results of one or more experimental genotoxicity studies on glyphosate or GBFs. Monitoring studies are not included in this review. Emphasis was placed on publications in peer-reviewed journals. Abstracts or other sources with incomplete information were not considered. Reviews without original data were not considered for the evaluation; however, these reviews were examined to determine if there were any cited publications that had not been detected in the literature searches.

Each relevant publication was examined using several criteria to characterize the scientific quality of the reported genetic toxicology studies. Useful, objective criteria for this purpose were international guidelines for genetic toxicology studies formulated by expert groups. These include principles for conducting studies, reporting results, and analyzing and interpreting data. Some of the principles of the guidelines are generally applicable to all studies, while others are specific for a particular type of test system and endpoint. Some of the

specific types of studies encountered in the review do not yet have international guidelines; however, some of the guideline elements should be generically applicable to these studies. The guidelines for genetic toxicology tests developed for the Organization for Economic Co-operation and Development (OECD) are a pre-eminent source of internationally agreed guidelines. Other international and national guidelines for regulatory genetic toxicology testing are usually concordant with the OECD guidelines. The "online supplementary material" contains a summary table of some key OECD guideline criteria that were found to be relevant to the analysis of the studies considered in this review.

Comparison of the published studies to the criteria in guidelines used for regulatory purposes does not represent an absolute judgment standard but can provide a way for evaluating the quality of the protocols used in various published studies. Some of the criteria are rarely met in scientific publications and should be given little or no weight in evaluating the studies. For example, data for individual cultures and individual animals are not commonly included in publications in scientific journals. These data are presumably collected but are usually summarized as group means with a measure of variance for the treatment and control groups. This is not considered to be a significant omission in a scientific publication. However, other guideline features are more essential as scientific quality standards and should be considered as having greater weight in evaluating a study. For example, there are consistent recommendations that assays involving visual scoring (e.g. chromosomal aberration, micronucleus and sister chromatid exchange (SCE) endpoints) should use slides that are independently coded so that scoring is performed without any knowledge of the treatment or control group being scored. This guidance is good scientific practice and studies that do not explicitly include a description of coding or "blind" scoring in the methodology would appear to have a deficiency either in the methodology, or perhaps a limitation in the description of the methodology used if coding was actually used and either not indicated or was assumed to be indicated by a reference citation. Other examples of guideline features that have clear experimental scientific value are the use of concurrent negative and positive controls and concurrent measurement and reporting of toxicity endpoints in main experiments, especially in *in vitro* mammalian cell assays.

Review and analysis of sponsored regulatory studies

Reports of sponsored genetic toxicology studies were provided by the companies. The studies were sponsored by companies for regulatory purposes and were conducted at in-house or contract toxicology laboratories. For brevity, the industry-sponsored regulatory studies will be subsequently referred to as regulatory studies.

Each study examined was stated to have been conducted in accordance with Good Laboratory Practice (GLP) standards with almost all studies citing the OECD Principles of Good Laboratory Practice (OECD GLP, 1982, 1997). Reports also cited compliance with various national and regional GLP Guidelines (e.g. European Commission GLP Directives 87/18/EEC or 88/320/EEC; U.S. Environmental Protection

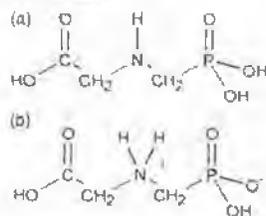


Figure 1. Chemical structure of glyphosate, (N-(phosphonomethyl)glycine, CAS 1071-83-6): (a) neutral form, (b) ionic form.

Agency Good Laboratory Practice Standards, 40 CFR Part 160, Japanese Ministry of Agriculture, Forestry, and Fisheries (MAFF) Good Laboratory Practice Standards, 11 Nousan No. 6283). Variations from GLPs were considered not to have significantly impacted the study results.

Almost all the studies were reported to have been conducted in accordance with the relevant OECD test guidelines applicable at the time of the study. Study reports were examined to determine that the protocols and experimental methods for the report were consistent with the OECD guidelines and any deviations were noted and considered. Report data were examined to confirm the conclusion of the report regarding whether treatment-related activity had been observed.

Glyphosate structure activity analysis

Glyphosate consists of the amino acid glycine joined with a phosphonomethyl group (Figure 1). Glyphosate was evaluated for mutagenic structural alerts using Derek for Windows software (Lhasa Ltd., Leeds, UK, Version 11.0.0, 24 October 2009). No structural alerts were identified for chromosomal damage, genotoxicity, mutagenicity or carcinogenicity. The structural components of the glyphosate molecule are not known to be genotoxic; therefore, the lack of structure activity alerts for glyphosate was expected.

GBF compositions

Glyphosate-based formulations are herbicide formulations which, by definition, contain the a.i. glyphosate typically in a salt form (e.g. isopropylamine or potassium glyphosate), but the % glyphosate may be expressed in acid equivalents (a.e.) as percent weight of glyphosate acid without the counter ion. In addition to the a.i., other compounds are included in the formulation to help achieve or improve the herbicidal activity for the desired application. A very common functional component, especially for terrestrial applications, is a compound (or compounds) with surfactant activity that enables better penetration of the a.i. through leaf surfaces. Because formulation compositions are considered proprietary, their specific compositions are not generally indicated in literature reports and are not publicly available for regulatory studies. GBF test materials are usually identified with names or designations and should include either % a.i. or a.e. detail.

It should be noted that a common problem encountered in the published literature is the use of the terms "glyphosate", "glyphosate salt" or "Roundup" to indicate any kind of GBF that contains additional components such as surfactants.

Published results from studies with different formulations have sometimes been incorrectly or inappropriately attributed to the a.i. The original RoundupTM-branded formulation (MON 2139), containing 41% isopropylamine glyphosate salt and 15.4% MON 0818 (a polyethoxylated tallowamine based surfactant blend), is no longer sold in many markets. However, other GBFs are sold under the RoundupTM brand name with varying glyphosate forms, concentrations and surfactant systems. Clear identification of the test material is very important in toxicology studies because the toxicity of formulations can be dramatically different from the a.i. The fact that test materials identified as RoundupTM-branded formulations may actually have different compositions should be considered when comparing results of different studies, as should the possibility that any observed effects may be due to specific GBF components other than the glyphosate active ingredient.

Gene mutation endpoint

Bacterial reversion assays

Glyphosate and glyphosate salts

As reviewed by Williams et al. (2000), six reports of bacterial reversion assays for glyphosate were all negative. No reports of bacterial reversion assays for glyphosate were encountered in the subsequent literature.

A large number of regulatory bacterial reversion assays have been conducted on technical glyphosate and glyphosate salt solutions. These 18 assays are presented in Table 1. Summary data tables and associated information for the regulatory studies are available in "online supplementary material". Methodology and experimental design for these studies was generally in compliance with OECD Guideline 471 (OECD 471, 1997) for studies conducted in or after 1997. The previous guidelines (OECD 471, 1983, for *Salmonella* strains; OECD 472, 1983, for *Escherichia coli* strains) were used for studies conducted before 1997. All of the assays employed a core battery of *Salmonella typhimurium* test strains (TA98, TA100, TA1535 and TA1537 or TA 97a) and most of the assays employed additional *S. typhimurium* TA102 or *E. coli* WP2-derived strains to detect oxidative and cross-linking effects as recommended in OECD 471 (1997). Limitations for some of the studies included three studies using larger than half-log dose level spacing and some studies did not employ a confirmatory assay. One study used positive controls not requiring exogenous metabolic activation for two strains in the presence of S9 (9000×g liver homogenate supernatant). Although this may be considered as a deficiency, in that the activity of the S9 was not thoroughly checked, it is only in one of the 18 studies. The top concentration employed in the assays ranged from 1000 to 5000 µg/plate with most of the studies using the OECD guideline limit dose of 5000 µg/plate. With only a couple of exceptions, the top dose tested produced the toxicity as evidenced by thinning of the background lawn, reduction in revertants/plate or both.

None of the studies exhibited revertants/plate exceeding threshold criteria for a positive response: greater than three times the control value for strains with low spontaneous

Test material/Solvent ^a	Strain ^b	S9 ^c	Method	Treatment ^d	Concn ^e	Toxicity	Mutagenicity	References
Glyoxalase and glyoxalase salts	G (98.6%) (W)	AR 4% (P1)	PI, PR	2500 µg (-S9)	C			Jensen (1991a)
	G (96.0%) (W)	AR 10%	PI	1000 µg	>HL, C, P			Suresh (1995a)
	G (95.68%) (W)	PR 10%	PR	5000 µg	C			Akanuma (1995b)
	G (95.3%) (W)	AR 10%	PI	5000 µg	C			Callander (1996)
	G (95.6%) (D)	PNR 10%	PI, PR	5000 µg	C			Callander (1996)
	G (95.3%) (W)	AR 10%	PI	5000 µg	C			Thompson (1996)
	GK (60%) (W)	PNR 10%	PI, PR	5000 µg	C			Callander (1999)
	GI (612.7 g/kg) (W)	AR 10%	PI	5000 µg	>HL, S			Ranzani (2000)
	G (95.1%) (W)	PNR 10%	PI, PR	5000 µg	C			Sokolowski (2007a)
	G (97.7%) (W)	PNR 10%	PI, PR	5000 µg	C			Sokolowski (2007b)
	G (95.0%) (W)	PNR 10%	PI, PR	5000 µg	C			Sokolowski (2007c)
	G (98.0) g/kg (D)	AR 2%	PI	5000 µg	S			Ribeiro do Val (2007)
	G (98.0) g/kg (D)	AR 5%	PI	1000 µg	>HL, S			Miyaji (2008)
	G (98.8 % w/w) (W)	AR 5%	PI, PR	3160 µg	C			Flüege (2009a)
	G (96.6% w/w) (D)	PNR 10%	PI, PR	5000 µg	C			Sokolowski (2009a)
G (96.3%) (W)	PNR 10%	PI, PR	5000 µg	C			Sokolowski (2009b)	
G (96.4%) (W)	AR 5%	PI, PR	3160 µg	C			Flüege (2010)	
G (96.0%) (D)	PNR 5%	PI, PR	5000 µg	C			Schreib (2010)	
G (98.2 g/kg) (D)	0.9,5,7,2	PNR 5%	PI, PR	5000 µg	C			Walner (2010)
Regulatory studies	G (98.6%) (W)	AR 4% (P1)	PI, PR	2500 µg (-S9)	C			Jensen (1991a)
	G (96.0%) (W)	AR 10%	PI	1000 µg	>HL, C, P			Suresh (1995a)
	G (95.68%) (W)	PR 10%	PR	5000 µg	C			Akanuma (1995b)
	G (95.3%) (W)	AR 10%	PI	5000 µg	C			Callander (1996)
	G (95.6%) (D)	PNR 10%	PI, PR	5000 µg	C			Callander (1996)
	G (95.3%) (W)	AR 10%	PI	5000 µg	C			Thompson (1996)
	GK (60%) (W)	PNR 10%	PI, PR	5000 µg	C			Callander (1999)
	GI (612.7 g/kg) (W)	AR 10%	PI	5000 µg	>HL, S			Ranzani (2000)
	G (95.1%) (W)	PNR 10%	PI, PR	5000 µg	C			Sokolowski (2007a)
	G (97.7%) (W)	PNR 10%	PI, PR	5000 µg	C			Sokolowski (2007b)
	G (95.0%) (W)	PNR 10%	PI, PR	5000 µg	C			Sokolowski (2007c)
	G (98.0) g/kg (D)	AR 2%	PI	5000 µg	S			Ribeiro do Val (2007)
	G (98.0) g/kg (D)	AR 5%	PI	1000 µg	>HL, S			Miyaji (2008)
	G (98.8 % w/w) (W)	AR 5%	PI, PR	3160 µg	C			Flüege (2009a)
	G (96.6% w/w) (D)	PNR 10%	PI, PR	5000 µg	C			Sokolowski (2009a)
G (96.3%) (W)	PNR 10%	PI, PR	5000 µg	C			Sokolowski (2009b)	
G (96.4%) (W)	AR 5%	PI, PR	3160 µg	C			Flüege (2010)	
Regulatory studies	Perceyd 10 SL (7)##	AR 2%##	PI	200 µg/##	##			Chrusciska et al. (2000)
	MON 78239 (36.6% a.c. GK) (W)	AR 10%	PI	3330 µg (-S9)	C			Mecchi (2003a)
	MON 78634	AR 10%	PI	5000 µg (+S9)	C			Mecchi (2003b)
	FSC 3090-H1	AR 5%	PI, PR	316 µg (PI, PR + S9)	C			Ude (2004)
	(360 µL G) (W)	AR 10%	PI	100 µg (PR -S9)	C			Ku (2006)
	MON 78910	AR 10%	PI	3330 µg (-S9)	C			
	(30.3% a.c.) (W)	AR 10%	PI	5000 µg	>HL, S			Lope (2008)
	MON 79672 (68.2% a.c. GA) (D)	AR 7.4%	PI	2000 µg	>HL, S			Mecchi (2008a)
	MON 79664 (38.7% a.c.) (W)	AR 10%	PI	5000 µg	C			Mecchi (2008b)
	MON 76313 (30.9% a.c.) (W)	AR 10%	PI	5000 µg	C			Mecchi (2008c)
	MON 76171 (31.1% a.c.) (W)	AR 5%	PI	5000 µg	C			Mecchi (2009)
	Glyoxalase liquid formulation (480 g/L G1) (W)	AR 5%	PI	200 µg	N			Camolesi (2009)
	MON 76190 (53.2% a.c. GM) (D)	AR 7.4%	PI	2000 µg	>HL, S			Canoyra (2009)
	MON 79991 (71.6% a.c.) (W)	AR 10%	PI	5000 µg	C			Mecchi (2009a)
	MON 76138 (38.5% a.c.) (W)	AR 10%	PI	5000 µg	C			Mecchi (2009b)

(continued)

Table 1. Bacterial reversion assays.

Table 1. Continued

Test material/Solvent ^a	Strains ^j	S9 ⁱ	Treatment ^g		Com ^h	Results ^j		References
			Method	Maximum		Toxicity	Mutagenicity	
MON 77280 (495.29 g/L a.e.) (W)	0,9,5,7,2	AR 5%	PI	200 µg	S	N	neg	Camolesi (2010)
TROP M (Glyphosate 480) (48.46% GI) (W)	0,9,5,7,2	AR 5%	PI, PR	1000 µg (PI) 31.6 µg (PR)	C	T(BR)	neg	Flügge (2010a)
Glyphosate 757 g/kg granular form (76.1% GA) (W)	0,9,5,7,2	AR 5%	PI, PR	100 µg (PI) 10 µg (PR)	C	T(BR)	neg	Flügge (2010d)

^aTest material and solvent used: G, glyphosate technical (acid); GK potassium salt of glyphosate; GI, isopropylamine salt of glyphosate; GA, monoammonium salt of glyphosate. First entry in () for glyphosate or glyphosate salts indicates purity or concentration. First entry in () for GBFs indicates active ingredient, if available, and ingredient concentration. a.e. after % indicates concentration in acid equivalents. Second entry in () indicates test material solvent: (W), water; (D), dimethyl sulfoxide.

^bTest strains used: 0, TA100; 9, TA98; 5, TA1535; 7, TA1537; 7a, TA97a; 2, TA102; 8, TA1538; PU, *E. coli* WP2 (uvrA); PUK, *E. coli* WP2 [pKM101]; PK, *E. coli* WP2 [pKM101].

^cS9 metabolic activation system: AR, Aroclor-induced rat liver; PNR, phenobarbital- and naphthoflavone-induced rat liver; PBR, phenobarbital- and benzoflavone-induced rat liver; percentage number indicates percentage of S9 in S9 Mix.

^dTreatment conditions: Method – treatment methodology: PI, plate incorporation; PR, preincubation. Maximum – maximum amount per plate tested. In some cases differences between treatment conditions were used as indicated.

^eComments on assay: >HL, more than half-log ($\sqrt{10}$) for one or more dose intervals; C, confirmatory experiment reported; S, single experiment reported; P, positive controls that didn't require S9 were used for two strains (TA1535 and TA1537) with S9.

^fResults reported for:

Toxicity: T, toxic effects at maximum concentration or lower; (B), reduced revertants/plate; (BR), reduced background lawn; (BR), reduced revertants/plate and background lawn; N, no toxic effects.

Mutagenicity: overall judgment of assay result for test material: neg, negative; individual study increases in revertants/plate or statistical findings are indicated as individual footnotes.

^gStatistically significant increase for TA100 (+S9) reported in text but not indicated in data tables. Increases were less than two-fold over control and judged not to indicate a treatment-related effect.

^hStatistically significant increases in revertants/plate in one experiment for TA100 +S9, WP2 [pKM101] +S9, TA98 –S9 and WP2 [pKM101] –S9. Increases were less than two-fold, not reproducible in separate experiments and not consistent with a dose-response (e.g. occurring at mid-dose levels). Increases were less than two-fold over control and judged not to indicate a treatment-related effect.

ⁱStatistically significant increases in revertants/plate for several strain/S9 combinations. Increases were all less than two-fold over control values, not reproducible and not consistent with a dose-response and judged not to indicate treatment-related effects.

^jStatistically significant increases in revertants/plate for TA98 +S9 and TA100 +S9. Increases were all less than two-fold, not consistent with a dose-response and judged not to indicate treatment-related effects.

^kStatistically significant ANOVA with increases for lowest dose levels for TA1537 +S9. Increases were all less and two-fold, not consistent with a dose-response and judged not to indicate treatment-related effects.

^lStatistically significant increases for TA98 →S9 (low to mid doses) and for TA100 +S9 at one dose. Increases were judged not to indicate treatment-related effects because they were less and two-fold and not consistent with a dose-response.

^mStatistical analysis suggested in text but not clearly evident in data tables.

ⁿNot clearly indicated in the publication. Numerical data for revertants/plate not presented but summarized as “–” for the lack of mutagenic activity.

^o5000 µg/plate maximum dose level for WP2uvrA –S9 and in one experiment for TA98 and TA1535 –S9 (Mecchi, 2003a).

^pSeveral dose levels exceeded control revertants/plate by more than three-fold in one experiment for TA98 –S9 and TA1535 –S9. There was no dose-response and the result was not observed in a second experiment. The result was considered due to a low control values rather than a treatment-related response.

revertants/plate (TA1535 and TA1537) or exceeding two times the control value for the other strains (Kier et al., 1986). Some studies reported statistical effects. However, none of these cases involved as much as two-fold elevations in revertants per plate and the observations were not consistent with biologically plausible dose-responses. In cases with repeated experiments, any increases in revertants/plate were generally not reproducible between experiments. Therefore, none of the statistically significant effects were judged to indicate mutagenic activity of the test material. Thus, all of the 18 bacterial reversion studies were concluded to be negative as judged by the absence of significant, reproducible, dose-related increases in revertants/plate. These studies provide abundant weight of evidence that glyphosate and glyphosate salt solutions are negative in bacterial reversion assays under experimental conditions that generally satisfy the OECD guidelines.

Glyphosate-based formulations

As reviewed by Williams et al. (2000) most bacterial reversion studies (Ames/*Salmonella* test strains) for GBFs were negative. Four studies reported negative results for Roundup™, Rodeo™, and Direct™-branded GBFs. A reported positive Ames/*Salmonella* result for a Roundup™-branded formulation was not replicated in these studies.

Subsequent to the Williams et al. (2000) review only one published GBF bacterial reversion assay was reviewed (Table 1). This publication reported a negative Ames/*Salmonella* assay result for a GBF of undefined glyphosate composition, Percosyd 10 SL (Chrucińska et al., 2000). Although this result is consistent with the majority of negative Ames/*Salmonella* results for GBFs, the reported study results have significant limitations. One of the recommended test strains, TA1535, was not used and results were only presented as “–” without a presentation of revertants/plate data.

A large number of regulatory bacterial reversion assays have been conducted on GBFs. These are presented in Table 1 with summary data tables in “online supplementary material”. Methodology and experimental design for these studies was generally in compliance with the OECD Guideline 471 (OECD 471, 1997) and with other guidelines. However, two of the studies used some dose level spacings that were larger than the recommended maximum half-log spacing and four studies did not employ a confirmatory assay. All of the assays employed a core battery of *S. typhimurium* test strains (TA98, TA100, TA1535 and TA1537) and employed an additional *S. typhimurium* TA102 or *E. coli* WP2-derived strain to detect oxidative and cross-linking DNA effects as recommended in OECD 471 (1997). The top concentration employed in the assays ranged from 100 to 5000 µg/plate for plate incorporation methodology. With only two exceptions the top dose tested produced the toxicity as evidenced by thinning of the background lawn, reduction in revertants/plate or both. For the two exceptions, the toxicity was noted at higher concentrations per plate in range-finder assays but the toxicity was not noted for the maximum dose selected for the mutagenicity assays.

Only one of the studies exhibited revertants/plate for some strains exceeding up to three-fold of the control value (Meechi

et al., 2003a). However, these increases were not reproducible between experiments and did not exhibit a dose-response pattern. These results were therefore judged to be due to low vehicle control revertants/plate and not to indeterminate treatment-related mutagenic activity. All of the 15 regulatory bacterial reversion studies of GBFs were concluded to be negative as judged by the absence of significant, reproducible, dose-related increases in revertants/plate. These studies provide abundant weight of evidence that a variety of GBFs are negative in properly conducted bacterial reversion assays.

In vitro mammalian cell assays

Glyphosate and glyphosate salts

As reviewed by Williams et al. (2000), a CHO/HGPRT *in vitro* mammalian cell gene mutation assay was reported negative for glyphosate when tested up to toxic dose levels of 22.5 mg/mL (≈ 133 mM), i.e. well above the current top limit of 10 mM (appropriate for glyphosate and glyphosate salts), in the presence and absence of mammalian metabolic activation.

Two regulatory mouse lymphoma tk locus gene mutation studies were reviewed (Table 2 and “online supplementary material”). One study was conducted according to the 1984 OECD guideline for *in vitro* mammalian gene mutation assays (Jensen, 1991b; OECD 476, 1984). Somewhat fewer cells were exposed (3×10^5 – S9, 1.8×10^5 + S9) than the 10^6 cells recommended in the updated OECD guideline (OECD 476, 1997) but this was not considered as a significant deficiency. Cells were exposed at four concentrations up to 4200 µg/mL with S9 (≈ 24.8 mM) or 5000 µg/mL without S9 (≈ 29.6 mM). Although no toxic effects (reduction in cloning efficiency) were seen on day 0 or day 2, these dose levels exceed the currently recommended upper dose level of 10 mM (1.69 mg/mL for glyphosate) for relatively non-toxic test materials (OECD 476, 1997). It should be noted that most OECD guidelines for *in vitro* mammalian cell genotoxicity assays specify an upper limit dose for soluble, relatively non-toxic substances of 10 mM or 5 mg/mL, whichever is lower. The lower and appropriate upper limit dose for glyphosate and glyphosate salts is 10 mM. A second study conducted later followed several updated recommendations for *in vitro* mammalian cell gene mutation assays adopted in 1997 (Clay, 1996; OECD 476, 1997). These included the use of at least 10^6 cells in exposed cultures and consideration of test material effects on pH and osmolality. The latter consideration proved to be important because concentrations of 1500 and 2000 µg/mL (≈ 8.9 – 11.8 mM) produced large (>1 pH unit) decreases in pH and the maximum dose level employed for mutation measurement (1000 µg/mL, ≈ 5.9 mM) was appropriate to avoid excessive effects on pH. This dose level did not produce effects on the day 0 cloning efficiency. Although three dose levels were used in the initial experiment, four dose levels (as recommended in OECD 476, 1997) were used in the confirmatory experiment.

Both of the regulatory mouse lymphoma studies were negative for glyphosate when tested up to dose levels that either exceeded the current limit dose or avoided excessive pH effects. These negative results provide important corroboration of a lack of gene mutation activity in the earlier negative CHO/HGPRT study. They also indicate a lack of

Table 2. *In vitro* mammalian cell assays of glyphosate, glyphosate salt solutions and GBFs.

Test material*	Endpoint	Cell type†	S9‡	Time			Treatment¶			Results			References
				-S9	+S9	Dose levels/ Replicates/ Ind. expts. #	pH	Score †	Tox**	Mutagenicity§§			
											Maximum dose**		
Gene mutation													
Glyphosate and glyphosate salts													
<i>Regulatory studies</i>													
G (98.6%) (M)	TK	ML	AR 30%	4 (48)	3 (48)	4/2C	5000 µg/mL (≈ 29.6 mM)	NI	NA	CE-	neg	Jensen (1991b)	
G (95.6% w/w) (D)	TK	ML	PNR 5%	4 (48)	4 (48)	3 and 4/2C	4200 µg/mL (≈ 24.8 mM) 1000 µg/mL (≈ 5.9 mM)	pH	NA	RS-	neg	Clay (1996)	
Chromosomal aberration or micronucleus													
Glyphosate and glyphosate salts													
<i>Literature studies</i>													
GI (62%) (W)	CB MN	BL	none	24	24	5/7C	0.56 mM	NI	1000BN (NC)	CBPI-	neg	Pisova (2004)	
GI (62%) (W)	CB MN	BL	none	48	48	5/7C	0.56 mM	NI	1000BN (NC)	CBPI-	equiv	Pisova (2005)	
GI (62%) (W)	CB MN	BL	AR 10%	2 (20)	2 (20)	5/7C	0.56 mM	NI	1000BN (NC)	CBPI-	equiv	Holickova (2006)	
GI (62%) (W)	CA (I)	BL	none	24	24	6/7C	1.12 mM	NI	350-900 (NC)	NI	neg##	Sivikova & Dianovsky (2006)	
GI (62%) (W)	CA	BL	none	24	24	6/7C	1.12 mM	NI	100M (NC)	MI+	neg	Mamas et al. (2009)	
G (96%) (M)	CA	HL	none	48	48	3 (>HL)/7C	6 mM	pHa	100M	MI-	neg	Mladinic et al. (2009b)	
G (98%) (P)	CB MN	HL	none	4 (72)	4 (72)	5 (>HL)/2C	580 µg/mL (≈ 3.43 mM)	pHa	1000BN (NC)	EA+	equiv^	Mladinic et al. (2009a)	
G (98%) (P)	CB MN	HL	H 10%	4 (72)	4 (72)	5 (>HL)/2C	580 µg/mL (≈ 3.43 mM)	pHa	1000BN (NC)	EA-	pos	Koller et al. (2012)	
G (98%) (P)	CB MN	HL	H 10%	4 (72)	4 (72)	5 (>HL)/2C	580 µg/mL (≈ 3.43 mM)	pHa	2000BN (NC)	CBPI-	equiv^^	Wright (1996)	
G (95.6%) (M)	CB MN	TR146	none	20 min. (48)	3 (30)	3/3S	20 mg/L (≈ 0.12 mM)	NI	>3000BN (NC)	AP+	pos	Fox (1998)	
Regulatory studies													
G (95.3% w/w) (M)	CA	CHL	AR 5%	6 (24), 24, 48	6 (24)	3/2S	1250 µg/mL (≈ 7.39 mM)	pH	200M	RG-	neg	Wright (1996)	
G (95.6%) (M)	CA	HL	PNR 25%	20	3 (30)	3 (>HL)/2C	1250 µg/mL (≈ 7.39 mM)	pH	300M	MI+(-S9)	neg	Fox (1998)	
G (95.6%) (M)	CA	HL	PNR 25%	44	3 (44)	1/2S	1250 µg/mL (≈ 7.39 mM)	pH	200M	MI-	neg	Fox (1998)	

(continued)

Table 2. Continued.

Test material*	Endpoint†	Cell type‡	S9§	Treatment¶			Dose levels/ Replicates/ Ind. exps. #	Maximum dose**	pH††	Score‡‡	Tox***	Mutagenicity§§	References
				Time	-S9	+S9							
G (95.68%) (H,M)	CA	CHL	PBR 30%	6 (24)		6 (24)	3/2/S	1000 µg/mL (≈ 5.92 mM)	pHn	200 M	M1-	neg	Matsumoto (1995)
				24			3/2/S	500 µg/mL (≈ 2.96 mM)	pHn	200 M	M1-	neg	
				48			3/2/S	500 µg/mL (≈ 2.96 mM)	pHn	200 M	M1-	neg	
GBFs													
<i>Literature studies</i>													
herbazed (R4% G) (M)	CA	MS	none	24			3 (>HL)/5/S	50 mM§§	NI	500 M	VC+	pos	Amer et al. (2006)
Roundup™ Max (450 g/L G) (M)	Ultra CB MN	TR146	none	20 min (48)			3/3/S	20 mg/L glyphosate (≈ 0.12 mM)	NI	>3000BN (NC)	AP+ NE- NB+	pos	Koeller et al. (2012)

*Test material and solvent used: G, glyphosate technical (acid); GK, potassium salt of glyphosate; GI, isopropylamine salt of glyphosate; GA, monoammonium salt of glyphosate. First entry in () for glyphosate indicates percent purity or concentration. First entry in () for GBFs indicates active ingredient and ingredient concentration. Second () entry indicates test material solvent. (W) water. (D) dimethyl sulfoxide; (M) culture medium; (H) Hanks balanced salt solution; (P), phosphate buffered saline.

†Assay endpoint: TK, gene mutation at the TK locus; CA, chromosomal aberration; CA (f), chromosomal aberration (FISH analysis of chromosome 1 for acentric fragments); CB MN, cytokinesis block micronucleus

‡ML, L5178Y mouse lymphoma; CHL, Chinese hamster lung; HL, human peripheral blood lymphocytes; BL, bovine peripheral blood lymphocytes; TR146, human buccal epithelial cell line; MS, mouse spleen cells

¶In cases where treatments differ in the presence and absence of exogenous metabolic activation treatment parameters are presented on separate lines

§Type of S9 used with %S9 homogenate in S9 Mix indicated in (): AR, Aroclor-induced rat liver; PNR, phenobarbital/naphthoflavone-induced rat liver; PBR, phenobarbital/5,6-benzoflavone-induced rat liver; H, human liver; ? S9 not clearly indicated; none, no experiments conducted with exogenous mammalian metabolic activation

||Duration of treatment in hours with total time or times to harvest in hours from treatment in () if treatment was not continuous. min indicates minutes of treatment for one study

#First number: number of analyzable treatment dose levels with (>HL) indicating spacing between one or more treatment levels greater than half-log; second number: number of replicates cultures for each treatment with ? indicating that number of replicates is not clear; third character: C, confirmatory experiments reported for cell lines or multiple donors for lymphocytes; S, no confirmatory experiment reported

**Maximum dose level tested and scored with calculated mM in () for glyphosate.

††Assessment or consideration of pH effects of test material: NI, no measurement or control of pH reported; pH, large pH effects noted at higher concentrations and maximum set to minimize pH effects; pHn, effects on pH noted but not used to set maximum treatment concentration; pHa, pH adjusted.

‡‡Number of cells or metaphases scored per treatment level/time point for chromosomal aberration and micronucleus assays. M, metaphases; BN, binucleated cells. (NC) indicates that coding of slides for scoring was not explicitly indicated. In some cases coding was not explicitly indicated but may have been implied by a reference citation. NA, not applicable.

¶¶Measurement of cytotoxicity with + indicating effects on endpoint at one or more treatment levels and - indicating no effects on endpoint up to maximum treatment level.

CE, cloning efficiency; RS, relative survival; RG, relative growth; MI, mitotic index; CBPI, cytokinesis block proliferation index; EA, early apoptosis; NE, necrosis; AP, apoptosis; NB, nuclear buds; LDH, LDH release (cell integrity); NR, neutral red (vital stain); VC, viable cell staining; NI, no concurrent cytotoxicity measurement reported.

§§ Evaluation of mutagenicity or chromosomal effects: neg, negative; pos, positive; equiv, equivocal. Evaluation different from publication or report indicated with individual footnote.

|||Statistically significant increases observed at a single different dose for each of two donors. Publications indicate dose responses were not observed and effects were weak or minimal with 48 h treatment. ##No positive control reported.

\$Lymphocytes apparently treated before exposure to mitogenic stimulus.

^Small increases in MN frequency in binucleate cells observed for a wide range of dose levels (3.5–580 µg/mL) but not statistically significant.

^^No statistically significant increases in MN frequency for any dose level. Statistically significant correlation observed between dose and MN frequency but approximately the same small increase was observed over a very wide range of doses (3.5–580 µg/mL) and this is considered to be questionable as a biologically plausible dose response.

SSCalculated from the stated concentration of 5×10^{-5} M glyphosate/mL.

induction of effects such as large deletions in DNA that may be detected in the autosomal *tk* locus assay (Aaron et al., 1994).

Glyphosate-based formulations

No *in vitro* mammalian cell gene mutation assays of GBFs were observed in the published literature or the regulatory study reports.

Other non-mammalian assays

Glyphosate and glyphosate salts

No gene mutation assays on glyphosate other than bacterial reversion or *in vitro* mammalian test systems were reported in Williams et al. (2000) or as regulatory studies. A positive result for glyphosate was reported in the *Drosophila* wing spot assay which can indicate both gene mutation and mitotic recombination endpoints (Kaya et al., 2000). Small increases in small wing spot frequencies were observed in one of four crosses of larvae treated with up to 10 mM (≈ 1.69 mg/mL) of glyphosate. Negative or inconclusive results were observed for the other crosses. The lack of a positive response in the balancer-heterozygous cross offspring, which are insensitive to mitotic recombination events, suggests that there is no evidence for effects on gene mutation endpoint events such as intragenic mutations or deletions in this publication.

Glyphosate-based formulations

Williams et al. (2000) described one report of a positive result for a GBF in the *Drosophila* sex-linked recessive lethal assay but this was contradicted by a negative result for the same GBF in this assay reported by another laboratory. Further, the positive study had some features that hampered interpretation, including the lack of concurrent negative controls (Williams et al., 2000). No non-mammalian cell gene mutation assays of GBFs other than bacterial reversion assays were observed in the published literature or the regulatory study reports.

Chromosomal effects endpoints

In vitro mammalian cell assays

Glyphosate and glyphosate salts

Two human and one bovine *in vitro* peripheral lymphocyte chromosomal aberration studies of glyphosate were considered in the earlier review (Williams et al., 2000). One human lymphocyte *in vitro* study had negative results for glyphosate tested up to 0.33 mg/mL and 0.56 mg/mL (≈ 2 –3 nM) in the absence and presence of an exogenous mammalian activation system, respectively. The other two studies with human and bovine lymphocytes and no metabolic activation system reported positive results at concentrations more than two orders of magnitude lower. The reasons for the conflicting results are unclear, but the Williams et al. (2000) review noted several unusual features about the positive studies including an unusual exposure protocol and discordant positive results for another chemical found negative in other laboratories.

Subsequent to the Williams et al. (2000) review, four publications have reported results for glyphosate salt solutions using cytokinesis block micronucleus (CB-MN) or

chromosomal aberration endpoints with cultured bovine lymphocytes (Table 2). These publications used a test material reported as 62% by weight isopropylamine salt of glyphosate from a Monsanto source. This test material appears to be a manufacturing batch of the isopropylamine salt of glyphosate in water without surfactants, which is not sold as a formulation. In two publications from one laboratory, no statistically significant increases in the frequencies of micronucleated binucleate cells were observed following the treatment with up to 560 μ M (≈ 94.7 μ g/mL, acid equivalent, a.e.) for 24 h in the absence of S9 (Piesova, 2004) or 2 h in the absence and presence of a mammalian metabolic activation system (Piesova, 2005). These two studies report a statistically significant increase in micronucleus frequency with 48 h of treatment without S9 in one donor at 280 μ M (≈ 47.3 μ g/mL, a.e.) but not at 560 μ M and in a second donor at 560 μ M but not 280 μ M. The lack of a consistent response pattern between donors suggests that the results after 48 h of treatment are questionable. Two other publications found negative results for the chromosomal aberration endpoint in cultured bovine lymphocytes with what appears to be the same isopropylamine glyphosate salt solution (Holeckova, 2006; Sivikova & Dianovsky, 2006). Both of these studies used a maximum concentration of 1.12 mM (≈ 0.189 mg/mL, a.e.), which was reported to induce a decrease in mitotic index of >50%, and treatments of 24 h without S9. These two studies have several limitations including no use of an exogenous mammalian metabolic activation system. In addition, Holeckova (2006) only examined effects detectable by staining of chromosome 1 and apparently did not use a positive control. These four studies consistently indicated the lack of chromosomal damaging effects in bovine lymphocytes in the absence of metabolic activation following up to 24 h of exposure to 0.56–1.12 mM (≈ 0.094 –0.189 mg/mL, a.e.) concentrations of glyphosate isopropylamine salt.

Three publications reported testing of technical glyphosate for micronucleus or chromosomal aberration endpoints in cultured human lymphocytes (Table 2; Munax et al., 2009; Mladinic et al., 2009a,b). The treatment schedule of the Mladinic et al. publications is not clear. Although standard procedures for human lymphocyte assays recommend the treatment of exponentially growing cells at 44–48 h after mitogenic stimulation (OECD 487, 2010), the methodology described in the Mladinic et al. publications suggests that the 4 h treatment took place before mitogen stimulation. The cultures were then centrifuged and washed before mitogen was added. Thus, only non-dividing cells would have been exposed and this is clearly not in accordance with the OECD guideline. It is also unclear how long the cultures were maintained after the treatment. It appears that they may have been cultured for 72 h after the treatment, which suggests that the cells would have passed through the required 1.5–2 cell cycles after reaching the exponential growth (OECD 487, 2010) even though it appears they were not exposed during the exponential growth. Negative or equivocal results for the micronucleus and chromosomal aberration endpoints were observed in the absence of exogenous metabolic activation (S9) in all three publications. The maximum exposure concentration in the absence of S9 was in the range of 3–6 mM (≈ 0.51 –1.0) mg/mL in these studies.

In contrast to the cultured bovine and human lymphocyte results, Koller et al. (2012) reported positive results for glyphosate in a CB MN assay using cultured human buccal epithelial cells in the absence of S9. Limitations of this study include no explicit indication of coding of slides or control of pH. However, pH effects would probably not have been observed at the concentrations used. Statistically significant effects were observed at treatment levels of 15–20 mg/L (≈ 0.09 – 0.12 mM) for 20 minutes. Statistically significant effects on nuclear morphology (nuclear buds and nucleoplasmic bridges) were observed at 10–20 mg/L, and statistically significant increases in apoptosis and necrosis were observed at 20 mg/L. The concentrations and exposure times reported as producing effects in this study are substantially lower than the upper dose levels and exposure times used in the previously discussed studies. The results for this discrepancy are not clear, although Koller et al. (2012) suggest that epithelial cells may be more sensitive to the effects of glyphosate than cells of the hematopoietic system such as lymphocytes. It should be noted that negative genotoxicity results have been observed in a number of regulatory *in vitro* mammalian cell genotoxicity studies using cultured cells other than lymphocytes (mouse lymphoma and CHL cells).

Mladinic et al. (2009a,b) reported increases in micronucleated cells using the cytokinesis-block method in cultured human lymphocytes exposed to glyphosate for 4 h in the presence of an exogenous human liver metabolic activation system (S9). As discussed above, the methodology used in these studies is unclear, but it appears that cells were treated before mitogenic stimulation and cultured for 72 h. In both publications, a statistically significant increase in micronuclei was observed with S9 at the highest dose level of glyphosate tested (580 $\mu\text{g}/\text{mL}$, ≈ 3.4 mM), but how this could be possible when undividing cells were exposed is unclear. Increased proportions of centromere- and DAPI-positive micronuclei were observed for the high-dose with S9 suggesting that the induced micronuclei were derived from chromosome loss rather than chromosomal fragments. This observation is somewhat unusual, because there do not appear to be any known aneuploidy-inducing agents that require metabolic activation (Kirsch-Volders et al., 2003). Statistically significant increases in the frequency of nuclear abnormalities (buds and bridges) and DNA strand breakage were also observed at the highest dose tested in both publications. In parallel experiments cytotoxic effects such as early apoptosis, late apoptosis and necrosis were observed and these effects tended to be enhanced in the presence of S9 (Mladinic et al., 2009a). Also, the negative control levels of such endpoints as necrosis and comet tail moment were significantly increased in the presence of S9 (Mladinic et al., 2009a). It should be noted that glyphosate is mostly excreted unmetabolized *in vivo* in mammals with only very small levels of aminomethylphosphonic acid (AMPA) or an AMPA-related structure observed (Anadon et al., 2009; Brewster et al., 1991). There is also one report that glyphosate is essentially unmetabolized *in vitro* in the presence of a rat liver S9 homogenate (Gohre et al., 1987). It also does not seem likely that human S9, used by Mladinic et al., would be expected to be more active than much more commonly used induced rat liver S9. These observations suggest that the S9

mediated effects reported by Mladinic et al. are not likely to be due to *in vivo* relevant metabolites. Given the unusual methodology in these studies, the chromosomal-damaging effects of glyphosate in the presence of S9 are not convincing, and it is possible that artifacts due to low pH in the presence of S9 (Cifone et al., 1987; Morita et al., 1989; Scott et al., 1991) may be responsible. Such effects would not be relevant to *in vivo* exposures.

Three regulatory *in vitro* mammalian cell chromosomal aberration studies were conducted on technical glyphosate (Table 2 and "online supplementary material"). These studies were conducted in accordance with the 1983 OECD Guideline 473 for the *in vitro* mammalian chromosomal aberration test (OECD 473, 1983). The study protocols employed exposures in both the presence and absence of an exogenous mammalian metabolic activation system. Treatment and harvest times were appropriate to assess cells exposed in different stages of the cell cycle. Treatment times included a shorter treatment with and without S9 and extended treatments without S9. Appropriate media and culture conditions for these assays were confirmed by experimental results for negative and positive control exposures. In these studies slides were coded before the analysis and 200 metaphases per treatment were scored for chromosomal aberrations, as recommended in the updated OECD Guideline 473 (OECD 473, 1997). The maximum dose levels used in two of the studies (1250 $\mu\text{g}/\text{mL}$, ≈ 7.4 mM; Fox, 1998; Wright, 1996) were set so as to avoid excessive pH shifts as recommended in the updated OECD Guideline 473. The third study (Matsumoto, 1995) used maximum dose levels (500–1000 $\mu\text{g}/\text{mL}$, ≈ 3 – 5.9 mM) set by rangefinder results but noted pH-related medium color changes at dose levels of 500 $\mu\text{g}/\text{mL}$ and higher.

No induction of chromosomal aberrations was observed in these regulatory studies employing cultured Chinese hamster lung (CHL) cells (two studies) or in two experiments with cultured human lymphocytes from different donors (third study). The two CHL studies also reported negative results for polyploidy induction. Taken together, these three studies provide clear evidence for the lack of *in vitro* mammalian cell clastogenic activity of glyphosate in robust assays for two different mammalian cell types conducted under a variety of exposure conditions in the absence and presence of S9.

The reviewed results for mammalian *in vitro* chromosomal effect assays demonstrate a weight of evidence that technical glyphosate and glyphosate salt concentrates are generally negative for this endpoint in cultured mammalian cells in the absence of an exogenous mammalian metabolic activation system. Three publications from three laboratories and three regulatory studies report negative *in vitro* mammalian cell chromosomal aberration or micronucleus results in the absence of exogenous activation. Two of the CHL regulatory studies also reported negative results for polyploidy induction. Two publications from one laboratory have questionably equivocal results for the micronucleus endpoint in human lymphocytes in the absence of exogenous activation, while two publications from another laboratory reported positive results for bovine lymphocytes only with extended treatment but these results did not exhibit a consistent dose-response between donors. One publication reported positive

results for human epithelial cells in the absence of S9 with a short exposure time. The negative studies were conducted at upper dose levels and with treatment times that were the same or higher than the studies with positive or equivocal results and include different cell types. These results reinforce the Williams et al. (2000) conclusion that positive chromosomal aberration results reported for glyphosate in cultured human lymphocytes in the absence of an exogenous metabolic activation system are not convincing.

Recent reports of positive chromosomal effect results for glyphosate in the presence of an exogenous mammalian activation system in cultured human lymphocytes in one laboratory (Mladinic et al., 2009a,b) were not reproduced in three *in vitro* mammalian cell chromosomal aberration regulatory studies, including a study that employed cultured human lymphocytes. These positive results are also discordant with one previously reviewed result demonstrating a negative result for glyphosate in cultured human lymphocytes with mammalian metabolic activation using the chromosomal aberration endpoint (Williams et al., 2000) and a negative result in the presence of S9 for the micronucleus endpoint in bovine lymphocytes (Plesova, 2005). They are also discordant with negative results for three *in vitro* mammalian cell gene mutation studies that included an exposure to S9. The unusual methodology used for cultured human lymphocytes in the Mladinic et al. studies further complicates the interpretation of results from these studies. Thus, the weight of evidence for the *in vitro* chromosomal effect assays generally indicates a lack of chromosomal effects in either the presence or absence of S9.

Glyphosate-based formulations

No *in vitro* mammalian cell chromosomal aberration assays of GBFs are described in Williams et al. (2000).

Only two publications with data from *in vitro* mammalian cell chromosomal aberration assays of GBFs have been found since the review of Williams et al. (2000). Results are in Table 2. Amer et al. (2006) reported positive *in vitro* chromosomal aberration effects in mouse spleen cells for a test material described as "herbazed" herbicide, which was reported to contain 84% glyphosate and 16% solvent, an unusually high glyphosate concentration for a formulation. The test material is not further characterized in the publication but is considered a GBF in this review. The glyphosate or GBF concentrations to which the cells in the study were exposed are not entirely clear because the most consistent concentration unit used in the report is M glyphosate/ml which is an unusual concentration unit. Assuming this means, moles of glyphosate per mL the maximum exposure would be 5×10^{-5} M glyphosate/mL medium or 50 mM. An upper exposure concentration of 50 mM (≈ 8.45 mg/mL glyphosate) would be well in excess of the limit level of 10 mM or 5 mg/mL currently recommended in the OECD guidelines (OECD 473, 1997). In addition to the uncertainty regarding the concentrations used, there are several other limitations to the reported study including no indication that pH of treatment solutions was controlled, no use of a mammalian metabolic activation system and no reported use of coded slides for scoring. Given these limitations, the uncertainty

about the concentrations used and the nature of the test material, these results should not be considered to have significant relevance with respect to typical GBFs.

Another publication reported positive results for Roundup™ UltraMax GBF for the CB MN assay in cultured human buccal epithelial cells (Koller et al., 2012). Limitations in conduct or reporting of this study included no indication that pH of treatment solutions was controlled and no explicitly reported use of coded slides for scoring. As noted earlier, pH effects would not be likely at the low concentrations used. Increased MN frequencies were reported for 20 minute treatments with 10–20 mg/L of glyphosate a.i. (≈ 0.06 – 0.12 mM glyphosate). Statistically significant effects on nuclear morphology (nuclear buds and nucleoplasmic bridges) were also observed at 10–20 mg/L and increases in apoptosis and necrosis were observed at 20 mg/L but only the necrosis effect was statistically significant.

There were no regulatory studies of GBFs in *in vitro* mammalian cell chromosomal aberration or micronucleus assays. Thus, there are only the two studies of different GBFs (discussed above) with uncertainties and limitations in this endpoint category. While the published literature reports suggest the possibility of activity of GBFs in *in vitro* chromosomal damage assays, the paucity of studies and their limitations do not permit a generic conclusion regarding this endpoint for *in vitro* mammalian cells for GBFs in general.

In vivo mammalian assays

Micronucleus and chromosomal aberration

Glyphosate and glyphosate salts

The Williams et al. (2000) glyphosate toxicity review presented results from *in vivo* mammalian chromosomal effect assays. Results from several mouse bone marrow erythrocyte studies of glyphosate were negative for micronucleus induction. These included the studies from different laboratories mostly following modern guidelines. The intraperitoneal (i.p.) route was used for most of the negative studies. In addition to i.p. studies, a 13-week mouse feeding study was also negative for the micronucleus endpoint with an estimated maximum daily glyphosate dose of over 11 000 mg/kg body weight/day. There was one published report of a weak positive mouse bone marrow micronucleus response observed for glyphosate. This study, which employed a smaller number of animals per group than other negative studies, clearly conflicted with the numerous other negative studies, not only in terms of increased micronucleus frequencies but also the finding of altered polychromatic erythrocyte to normochromatic erythrocyte (PCE/NCE) ratios. The overall weight of evidence from the earlier reviewed studies was that glyphosate and glyphosate formulations were negative in the mouse bone marrow erythrocyte micronucleus assay. The earlier review also noted a negative mouse dominant lethal result for glyphosate administered by gavage at a maximum dose level of 2000 mg/kg body weight.

As indicated in Table 3, two publications reported results for glyphosate in the mouse bone marrow erythrocyte micronucleus assay. It should be noted that there are some fairly

consistent limitations in the reported conduct of these studies compared to the OECD guidelines. In these studies, concurrent indications of the toxicity other than PCE/NCE ratio effects on the bone marrow and mortality are not reported, coding of slides for scoring is not explicitly reported and fewer than the currently recommended number of 2000 PCEs or erythrocytes per animal were scored. As noted earlier, failure to explicitly report coding of slides in the methodology may reflect either failure to code slides or failure to explicitly indicate this in the methodology description in the publication.

Negative results were reported in one study which used a dose of 300 mg/kg body weight of glyphosate administered once i.p. with sacrifices at 24, 48 and 74 h after dosing (Chruscielska et al., 2000). This study had some limitations including the use of only one dose level (several dose levels should be used except when there is no toxicity up to the limit dose), and no explicit reported coding of slides for scoring and scoring of only 1000 PCEs per animal. A second publication reported positive results for glyphosate administered at 50, 100 and 200 mg/kg body weight via two i.p. injections 24 h apart, with sacrifice at 24 h after the second dose (Munus et al., 2009). A statistically significant increase in micronucleated erythrocytes was observed in the high-dose group in this study. A particular concern with this second publication is that "erythrocytes" rather than polychromatic erythrocytes were indicated as scored for micronuclei. This does not appear to be a case of using "erythrocytes" to mean polychromatic erythrocytes because the term "polychromatic erythrocytes" is used elsewhere in the publication describing measurements of PCE/NCE ratios. Scoring of all erythrocytes instead of immature polychromatic erythrocytes for micronuclei would be inappropriate in an assay with the stated treatment and harvest times because of the transient nature of micronucleated PCEs in bone marrow (OECD 474, 1997). PCEs containing micronuclei would not have reached maturity in such a short time, so micronuclei in matured erythrocytes could not have been induced by the chemical treatment.

There is no definitive explanation for the discrepancy between the two publications. Although one study used a single dose with multiple harvest times and the second used two doses and a single harvest time, both are acceptable protocols and would not be expected to lead to such discordant results (OECD 474, 1997). The negative result reported for the 13-week feeding study in the earlier review (Williams et al., 2000) confirms that positive results are not simply due to the repeated dosing. The reported negative result (Chruscielska et al., 2000) seems to be in accordance with a majority of earlier reviewed mouse bone marrow micronucleus studies of glyphosate using similar doses and the i.p. or feeding routes (Williams et al., 2000). Also, the apparent scoring of micronuclei in erythrocytes at such an early time point raises questions regarding the reported positive study.

A large number of regulatory rodent bone marrow assays were conducted on technical glyphosate or glyphosate salt solutions (Table 3 and "online supplementary material"). Most of these were mouse bone marrow erythrocyte micronucleus studies, but there is also one rat bone marrow erythrocyte micronucleus assay and one mouse bone marrow chromosomal aberration study. Most of the rodent bone marrow erythrocyte micronucleus studies were reported to be

conducted in accordance with the OECD Guideline 474 (1983) for studies conducted prior to 1997 and the OECD Guideline 474 (1997) for studies conducted after 1997. The mouse bone marrow chromosomal aberration study was reported as conducted according to the OECD Guideline 475 (OECD 475, 1984). Protocol features for the micronucleus studies included single dosing with harvest at 24 and 48 h after the treatment (also 72 h in one study) or two treatments 24 h apart with a single harvest at 24 h after the last treatment. These treatment and harvest time alternatives are both considered acceptable in the most recent guideline (OECD 474, 1997) for bone marrow erythrocyte studies. For the bone marrow chromosomal aberration study, the use of a single 24 h sampling time after two treatments separated by 24 h deviates from an earlier recommendation to have 6 h and 24 h sampling times with multiple dosing (OECD 475, 1984), but differs slightly from more recent recommendations to sample approximately 1.5 cell cycles (usually around 12–18 h) after two daily doses (OECD 475, 1997). Some studies used only males when there was no evident difference in toxicity to both sexes, which is acceptable under the most recent guideline (OECD 474, 1997). Three treatment groups were generally used but some studies only used a single high-dose group when a limit dose had little or no toxicity as accepted in OECD 474 (1997). In most studies, 2000 PCEs per animal were scored as recommended in the most recent guideline (OECD 474, 1997). The earlier guideline had recommended scoring 1000 PCEs per animal (OECD 474, 1983). In the mouse bone marrow chromosomal aberration study, 50 metaphases per animal were scored, which is lower than the currently recommended 100 metaphases per animal (OECD 475, 1997).

Eleven mouse and one rat bone marrow erythrocyte micronucleus regulatory studies for technical glyphosate or glyphosate salt solutions were conducted. The upper dose levels for orally administered glyphosate were, with one exception, the earlier suggested limit dose of 5000 mg/kg body weight or the more recently recommended limit dose of 2000 mg/kg body weight. In these studies little or no toxicity was observed at the limit dose. One study (Zoriki Hosomi, 2007) observed considerable toxicity and lethality at an oral dose of 50 mg/kg body weight and employed a lower maximum dose level for the main study (30 mg/kg body weight). The reason for the higher reported toxicity in this study compared to other glyphosate studies is not apparent. Studies of glyphosate employing the intraperitoneal route generally employed lower maximum dose levels (62.5 to 3024 mg/kg body weight) and the maximum dose levels were set by observations of toxicity and lethality in range-finder studies.

Micronucleated PCE frequency results for the maximum dose levels of the regulatory rodent bone marrow micronucleus studies of glyphosate and glyphosate salts are presented in Table 4. For eight of the 12 regulatory bone marrow erythrocyte micronucleus studies there were no statistically significant increases in micronucleated PCEs observed for any of the glyphosate treated groups. Three studies had small statistically significant increases in micronucleated PCE frequency that were judged not to be treatment related because the frequencies were well within historical

Table 3. *In vivo* mammalian chromosomal effect studies.

Test material*	Endpt†	Strain/Species	Treatment‡					Maximum dose	Scoring*	Results‡ Tox	Mutagenicity	References
			Veh	Rte	No/Sex	Grps	Schedule					
Glyphosate and glyphosate salts												
<i>Literature MN studies</i>												
G	BM MN	C3H mice	W	i.p.	6M	1	S (24, 48C, 72)	300	1000P (NC)	M-, R-	neg	Chruscielska et al. (2000)
G (96%)	BM MN	BalbC mice	S?	i.p.	5M 5F	3	T (24)	300	1000E(NC)	M-, C-, R-	pos	Manas et al. (2009)
<i>Regulatory MN studies</i>												
G (98.6%)	BM MN	NMR1 SPF mice	0.5% CMC	p.o.	5M 5F	1	S (24, 48C, 72)	5000	2000P *N	M-, R-	neg	Jensen (1991c)
G (96.8%)	BM MN	Swiss mice	PO	p.o.	5M 5F	3 (>HL)	T (24)	5000	≈2000E (NC) ≈1000P	M-, C-, R-	inc#	Suresh (1993b)
G (95.6% w/w)	BM MN	CD-1 mice	PS	p.o.	5M 5F	1	S (24, 48)	5000	2000P	M-, C-, R-	neg	Fox & Mackay (1996)
GK (59.3%)	BM MN	CD-1 mice	W	p.o.	5M	1	S (24, 48)	2000	2000P	M-, C-, R-	neg**	Jones (1999)
G (954.9 g/kg)	BM MN	Swiss albino mice	W	i.p.	5M 5F	3	T (24)	562.5	1000P 1000N	M-, R-	neg	Marques (1999)
G† (612.7 g/kg)	BM MN	Swiss albino mice	W	i.p.	5M† 5F††	3	T (24)	3024	1000P *N	M+, R-	neg	Gava (2000)
G (97.73%)	BM MN	NMR1 mice	PEG 400	p.o.	5M 5F	3	S (24, 48 H)	2000	2000P	M-, C-, R-	neg	Honarvar (2005)
G (95.7% w/w)	BM MN	Cr:CD-1 ⁴ (ICR) BR mice	PBS	i.p.	7M	3	S (24, 48 CH)	600	2000P	M-, C+, R+	neg††	Durward (2006)
G (980.1 g/kg)	BM MN	Swiss mice	W	p.o.	6M	3	T (24)	30	3000P	M-, R-	neg**	Zoriki Hosomi (2007)
G (99.1% w/w)	BM MN	NMR1 mice	0.5% CMC	p.o.	5M	3 (34 h)	S (24, 48 CH)	2000	2000P	M-, C-, R-	neg	Honarvar (2008)
G (980.0 g/kg)	BM MN	Swiss albino mice	CO	i.p.	5M 5F	3	T (24)	62.5	2000P *N	M-, R-	neg	Costa (2008)
G (98.8% w/w)	BM MN	Cr(CD)(SD) rats	0.8% HPMC	p.o.	5M 5F	3	S (24, 48 CH)	2000	2000P	M-, C-, R-	neg	Flügge (2009b)
<i>Regulatory CA study</i>												
G (96.8%)	BM CA	Swiss albino mice	PO	p.o.	5M 5F	1	T (24)	5000	50M	M-, C+, MI-	neg	Suresh (1994)
GBFs												
<i>Published studies</i>												
Perzocyd 10 SL	BM MN	C3H mice	W	i.p.	6M	1	S (24, 48C, 72)	90	1000P (NC)	M-, R-	neg	Chruscielska et al. (2000)
Roundup™ 69	BM MN	mice	NI	i.p.	6M	3	T (25)	200	1000P (NC) 1000N	M-, R-	neg	Continho do Nascimento & Grisolia (2000)
Roundup (480 g/L GI)	BM MN	Swiss mice	W?	i.p.	8M 8F	3	T (24)	200	2000E(P) NC	M-, R-	neg	Grisolia (2002)
Roundup (480 g/L GI)	BM CA	New Zealand white rabbits	W	d.w.	5M	2§§	60 days	750 ppm	50M (NC)	M-	pos	Helal & Moussa (2005)
Herbazed (84% G)	BM CA	Swiss mice	NI	i.p.	5M	1	1, 3, 5d (24)	50 gly?	100M (NC)	M-	inc	Amer et al. (2006)
Herbazed (84% G)	SC CA	Swiss mice	NI	i.p.	5M	1	1, 3, 5d (24)	50 gly?	100M (NC)	M-	pos	
Herbazed (84% G)	BM CA	Swiss mice	NI	p.o.	5M	2	1, 7, 14, 21d (24)	100 gly?	100M (NC)	M-	pos	
Herbazed (84% G)	SC CA	Swiss mice	NI	p.o.	5M	2	1, 7, 14, 21d (24)	100 gly?	100M (NC)	M-	pos	
Roundup	BM CA	C57BL mice	W	p.o.	8M	1	S (6, 24, 48, 72, 96, 120)	1080	50M	M-	neg	Dimitrov et al. (2006)

(continued)

Table 3. Continued.

Test material*	Endpt†	Strain/Species	Treatment‡					Maximum dose	Scoring*	Results§		References
			Veh†	Rtc	No/Sex	Grps	Schedule			Tox	Mutagenicity	
Roundup (41% GI)	BM MN	C57BL mice	W	p.o.	8M	1	S (24, 48, 72, 96, 120)	1080	500P	M-, R-	neg	Dimitrov et al. (2006)
	BM CA	Swiss mice	DMSO	i.p.	5M	2	S (24, 48, 72)	50 gly ²	75M (NC)	M-, MI+	pos	Prasad et al. (2009)
	BM MN	Swiss mice	DMSO	i.p.	5M	2	S (24, 48, 72)	50 gly ²	2000(P) (NC)	M-, MI+	pos	
<i>Regulatory studies</i>												
MON 78239 (36.6% a.e. GK)	BM MN	Cr:CD-1 ⁹ (ICR) BR mice	W	p.o.	5M	3	S (24, 48CH)	2000	2000P	M-, C-, R-	neg##	Erexson (2003a)
MON 78634 (65.2% a.e.)	BM MN	Cr:CD-1 ⁹ (ICR) BR mice	W	p.o.	5M	3	S (24, 48CH)	2000	2000P	M-, C-, R-	neg	Erexson (2003b)
MON 78910 (30.3% a.e.)	BM MN	CD-1 ⁹ (ICR)BR mice	W	p.o.	5M	3	S (24, 48CH)	2000	2000P	M-, C-, R-	neg	Erexson (2006)
MON 79864 (38.7% a.e.)	BM MN	Hsd:ICR(CD-1) mice	W	p.o.	5M	3	S (24, 48CH)	2000	2000P	M-, C+, P-	neg##	Xu (2008a)
MON 76171 (31.1% a.e.)	BM MN	CD-1 ⁹ (ICR)BR mice	W	p.o.	5M	3	S (24, 48CH)	2000	2000P	M-, C-, R-	neg	Xu (2008b)
MON 79991 (71.6% a.e.)	BM MN	CD-1 ⁹ (ICR)BR mice	W	p.o.	5M	3	S (24, 48CH)	2000	2000P	M-, C-, R+?	neg	Xu (2009a)
MON 76138 (38.5% a.e.)	BM MN	CD-1 ⁹ (ICR)BR mice	W	p.o.	5M	3	S (24, 48CH)	2000	2000P	M-, C-, R-	neg	Xu (2009b)
MON 76313 (30.9% a.e.)	BM MN	Hsd:ICR(CD-1) mice	W	p.o.	5M	3	S (24, 48CH)	2000	2000P	M-, C-, R-	neg	Xu (2009c)
A17035A (280.7 g/L G)	BM MN	Swiss mice	W	p.o.	6M	1	T (24)	2000	3000P	M-, C-, R-	neg	Negro Silva (2009)
TROP M (483.6 g/l GI)	BM MN	NMRI mice	.8% CMC	p.o.	5M 5F	3	S (24, 48CH)	2000	2000P	M-, C-, R-	neg	Flugge (2010c)
Glyphosate 757 g/kg formulation (69.1% a.e. G)	BM MN	Cr(CD)1(SD) rat	0.8% HPMC	p.o.	5M 5F	3	S (24, 48CH)	2000	2000P	M-, C-, R-	neg	Flugge (2010c)
Glyphosate SL (499.35 g/L G)	BM MN	Swiss mice	W	p.o.	6M	1	T (24)	2000	3000P	M-, C-, R-	neg	Negro Silva (2011)

*G, glyphosate technical acid; GK, potassium glyphosate salt; GI, isopropylamine glyphosate salt; () indicates purity or concentration for glyphosate or glyphosate salts or a.i. content for GBFs. Concentration in acid equivalents indicated as a.e.

†Endpoint: BM MN, bone marrow erythrocyte micronucleus; BM CA, bone marrow chromosomal aberration; SC CA, spermatocyte chromosomal aberration.

‡Treatment:

Veh – Vehicle used: W, water; S, saline; PO, peanut oil; PS, physiological saline; PEG 400, polyethylene glycol; PBS, phosphate buffered saline; CO, corn oil; HMC, DMSO, dimethylsulfoxide; CMC, carboxymethylcellulose; HPMC, hydroxypropylmethylcellulose; NI, not indicated.

Route – Route of administration: p.o. oral (gavage); i.p., intraperitoneal injection; d.w., drinking water.

Nd/Sex – Number of males (M) and females (F) scored for each glyphosate or GBF treatment group.

Grps – Number of glyphosate or GBF dose level treatments scored for micronuclei or chromosomal aberrations. >HL indicates spacing between one or more treatment groups greater than half-√10.

Schedule – Treatment schedule for glyphosate treatments: S, single treatment; T, two treatments 24 h apart; d, consecutive days of treatment with a separate group for each number of days. Numbers in parentheses are harvest times in hours after treatment or last treatment with a separate group for each harvest time. Treatment or harvest conditions used specifically for other groups are indicated as C, vehicle control, H, high-dose.

Maximum dose – Maximum glyphosate or GBF treatment dose level in mg/kg body weight except for ppm which indicates amount in drinking water. gly for GBFs indicates that dose units were reported as mg/kg body weight of glyphosate.

*Number indicates cells or metaphases scored per animal for P (PCEs), N (NCEs), E (erythrocytes), M (metaphases). *N, variable NCEs scored for micronuclei while scoring the indicated number of PCEs. E(P) indicates number of erythrocytes scored with results for PCEs reported separately. NC, coding of slides for scoring not explicitly indicated in report or publication. In some cases coding was not explicitly indicated but may have been implied by a reference citation.

§Results:

Tox – Measures of toxicity reported: M, mortality; C, clinical signs; R, PCE/NCE ratio; MI, mitotic index. A “+” after the measure indicates treatment-related effects. A “-” after the measure indicates no treatment-related effects; +? Indicates a decrease in (R) but control (R) value for the corresponding time point was unusually high. No mortality (M-) was assumed unless mortality was indicated.

Mut – Overall evaluation of study results as negative (neg), positive (pos) or or inconclusive (inc) for treatment-related effects. Individual footnotes used to indicate statistically significant effects or difference from conclusion of publication or report authors.

|| Statistically significant increase reported for micronucleated erythrocytes. Results not reported for micronucleated PCEs

Statistically significant increase in MN erythrocytes for high-dose females. Control MN PCE frequencies were unusually high and historical control data not presented.

** Statistically significant increase in MN PCE frequency at 24 h only, within historical control, not judged to be treatment related

†† Only four males and four females scored for high-dose group.

‡‡ Statistically significant increase in MN PCE frequency only for 24 h high-dose, within historical control, not judged to be treatment related.

¶ Statistically significant increase for high-dose MN PCE frequency, within historical control, not judged to be treatment related.

§§ Two groups treated with same level of Roundup GBF but one group also treated with vitamin E.

||| Increases in abnormal metaphases not statistically significant excluding gaps from aberrant cells. Authors conclude positive result based on statistically significant increases in abnormal metaphases including gaps.

Statistically significant increase for high-dose at 48 h, within historical control, but judged to be due to a low control group value and not treatment-related.

Table 4. High-dose and control MN PCE frequencies for regulatory glyphosate and glyphosate salt studies.

Test material [†]	Sex	Dose (mg/kg bw)	Route	Harvest (h)	Micronucleated PCE per 1000 PCE (mean \pm std. dev.)		References
					Control	High-dose	
G	M	5000	p.o.	24		1.7 \pm 0.6	Jensen (1991c)
				48	1.5 \pm 0.7	1.1 \pm 0.4	
				72		0.9 \pm 0.7	
	F	5000		24		1.5 \pm 0.7	
				48	1.2 \pm 0.3	1.7 \pm 0.8	
				72		0.8 \pm 0.6	
G	M	5000	p.o.	24	6.7 \pm 5.5	8.8 \pm 1.8	Suresh (1993b)
	F	5000		24	4.9 \pm 2.7	10.4 \pm 4.9*	
G	M	5000	p.o.	24	4.6 \pm 0.8	2.1 \pm 1.6	Fox & Mackay (1996)
				48	1.7 \pm 1.3	2.1 \pm 1.9	
				72		2.1 \pm 2.5	
	F	5000		24	1.4 \pm 0.7	0.8 \pm 0.8	
				48	0.7 \pm 0.6	0.9 \pm 0.4*	
				72		0.9 \pm 1.0	
GK	M	2000	p.o.	24	0.2 \pm 0.4	0.4 \pm 0.9	Jones (1999)
				48	0.8 \pm 1.0	0.6 \pm 0.5	
G	M	562.5	i.p.	24	0.4 \pm 0.5	0.7 \pm 1.0	Marques (1999)
	F	562.5		24	0.8 \pm 0.8	0.7 \pm 1.0	
GI	M	3024	i.p.	24	0.6 \pm 0.5	0.7 \pm 1.0	Gava (2000)
	F	3024		24	0.4 \pm 0.5	0.7 \pm 1.0	
G	M	2000	p.o.	24	0.9 \pm 0.6	0.9 \pm 0.7	Honarvar (2005)
				48	0.7 \pm 0.8	0.6 \pm 0.7	
				72		1.5 \pm 1.0	
	F	2000		24		1.1 \pm 0.9	
				48		1.9 \pm 0.7*	
				72		0.9 \pm 1.1	
G	M	600	i.p.	24	0.6 \pm 0.6	1.4 \pm 0.4*	Zoriki-Hosomi (2007)
				48	1.0 \pm 1.2	0.7 \pm 0.4	
G	M	30	p.o.	24	0.6 \pm 0.3	0.8 \pm 0.6	Honarvar (2008)
	M	2000	p.o.	24	0.7 \pm 0.7	0.3 \pm 0.7	
G	M	62.5	i.p.	24	0.0 \pm 0.0	0.0 \pm 0.0	Costa (2008)
				48	0.0 \pm 0.0	0.0 \pm 0.0	
G	M (rat)	2000	p.o.	24	0.8 \pm 0.6	0.6 \pm 0.4	Flugge (2009b)
				48	1.0 \pm 0.9	0.8 \pm 0.4	
				72		0.4 \pm 0.4	
	F (rat)	2000		24	0.9 \pm 0.2	0.4 \pm 0.4	
				48	1.1 \pm 0.7	0.4 \pm 0.4	
				72			

*Statistically significant increase over control value.

†G, glyphosate technical acid; GK, potassium salt of glyphosate; GI, isopropylamine salt of glyphosate.

control values (Durward, 2006; Jones, 1999; Zoriki-Hosomi, 2007).

A statistically significant increase in the micronucleated polychromatic erythrocyte (MN PCE) frequency was observed for females, but not for males, treated with 5000 mg/kg in the study of Suresh (1993b). This increase was only about two-fold over the concurrent control and no increase was observed for frequencies of micronucleated normochromatic erythrocytes for this group, although at such an early sampling time this would not be expected. Historical control data were not presented. Suresh (1993b) employed a high level of glyphosate treatment, 5000 mg/kg body weight, which is well above the currently recommended limit dose of 2000 mg/kg body weight (OECD 474, 1997) as well as an unusual use of groundnut oil as a vehicle for a water soluble test material. The negative control MN PCE frequencies in this study (4.9 and 6.7 MN per 1000 PCEs for females and males, respectively) exceeded control MN PCE frequencies commonly observed in mice (Salamone & Mavournin, 1994). The recommendation by Salamone & Mavournin (1994) is that MN PCE frequencies above 5/1000 MN PCE should be questioned and in most cases confirmed. Two other bone marrow erythrocyte studies which employed 5000 mg/kg body weight treatment did not observe any statistically

significant increases in MN PCE frequency (Fox & MacKay, 1996; Jensen, 1991c). A mouse bone marrow chromosomal aberration study conducted in the same laboratory using the same vehicle and a 5000 mg/kg body weight dose level (Suresh, 1994) was negative. These observations provide a strong weight of evidence that the statistically significant increase observed in Suresh (1993b) is not evidence of a treatment-related effect.

The results presented in Table 3 clearly indicate a very strong overall weight of evidence that glyphosate or glyphosate salt solutions do not induce micronucleated PCEs in rodent bone marrow erythrocyte micronucleus assays conducted with maximum dose levels which are appropriate either because of toxic effects or are recommended limit doses for relatively non-toxic compounds. Statistically significant increases in MN PCE frequency in isolated studies were not reproducible in a number of other studies. Furthermore, these studies include several examples of negative results for i.p. administration at maximum doses that exceed those employed by Manas et al. (2009). It should also be noted that the i.p. route of administration is not relevant to human exposure. In combination with the results presented in Williams et al. (2000), there is overall a strong weight of evidence that technical glyphosate and glyphosate

salt solutions are not genotoxic in *in vivo* mammalian micronucleus assays at high dose levels.

Glyphosate-based formulations.

The Williams et al. (2000) glyphosate toxicity review presented results from several mouse bone marrow erythrocyte micronucleus studies of GBFs (e.g. RoundupTM, RodeoTM and DirzelTM-branded formulations) that were mostly negative for micronucleus induction. The i.p. route was used for most of the negative studies and maximum doses for many of the studies were toxic or appropriately close to LD₅₀ values. There was one published report of a weak positive mouse bone marrow micronucleus response observed for a RoundupTM-branded GBF. This study, which employed a smaller number of animals per group than other negative studies, was clearly aberrant from the numerous other negative studies not only in micronucleated cell frequency finding but also the finding of altered polychromatic erythrocyte to normochromatic erythrocyte (PCE/NCE) ratios. The overall weight of evidence from the earlier reviewed studies was that GBFs were negative in the mouse bone marrow erythrocyte micronucleus assay.

As indicated in Table 3, seven publications reported results for GBFs in *in vivo* mammalian micronucleus or chromosomal aberration assays. It should be noted that there are some fairly consistent limitations in the reported conduct of these studies compared to the OECD guidelines. In most studies, concurrent indications of toxicity other than effects on bone marrow are not reported, coding of slides for scoring is not explicitly indicated and, in many studies, fewer than the currently recommended number of 2000 polychromatic erythrocytes or 100 metaphases per animal were scored.

Three publications report negative results for RoundupTM-branded GBFs in mouse chromosomal aberration or micronucleus assays. In two of these publications, negative results in mouse bone marrow erythrocyte micronucleus assays were reported for different RoundupTM-branded GBFs administered at 200 mg/kg body weight twice 24 h apart by the i.p. route (Coutinho do Nascimento & Grisolia, 2000; Grisolia, 2002). The third publication reported negative results in mouse bone marrow studies for both the chromosomal aberration and erythrocyte micronucleus endpoints using a single oral dose of 1080 mg/kg body weight of a RoundupTM-branded GBF (Dimitrov et al., 2006).

In contrast, one publication reported positive results for a RoundupTM-branded GBF in mouse bone marrow for the chromosomal aberration and erythrocyte micronucleus endpoints using a single maximum dose of 50 mg glyphosate/kg body weight i.p. (Prasad et al., 2009). Both the positive results and the magnitude of the increases in frequencies of chromosomal aberrations and micronuclei reported in this study are remarkably discordant with other reported results for RoundupTM-branded and other GBFs in mouse bone marrow chromosomal aberration and micronucleus studies in a number of laboratories and publications (Table 3 and Williams et al., 2000). The reasons for this discordance are not clear. One unusual feature of the Prasad et al. (2009) study is that the RoundupTM-branded GBF was administered in dimethylsulfoxide (DMSO) vehicle. This is

an unusual vehicle to use in *in vivo* genotoxicity studies, particularly using the i.p. route and for a test material which is water soluble. A published toxicity study has reported that use of a DMSO/olive oil vehicle by the i.p. route dramatically enhanced the toxicity of glyphosate formulation or the formulation components without glyphosate compared to saline vehicle (Heydens et al., 2008). The enhanced toxicity observed with this vehicle was not observed when the oral route was used. DMSO has also been shown to enhance the toxicity of other hydrocarbons when administered via the i.p. route (Koesis et al., 1968). These observations suggest that use of DMSO as a vehicle for administration of chemicals or formulations by the i.p. route might produce unusual toxic effects that are not relevant to normally encountered exposures. Furthermore, the i.p. route is considered by many regulatory agencies to be an unphysiological route and is not recommended for the safety evaluation of chemicals. Regardless of the reasons for the discordant positive results, it is clear that a large preponderance of evidence indicates that RoundupTM-branded GBFs are typically negative in mouse bone marrow chromosomal aberration and erythrocyte endpoints.

One publication reported positive results for bone marrow chromosomal aberration in rabbits administered RoundupTM-branded GBF in drinking water at 750 ppm for 60 days (Helal & Moussa, 2005). This study is unique in terms of species and route of administration. The publication does not report water intake in the test and control groups. Given the potential for water palatability issues with a formulated product, this is a significant shortcoming, as any effects noted might be attributable to dehydration (Saunders, 2005). This study had further limitations including the use of only a single dose level and not explicitly indicating the coding of slides for scoring. This study did not include a positive control for chromosomal aberration effects. Examination of the chromosomal aberration scoring results showed that, for the treated group, large increases were observed for gaps and "centromeric attenuation" that were included in the summation and evaluation of structural chromosomal aberration effects. Ordinarily gaps are scored but are not included in the total aberration frequency, and centromeric attenuation is not included in conventional identification of structural aberrations (OECD 475, 1997; Savage, 1976). These unusual scoring and interpretive features raise significant questions about using this study to make conclusions about clastogenicity of the GBF tested.

Two other publications report *in vivo* mammalian chromosomal aberration or micronucleus results for non-RoundupTM-branded GBFs. In one of these, an uncharacterized GBF, Percozyd 10 L, was reported to be negative in a mouse bone marrow erythrocyte micronucleus assay (Chruscielska et al., 2000). The maximum dose level tested, 90 mg/kg i.p., was reported to be 70% of the i.p. LD₅₀ as determined experimentally by the authors, and so may have exceeded the maximum tolerated dose. This study had several limitations including use of less than three dose levels and no explicit reported coding of slides for scoring.

In an other study, positive results were reported for another uncharacterized GBF, herbazed, in mouse bone marrow and spermatocyte chromosomal aberration studies (Aimer et al., 2006) using oral and i.p. routes and treatments from 1 to up to

5 d (i.p.) or 21 d (oral). Although i.p. exposures of 1, 3 and 5 d produced statistically significant increases in bone marrow abnormal metaphase frequency when gaps were included, the increases were not significant excluding the gaps and the OECD 475 (1997) recommends not including gaps in total aberration frequency. Statistically significant positive results were observed after multiple i.p. exposures (3–5 d bone marrow only including gaps; 5 d for spermatocytes) and after extended oral treatments (14–21 d, bone marrow; 7–21 d spermatocytes). Although not a genotoxic endpoint *per se*, it should be noted that statistically significant increases in frequency of sperm with abnormal morphology were observed in mice treated with 100 and 200 mg/kg body weight glyphosate p.o. for 5 d. The fact that positive results were not observed in an erythrocyte micronucleus test of mice treated with glyphosate up to 50 000 ppm in feed for 13 weeks (Williams et al., 2000) indicates that, by contrast, extended glyphosate treatment by the oral route does not induce detectable chromosomal effects. This treatment was longer and up to much higher glyphosate exposures than those used for the Amer et al. (2006) studies. Thus, it appears likely that these effects were due to some component(s) of the specific herbazed GBF tested rather than glyphosate. It is noteworthy that the Amer et al. (2006) publication is unique in reporting positive responses for such a large number of endpoints for a single test material.

A total of 12 mouse bone marrow erythrocyte micronucleus regulatory studies of GBFs were available (Table 3 and "online supplementary material"). These studies were designed to be in compliance with the OECD 474 (1997) guidance for rodent erythrocyte micronucleus assays. The treatment regimen was either a single oral dose with harvests at 24 and 48 h after dosing or two oral doses 24 h apart with a single sacrifice at 24 h after the last dose. Either of these treatment regimens is acceptable under the most recent OECD guideline for this assay (OECD 474, 1997). Many of the studies used only males but reported no significant differences in gender response in preliminary toxicity studies. All of these studies employed a maximum dose of 2000 mg/kg body weight and most of the studies also used lower doses. This is consistent with a limit dose recommendation of 2000 mg/kg body weight in the OECD guideline. The upper dose level was not reported to induce mortality in any of the studies but in a few studies clinical signs were observed in high-dose animals. No toxic effects on bone marrow were generally observed in these studies as judged by PCE/NCE ratios. A decrease in PCE/NCE for 48 h high-dose animals was observed in one study (Xu, 2009a) but this may not have been treatment-related because the control PCE/NCE ratio was unusually high.

Ten of the studies did not exhibit a statistically significant increase in MN PCE for any treatment group. Two studies had statistically significant increases in MN PCE frequency at the 48 h time point but the MN PCE frequencies were within historical control levels and judged in each case to be due to a statistical anomaly from a low vehicle control MN PCE frequency and is not treatment-related (Erexson, 2003a, Xu, 2008a). Thus, none of these 12 studies indicated treatment-related increases in MN PCE frequencies and all studies were considered negative for this endpoint.

In summary, in addition to the *in vivo* rodent bone marrow chromosomal effect studies presented in Williams et al. (2000), a majority (three of four) of the rodent bone marrow studies in the subsequent published literature are negative for Roundup™-branded formulations at maximum dose levels that significantly exceed the maximum dose level of the study reporting positive results. One noteworthy feature of the positive study is the use of a DMSO vehicle which is unusual, if not inappropriate, for a water soluble test material. A rabbit drinking water study found positive effects for a Roundup™-branded GBF; however, this study had a large number of limitations including not presenting information on palatability and no positive control. Publication reports for other GBFs included a negative study for Perzocyd 10 SL and positive chromosomal aberration results for both bone marrow and spermatocytes for a herbazed GBF using extended oral and i.p. treatments. A very large number of well-conducted regulatory mouse bone marrow micronucleus studies indicated that a variety of GBFs are negative in this assay system up to the limit dose of 2000 mg/kg body weight. While the possibility that GBFs with different compositions might have different properties cannot be excluded, the overall data certainly indicate that a typical GBF is negative for the induction of chromosomal damage *in vivo*.

Rodent dominant lethal

The Williams et al. (2000) review notes a negative result in a mouse dominant lethal assay of glyphosate using a maximum treatment level of 2000 mg/kg body weight administered by gavage.

No rodent dominant lethal assays of glyphosate or GBFs were encountered in the subsequent literature.

One regulatory rat dominant lethal study was available (Suresh, 1992; "online supplementary material"). This study was reported to be conducted in accordance with the OECD 478 (1984). In this study, groups of 30 male Wistar rats were given a single oral administration of glyphosate (suspension in groundnut oil vehicle) at dose levels of 200, 1000 and 5000 mg/kg body weight. Control groups received vehicle only or ethyl methane sulfonate as a positive control. Each week for 10 consecutive weeks males were mated 1:1 to separate groups of untreated virgin females. Each week's paired females were removed after co-housing for 6 d and were sacrificed on the 16th day after pairing and reproductive parameters were measured (pregnancy status, corpora lutea, early and late resorptions, and live implants). One unusual aspect of this study is that mean body weights of all treatment groups were initially statistically higher than the control group mean body weight and this pattern persisted throughout the study. The following effects were observed in the first group of week 1 females mated to high-dose males: reductions in pregnancy rate, decreases in live implants and increases in pre- and post-implantation loss. There were also increases in embryonic resorptions ("small moles") in week 1 females mated to mid-dose males. These effects were attributed to significant acute toxic effects of glyphosate (not dominant lethal effects) exhibited after the treatment in week 1 as evidenced by body weight loss in the mid and high-dose males and clinical signs. Although some

Table 5. Blood erythrocyte micronucleus assays in non-mammalian systems.

Test system	Test material	Maximum dose*	Result	Comment†	Reference
<i>Oreochromis niloticus</i> (fish)	Roundup 69	170 mg/kg i.p. (maximum tolerated)	Equivocal‡		Coutinho do Nascimento & Grisolia (2003)
<i>T. rendalli</i> (fish)	Roundup™ formulation	170 mg/kg (abdominal injection)	Positive		Grisolia (2002)
<i>Carassius auratus</i> (fish)	Roundup™ formulation	15 ppm glyphosate in water (2, 4 and 6 d)	Positive		Cavas & Konen (2007)
<i>Pseudorasbora parva</i> (fish)	Roundup™ formulation	10 mg/L in water (6, 24 and 96 h)	Negative	NC	Cavalcante et al. (2008)
Cannan eggs/hatchlings	Roundup® Full II formulation	1750 µg/egg	Positive		Poletta et al. (2009)
Cannan eggs/hatchlings	Roundup® Full II formulation	Nest sprayed 3% (3 L/100 L water/ba)	Positive		Poletta et al. (2011)
<i>O. cordobae</i> (amphibian)	Roundup formulation	100 mg a.i./L	Equivocal*		Bosch et al. (2011)
<i>R. arenarium</i> (amphibian)	Roundup formulation	800 mg a.i./L	Equivocal‡		
<i>Corydoras paleatus</i> (fish)	Roundup® formulation	6.67 µg/L in water (3.2 µg/L a.e.) (3, 6 and 9 d)	Negative	PC, NC	de Castilhos Ghisi & Cestari (2012)

*a.e., concentration in glyphosate acid equivalents; a.i., concentration of active ingredient

†PC, no concurrent positive control; NC, independent coding of slides for scoring not explicitly indicated for visually scored slides. In some cases coding may have been implied by reference citation.

‡Statistically significant increase in micronucleated erythrocyte frequency only at mid-dose level

*Increase in micronucleated erythrocyte frequency not statistically significant for single group surviving treatment; authors appear to conclude increase may have been treatment-related.

‡Authors appear to conclude increases in micronucleated erythrocytes were treatment-related. No statistically significant differences were observed among the experimental groups by the analysis of variance. A statistically significant positive correlation between concentration and micronucleated erythrocyte frequency but this analysis apparently omitted the high-dose group.

statistically significant findings in post-implantation loss were sporadically observed in subsequent weeks these were not considered to be treatment-related because they were not consistent with a biologically plausible dose-response or a biologically plausible time course (see post-implantation loss data table in "online supplementary material"). This conclusion was also indicated in an EU monograph report (BBA, 1998–2000). This study appears to be in accordance with the study noted in Williams et al. (2000) indicating that glyphosate is not active as a rodent germ cell mutagen.

Non-mammalian assays

Glyphosate and glyphosate salts

The Williams et al. (2000) review reported negative results for isopropylamine salt of glyphosate in an onion root tip chromosomal aberration assay.

One subsequent published study reported a weak positive result for technical glyphosate in a *Drosophila* wing spot assay (Kaya et al., 2000). Statistically significant positive increases were found only in one of four crosses for small twin spots and not for the two other wing spot categories (large wing spots and twin wing spots). As discussed above, only negative or inconclusive results were observed for crosses that were not subjected to mitotic recombination effects. If the result was actually treatment-related it would only indicate an increase in recombination events and not in somatic mutations.

Glyphosate-based formulations

The Williams et al. (2000) review reported a positive result for a Roundup™-branded GBF for chromosomal aberrations

in an onion root tip assay and it was noted that this may have been caused by toxic effects of the GBF surfactant.

Negative results were observed in subsequently published *in vitro* assays for the chromosomal aberration and micronucleus endpoints in *Crepis capillaris* root meristems exposed to a Roundup™-branded GBF at concentrations up to 0.5% a.i. (Dimitrov et al., 2006).

Subsequent to the earlier review a number of publications have reported discordant results for blood erythrocyte micronucleus assays conducted on GBFs in several non-mammalian fish, reptile and amphibian species (Table 5). One publication reported what might arguably be considered as equivocal results for the erythrocyte micronucleus test in *Oreochromis niloticus* (Nile tilapia), administered a test material described as Roundup™ 69 GBF at an upper dose of 170 mg/kg i.p. (Coutinho do Nascimento & Grisolia, 2000). Although there was a statistically significant increase in micronucleated erythrocyte frequency at the mid-dose level, a significant increase was not observed at the high-dose level and considerable variability in frequencies in different groups was noted. Negative results were reported in another fish species (*Pseudorasbora parva*) exposed to 10 mg/L Roundup™-branded GBF for 6, 24 and 96 h (Cavalcante et al., 2008). This concentration was reported to be 75% of a 96-h LC₅₀. Negative results were also reported for the micronucleus endpoint in the fish *Corydoras paleatus* exposed to 6.7 µg/L Roundup™-branded GBF (calculated 3.2 µg/L glyphosate) for 3, 6 and 9 days (de Castilhos Ghisi & Cestari, 2012). Positive results were reported for the erythrocyte micronucleus assay conducted in the fish *T. rendalli* exposed to up to 170 mg/kg body weight i.p. of another Roundup™-branded GBF (Grisolia, 2002). Examination of the micronucleus frequencies in this publication indicated that

the negative control micronucleus frequency was considerably lower than the frequencies for all but one of 21 treatment groups for seven different test materials. This suggests an unusually low control frequency and at least one treatment group had statistically significant increases in MN frequencies for each of the seven test materials. In the absence of historical negative control data and few publications from which to estimate negative control ranges, the possibility that the apparently significant increases were due to a low negative control value that should be considered for this publication. Another publication reported positive erythrocyte micronucleus results in goldfish (*Carassius auratus*) exposed to 5 to 15 ppm glyphosate concentration of a Roundup™-branded GBF for 2 to 6 d (Cavas & Konec, 2007).

The reasons for the discordant results are not clear for the fish erythrocyte micronucleus assays of Roundup™-branded GBFs. Although different species and GBFs were used in different studies there were pairs of studies with positive and negative or equivocal results that used similar treatment conditions (e.g. 170 mg/kg i.p. or 10-15 mg/L in water).

An amphibian erythrocyte micronucleus study reported questionable effects of a Roundup™-branded GBF (Bosch et al., 2011). For one species (*O. cordobae*), toxicity and lethality were observed at exposures to concentrations of 200-800 mg/L a.i. (glyphosate active ingredient) of Roundup™-branded GBF. The surviving 100 mg/L a.i. treatment group had an increase in micronucleated erythrocyte frequency after 5 d but the increase was not statistically significant. A second species (*R. arenarum*) tolerated exposure up to 800 mg/L a.i. Roundup™-branded GBF. No statistically significant differences were found in the experimental groups by the analysis of variance. Although a statistically significant correlation between dose and micronucleated erythrocyte frequency was observed at day 2 of the treatment this analysis apparently omitted the high-dose group which had a mean micronucleus frequency comparable to negative control values. The downturn in dose-response and apparent omission of the high-dose from the statistical analysis is peculiar, because significant toxicity was not reported in this species at the 2-day sampling time. The results reported in this publication do not clearly support a conclusion of a micronucleus effect of a GBF in these species.

Results for an unusual test system of exposed caiman eggs are reported in two publications. In one study, eggs were typically exposed in a laboratory setting to Roundup™ Full II GBF, and erythrocyte micronucleus formation was measured in hatchlings (Poletta et al., 2009). The tested GBF was reported to contain the potassium salt of glyphosate. Statistically significant increases in micronucleated erythrocytes were observed in hatchlings from eggs treated with 500-1750 µg/egg. This system is quite unusual in the species tested and even more so in using an egg application with measurement of effects in hatchlings. Although there is some experience with a hen's egg erythrocyte micronucleus assay using *in ovo* exposure, the erythrocytes were evaluated in embryos only a few days after the treatment (Wolf et al., 2008). In the caiman egg assay reported by Poletta et al. (2009), there was presumably a single topical exposure followed by an egg incubation period of about 10 weeks

before hatching. It is difficult to envisage that genotoxic events *in ovo* could produce elevated micronucleated erythrocyte frequencies detectable after 10 weeks, given the number of cell divisions occurring in development of a hatchling, and dilution of any micronucleated cells in a larger population as a result of this.

A second publication by Poletta et al. (2011) described two field experiments evaluating caiman hatched from eggs in artificial nests that were sprayed with Roundup™ Full II GBF. Increases in micronucleated erythrocyte frequency in hatchlings were reported for both experiments. Additional measurements of growth in one experiment showed small but statistically significant differences in total length and snout-vent length in 3-month-old, but not 12-month-old, animals. Alanine aminotransferase and creatine kinase enzyme levels in serum of 3-month-old animals were significantly elevated (>two-fold control values). Alterations in these parameters suggest that the treated groups have some persistent biological differences or toxic effects either as a result of the treatment or some other factor. It is certainly possible that the micronucleus effects in both publications are associated with these persistent biological differences or toxic effects rather than from genotoxic effects induced in the embryos.

There were no regulatory reports of non-mammalian chromosomal effect assays.

In summary, the above *in vivo* micronucleus assays in non-mammalian systems have given discordant results for reasons that cannot be precisely defined. Typically these results would be given lower weight than mammalian systems in terms of prediction of mammalian effects, especially since there is very little experience with these systems in comparison with *in vivo* mammalian chromosomal effect assays, such as the rat or mouse bone marrow chromosomal aberration or erythrocyte micronucleus assays.

DNA damage

In vitro mammalian cell assays

Glyphosate and glyphosate salts

Some positive results for glyphosate for induction of SCE were reported in cultured human and bovine lymphocytes in the earlier review (Williams et al., 2000). These results tended to be weak, inconsistent and with limited evidence for dose-response. A number of limitations were observed for these studies such as the failure to control pH and abnormally low control values. Negative results were reported for technical glyphosate in a *B. subtilis* DNA damage assay and a rat primary hepatocyte unscheduled DNA synthesis (UDS) assay.

Subsequent to the review there is one publication of a positive *in vitro* SCE result in cultured bovine lymphocytes (Table 6; Sivikova & Dianovsky, 2006). It is noteworthy that negative effects for the chromosomal aberration endpoint were reported in this publication.

Positive results for technical glyphosate have been reported for the comet (alkaline single cell gel electrophoresis, alkaline SCGE) endpoint in *in vitro* mammalian cell assays in four publications subsequent to the Williams et al. (2000) review (Table 6). Some general protocol concerns for these studies are

Table 6. DNA damage assays of glyphosate, glyphosate salts and GBFs in *in vitro* and *in vivo* mammalian systems.

Endpoint	Test system	Test material	Maximum dose	Result	Comment ^a	References
<i>In vitro</i> studies glyphosate and glyphosate salts						
Literature studies						
Comet	GM38 human fibroblasts	glyphosate (technical)	6.5 mM	Positive	MA, PH, NC	Monroy et al. (2005)
	HT1080 human fibrosarcoma	glyphosate (technical)	6.5 mM	Positive	MA, PH, NC	Monroy et al. (2005)
SCE	bovine lymphocytes	glyphosate (62% isopropylamine salt)	1.12 mM (toxic)	Positive (-S9) Equivalocal (+S9)	PH, NC	Sivikova & Dianovsky (2006)
Comet	Hep-2 cells	glyphosate (analytical, 96%)	7.5 mM (limited by toxicity)	Positive	MA, PH ^b , NC	Manas et al. (2009)
Comet	Human lymphocytes	Glyphosate (technical, 98%)	580 µg/mL (toxic) ≈ 3.43 mM	Positive (-S9) Positive (+S9)	NC	Mladinic et al. (2009a)
Comet	TR146 human buccal epithelial	Glyphosate (95%)	2000 mg/L ≈ 11.8 mM	Positive	MA, PH, NC	Koller et al. (2012)
Regulatory study						
UDS	Primary rat hepatocyte	Glyphosate (>98%)	111.69 mM	Negative	PH	Rossberger (1994)
<i>In vitro</i> studies GBF						
Literature studies						
SCE	mouse spleen cells	herbazed formulation (84% glyphosate)	50 mM glyphosate ^c	Positive	MA, PH, TO, NC	Amer et al. (2006)
Comet	TR146 human buccal epithelial	Roundup TM Ultra Max	200 mg/L glyphosate (≈ 1.18 mM)	Positive	MA, PH, NC	Koller et al. (2012)
<i>In vivo</i> studies GBF						
Literature studies						
Bone marrow SCE	Mouse	herbazed formulation (84% glyphosate)	200 mg/kg p.o. glyphosate	Positive	NC	Amer et al. (2006)

^aMA, Mammalian metabolic activation system not used; PH, no indication of pH or osmolality control; TO, no concurrent measurement of toxicity reported or toxicity not observed for highest dose level; NC, independent coding of slides for scoring not explicitly indicated.

^cCalculated from the stated concentration of 5×10^{-5} M glyphosate/mL.

failure to explicitly indicate the assessment or control of pH or to explicitly indicate the coding of slides for scoring. It is possible that these may be deficiencies or limitations in reporting rather than conduct. Positive Comet results were observed for two mammalian cell lines exposed to glyphosate for 4 h at concentrations of 4.0–6.5 mM (≈ 0.68 –1.10 mg/mL, GM38 cells) and 4.75–6.5 mM (≈ 0.80 –1.10 mg/mL, HT1080 cells) (Monroy et al., 2005). These concentrations are close to the upper limit dose of 10 mM (appropriate for glyphosate) generally recommended for *in vitro* mammalian cell assays in the current OECD guidelines. Positive Comet results were also reported in Hep-2 cells exposed for 4 h to 3.0–7.5 mM (≈ 0.51 –1.27 mg/mL) glyphosate (Manas et al., 2009). This publication reported negative results for the chromosomal aberration endpoint in cultured human lymphocytes exposed to up to 6 mM (≈ 1.01 mg/mL) glyphosate for 48 h and it should be noted that pH control of the culture medium was reported for the chromosomal aberration endpoint. Positive Comet results have also been reported for cultured human lymphocytes exposed to glyphosate at concentrations of up to 580 μ g/mL (≈ 3.4 mM) for 4 h (Mladinic et al., 2009a). Effects were observed both in the presence and absence of S9. A modification of the Comet assay by employing a human 8-hydroxyguanine DNA-glycosylase (hOGG1) to detect an oxidative damage indicated only statistically significant effects on comet tail length for 580 μ g/mL with S9. Measurements of total antioxidant capacity and thiobarbituric acid reactive substances showed statistically significant increases at 580 μ g/mL in the presence or absence of S9. Interpretation of the significance of metabolic activation effects is complicated by the observation that several of the endpoints (e.g., comet tail intensity and nuclear abnormalities) tended to show increases in the presence of S9 in negative controls or at the very lowest concentrations of glyphosate (0.5–3.5 μ g/mL, ≈ 2.9 –20.7 μ M). A reasonable summation of the results in this publication is that comet effects and other effects such as nuclear abnormalities, early apoptosis, necrosis and oxidative damage were consistently observed at 580 μ g/mL. Positive Comet effects were also reported in a human epithelial cell line at dose levels up to 2000 mg/L (≈ 11.8 mM) (Koller et al., 2012). An unusual feature of these results is that statistically significant increases in comet tail intensity were reported as low at 20 mg/L (0.118 mM) with not much dose-response between 40 and 2000 mg/L. These dose levels of glyphosate were observed to produce little or no effects on a cellular integrity marker but statistically significant effects on necrosis and apoptosis markers were observed at 20 mg/L in parallel experiments.

One regulatory study of technical glyphosate was reported for a primary rat hepatocyte UDS assay (Rossberger, 1994; Table 6 and "online supplementary material"). In this study, cultures of hepatocytes were exposed to glyphosate concentrations of 0.02–48.98 mM (≈ 0.34 –8.28 mg/mL) and 0.14–111.69 mM (≈ 0.19 –18.88 mg/mL) for 18 h in two experiments. Radio-labeled and halogen-substituted nucleosides were used to enable replicative and unscheduled DNA synthesis to be identified by density-gradient centrifugation and radioactivity counting. No effects on an unscheduled DNA synthesis were observed in this study in two separate experiments. Measurements of replicative DNA synthesis indicated that cytotoxic concentrations were tested and the

maximum concentrations were in any case much higher than recommended for other *in vitro* mammalian cell assays (10 mM for glyphosate). This study is limited by the use of only single cultures per experimental point, although there were two separate experiments. The relatively narrow distribution of repair synthesis values with no dose-response in glyphosate-treated cultures, and the clear increases in repair induced by the positive control, suggest that this study provides reasonable evidence for a lack of induced-DNA repair following the exposure of rat primary hepatocytes to very high concentrations of glyphosate.

Overall there are a number of *in vitro* mammalian cell studies in which glyphosate has been reported to produce positive responses in SCE or Comet assays. Most of these positive responses have occurred at high exposures to glyphosate in the millimolar range. Although lower than the limit dose of 10 mM (appropriate for glyphosate) recommended for several *in vitro* mammalian cell culture assays (OECD 473, 1997, OECD 476, 1997, OECD 487, 2010), there have been some suggestions that lower dose levels may be more appropriate, particularly because of concerns about relevance of positive *in vitro* findings observed at higher dose levels (ICHS2(R1), 2011; Morita et al., 2012; Parry et al., 2010). In addition, many of the studies have functional limitations such as the lack of pH control and no explicit statement regarding the coding of slides for visual scoring.

Concerns over the possibility of effects induced by toxicity have led to several suggestions for experimental and interpretive criteria to distinguish between genotoxic DNA-reactive mechanisms for induction of comet effects and cytotoxic or apoptotic mechanisms. One recommendation for the *in vitro* Comet assay is to limit the toxicity to no more than a 30% reduction in viability compared to controls (Henderson et al., 1998; Storer et al., 1996; Tice et al., 2000). Importantly, dye exclusion measurements of cell membrane integrity, such as those reported in some of the above publications, may significantly underestimate cytotoxicity that could lead to comet effects (Storer et al., 1996). Other recommendations include conducting neutral diffusion experiments to determine if apoptotic processes might be responsible for comet effects (Tice et al., 2000).

In contrast to the SCE and comet endpoints, two independent studies of technical glyphosate in the primary rat hepatocyte UDS assay have both been negative. These results provide evidence that this endpoint is not affected by glyphosate at high concentrations in cell lines with endogenous mammalian metabolic activation capability.

Glyphosate-based formulations

Some positive results for glyphosate or GBFs in the SCE endpoint were reported in cultured human and bovine lymphocytes in the earlier review (Williams et al., 2000). These results tended to be weak, inconsistent and with limited evidence for dose-response.

Subsequent publications of DNA damage assays of GBFs in *in vitro* mammalian cell assays are presented in Table 6. Positive SCE results were observed for the uncharacterized herbicide GBF in mouse spleen cells (Amer et al., 2006). Limitations of this study are in common to those described

above (see the section "In vitro mammalian cell assays") for the chromosomal aberration endpoint portion of the study. The magnitudes of the increases in SCE/cell were less than two-fold of the control value which may not be considered biologically significant. Given these limitations, and the fact that the mechanism(s) by which SCE are induced is not understood, these positive findings should be viewed with caution. Koller et al. (2012) reported positive Comet results for human epithelial cells exposed to Roundup™ UltraMax formulation. Statistically significant effects on comet tail intensity were observed from exposure to 20–200 mg/L of glyphosate (≈ 0.12 – 1.18 μM) for 20 min.

There were no regulatory DNA damage studies of GBFs in *in vitro* mammalian systems. The Amer et al. (2006) report of a positive result for an uncharacterized GBF in the SCE endpoint agrees with other positive findings for this GBF in this publication but because of the discussed limitations does not add significantly to an evaluation of general genotoxic properties for GBFs. Similarly, the single observation of comet effects for a different GBF in an *in vitro* cellular assay is of limited value for assessing general GBF properties.

In vivo mammalian assays

Glyphosate and glyphosate salts

In the earlier review (Williams et al., 2000), positive results for DNA strand breakage were reported in kidney and liver tissue of mice treated by the i.p. route with glyphosate. The earlier review also noted reports of the absence of DNA adducts in mice treated by the i.p. route with the isopropylamine salt of glyphosate and a possible increase in 8-hydroxydeoxyguanosine (8-OHdG) in DNA of mice treated with technical glyphosate.

No new *in vivo* mammalian studies of DNA damage or DNA-reactivity of glyphosate were encountered in publications since 2000 and there were no regulatory studies of this category.

Glyphosate-based formulations

In the earlier review of Williams et al. (2000), positive results for DNA adducts (^{32}P -postlabeling) and DNA strand breakage were reported for mice treated by the i.p. route with Roundup™ GBF. For a number of reasons these observations were not considered to be clear evidence for DNA-reactive genotoxicity of the Roundup™ GBF.

Only one *in vivo* mammalian DNA damage study of a GBF has since been reported. This publication indicated an increase in SCE frequency in bone marrow cells of mice treated with uncharacterized herbaced GBF (Table 6; Amer et al., 2006). Statistically significant positive effects were only observed at the highest dose level tested (200 mg/kg body weight glyphosate administered p.o.) and were less than two-fold of the control value. As noted above, since the mechanism(s) by which SCEs are induced is not understood, this report for one GBF does not add significantly to an evaluation of general genotoxic potential for GBFs.

In a follow-up to ^{32}P -postlabeling, DNA strand breakage and 8-OHdG studies cited in Williams et al. (2000), Heydens

et al. (2008) reported on studies in mice to further investigate toxic effects and 8-OHdG levels associated with the routes, vehicles and dose levels of the earlier studies. The Heydens et al. (2008) publication reported significant GBF-induced liver and kidney toxicity for high i.p. doses but no liver or kidney toxicity for comparable oral doses. Statistically significant increases in 8-OHdG were not observed in the latter study under the same conditions as employed by the earlier study. The DMSO/olive oil vehicle dramatically enhanced the toxicity of GBF administered by the i.p. route and the toxicity was also observed for formulation components without glyphosate. These results indicated that the effects reported in the earlier studies were associated with high liver and kidney toxicity that was primarily due to the non-glyphosate components of the formulation when administered at very high doses via the i.p. route of exposure. The toxicity enhancement by the unusual DMSO/olive oil dosing vehicle further calls into question whether the ^{32}P -postlabeling finding represented effects associated with unusual toxicity rather than being indicative of adducts formed from glyphosate or glyphosate formulation components.

Non-mammalian assays

Glyphosate and glyphosate salts

The Williams et al. (2000) review noted a negative result for glyphosate in the *B. subtilis* H17/M45 *rec* bacterial differential killing assay.

As presented in Table 7, two subsequent publications reported positive Comet results for glyphosate on *Tradescantia* flowers and nuclei (Alvarez-Moya et al., 2011) and negative Comet results for oyster sperm cells exposed to glyphosate (Akeha et al., 2012). The latter study employed a very low maximum exposure of 5 $\mu\text{g/L}$ (≈ 0.03 μM).

There was one regulatory study of technical glyphosate (95.68%) in the *B. subtilis* H17/M45 differential DNA damage (*rec*) assay (Table 7 and "online supplementary material"; Akanuma, 1995a). This study employed multiple levels of glyphosate on paper disks (up to 240 $\mu\text{g/disk}$) and measured zones of inhibition. No differential toxicity was observed indicating a lack of genotoxicity in this assay system. This result is in agreement with the earlier reported negative result for this assay by Williams et al. (2000).

Glyphosate-based formulations

In the earlier review of Williams et al. (2000), positive results were reported for DNA strand breakage in mouse tissues and for the comet endpoint in tadpoles of the frog *Rana catesbeiana* exposed to a GBF.

There have been several subsequent publications of results for GBFs in a variety of non-mammalian DNA damage assay systems (Table 7). Two published DNA damage assays *in vivo* reported a positive result for a GBF in the *E. coli* SOS DNA damage test (Raipulis, 2009) and a negative Comet result for oyster sperm cells exposed to a very low (5 $\mu\text{g/L}$ glyphosate, ≈ 0.03 μM glyphosate) concentration of a Roundup™-branded GBF (Akeha et al., 2012).

Several recent publications report Comet results for GBFs in aquatic species and a reptile (Table 7). Negative Comet

Table 7. DNA damage assays of glyphosate, glyphosate and GBF's in non-mammalian systems.

Endpoint	Test system	Test material	Maximum dose	Result	Comment	References
<i>In vitro</i> studies glyphosate and glyphosate salts						
<i>Literature studies</i>						
Comet	Tradescantia flowers and nuclei	Glyphosate (technical, 96%)	0.7 mM	Positive	NC	Alvarez-Moya et al. (2011)
Comet	Oyster sperm	Glyphosate	5 µg/L (≈ 0.03 µM)	Negative	NC	Akcha et al. (2012)
<i>Regulatory study</i>						
Rec assay	<i>B. subtilis</i>	Glyphosate 95.68%	240 µg/disk	Negative		Akanuma (1995a)
<i>In vitro</i> studies GBF's						
<i>Literature studies</i>						
SOS*	<i>E. coli</i>	Roundup™ BID formulation	0.25 µg/sample	Positive		Raipuis (2009)
Sperm Comet	Oyster	Roundup Express®	5 µg/L glyphosate (≈ 0.03 µM)	Negative	NC	Akcha et al. (2012)
<i>In vivo</i> studies GBF's						
<i>Literature studies</i>						
Comet	Freshwater mussel larvae	Roundup™ formulation	5 mg/L glyphosate	Negative	NC	Connors & Black (2004)
Erythrocyte	<i>Carassius auratus</i> (fish)	Roundup™ formulation	15 ppm glyphosate in water (2, 4 and 6 d)	Positive		Cavas & Konen (2007)
Comet						
Erythrocyte and gill cell Comet	<i>Prochilodus lineatus</i> (fish)	Roundup™ formulation	10 mg/L in water (6, 24 and 96 h)	Positive		Cavalcante et al. (2008)
Erythrocyte	Caiman eggs /hatchlings	Roundup® Full II formulation	1750 µg/egg	Positive		Poletta et al. (2009)
Comet						
Erythrocyte	<i>Anguilla anguilla</i> (eel)	Roundup™ formulation	116 µg/L (1 and 3 d)	Positive	NC	Guilherme et al. (2010)
Comet						
Erythrocyte	Caiman eggs /hatchlings	Roundup® Full II formulation	Nest sprayed 3% (3 L/100 L water/ha)	Positive		Poletta et al. (2011)
Comet						
Liver and gill cell	<i>Anguilla anguilla</i> (eel)	Roundup® Ultra	116 µg/L (1 and 3 d)	Positive	NC	Guilherme et al. (2012)
Comet						
Erythrocyte	<i>Corvodoras paleatus</i> (fish)	Roundup™ formulation	6.67 µg/L (3, 6 and 9 d)	Positive	NC	de Castilhos Ghisi & Cestari (2012)
Comet						

*SOS response DNA damage assay.

†NC, independent coding of slides for scoring not indicated for visually scored slides. In some cases, coding may have been implied by reference citation.

results were reported in cells of freshwater mussel larvae exposed to a RoundupTM-branded GBF at 5 mg/L (glyphosate a.i.) in water for 24 h (Connors & Black, 2004). This concentration was reported to be one-half of a no observable effect concentration and the 24-h LC₅₀ for this GBF was reported to be 18.3 mg/L in parallel experiments. Four publications reported positive Comet results in aquatic vertebrates exposed to RoundupTM-branded GBFs in water. These publications have a common feature that Comet results were reported as categories of visually damaged cells. In one publication, increases in nuclei exhibiting comet visual damage effects were observed in erythrocytes and gill cells of the tropical fish *Prochilodus lineatus* exposed to 10 mg/L of a RoundupTM-branded GBF in water (Cavalcante et al., 2008). Measurement of erythrocyte micronucleus frequency and nuclear abnormalities did not show statistically significant increases in these endpoints. A second publication reported positive Comet results in erythrocytes of the goldfish, *Carassius auratus*, exposed to up to 15 ppm glyphosate concentration of a RoundupTM-branded GBF for 2, 4 or 6 d (Cavas & Konen, 2007). Positive comet results were also reported in erythrocytes and liver and gill cells of the European eel, *Anguilla anguilla*, exposed to 0.058 and 0.116 µg/mL of a RoundupTM-branded GBF in water for 1 or 3 d (Guilherme et al., 2010; Guilherme et al., 2012). Positive comet effects were also observed in liver and blood cells isolated from the fish species *Corydoras paleatus* exposed to 0.067 µg/mL of RoundupTM-branded GBF for 3, 6 or 9 days (de Castilhos Ghisi & Cestari, 2012). No toxicity data other than the absence of mortality were presented but results were negative for the piscine micronucleus endpoint in this study. Two publications previously discussed reported positive erythrocyte Comet results in caiman hatchlings from eggs exposed to RoundupTM Full II GBF (Poletta et al., 2009; Poletta et al., 2011).

Significance of DNA damage endpoint results

DNA damage endpoints such as SCE or comets are generally regarded as supplementary to the gene mutation and chromosomal damage endpoint categories. They are considered indirect measures of genotoxicity. As mentioned above, the precise mechanism(s) behind SCE induction are not understood. DNA damage as measured by Comet assays does not provide information on the consequences of that damage (e.g. repair, mutation or cell death) and such endpoints, therefore do not directly measure effects on heritable mutations or events closely associated with chromosomal mutations. It is widely recognized that *in vitro* DNA damage endpoints such as the SCE or Comet assay can be induced by cytotoxicity and cell death processes rather than from DNA-reactive mechanisms, as discussed below.

There are numerous examples of SCE positive responses which are unique compared to other genotoxic endpoints, are not concordant with carcinogenicity, or which are induced by oxidant stress (Benigni, 1989; Bradley et al., 1979; Declyper-Debergh et al., 1989; Djelic et al., 2006; Eckl et al., 1993; Speit, 1986; Tayama and Nakagawa, 1994; Zeiger et al., 1990). These examples indicate that the SCE endpoint, particularly in *in vitro* assays, should not be assumed to

indicate DNA-reactive genotoxicity or to have the same weight as genotoxicity assays using other endpoints such as gene mutation or chromosomal effects.

Similarly, there are abundant data supporting the concept that induction of DNA strand breakage or comet effects can be secondary to necrotic or apoptotic processes that do not involve DNA reactivity (Amin et al., 2000; Burlinson et al., 2007; Henderson et al., 1998; Kiffe et al., 2003; Storer et al., 1996; Tice et al., 2000). Several clear specific examples exist of *in vitro* induction of comet effects in mammalian cells by conditions which do not appear to be relevant to genotoxic potential at lower doses or which occur by mechanisms that do not involve direct interaction with DNA. These include the induction of comet effects by apoptosis inducers which inhibit topoisomerases (Boas & Stopper, 2000; Griexler et al., 1999); cytokine treatment of cultured cells (Delaney et al., 1997); sodium dodecyl sulfate and potassium cyanide (Henderson et al., 1998); colchicine, dl-menthol and sodium acetate (Kiffe et al., 2003); luteolin (Michels et al., 2005); gossypol (Quintana et al., 2000); carbon tetrachloride (Sasaki et al., 1998) and vitamin C (Anderson et al., 1994). Further examples of induction of comet effects of questionable genotoxic biological significance include dietary flavonoids quercetin, myricetin and silymarin (Duthie et al., 1997); hemoglobin (Glei et al., 2006); olive oil extracts (Nousis et al., 2005) and capsaicin (Richeux et al., 1999).

The observation of effects of sodium dodecyl sulfate is particularly interesting because it suggests responses to surfactants, which are typically components of GBFs. As a more specific example, polyoxyethylenealkylamine (POEA), a surfactant component of some GBFs, has been shown to elicit cytotoxic effects such as perturbation of the mitochondrial membrane and disruption of mitochondrial membrane potential in cultured mammalian cells (Levine et al., 2007). Surfactant effects provide a very plausible mechanism for observations of GBFs inducing DNA damage responses. Such responses would be expected to be associated with cytotoxic exposures and to exhibit a threshold.

Some data suggest better concordance of the Comet assay with other genotoxic endpoints or carcinogenicity in *in vivo* mammalian studies (Brendler-Schwaab et al., 2005; Hartmann et al., 2004; Kirkland & Speit, 2008). However, there are examples of *in vivo* studies of comet effects with questionable significance for genotoxicity because of negative results for other *in vivo* genotoxic endpoints or carcinogenicity assays, or which appear to be due to toxicity. Some examples of non-concordance between comet effects and carcinogenicity include thiabendazole, saccharine, tartrazine and ortho-phenylphenol (Brendler-Schwab et al., 2005). Discordance between carcinogenicity species specificity and *in vivo* Comet assay results has also been observed (Sekihashi et al., 2002), as well as other positive results for non-carcinogens (Kirkland & Speit, 2008). Another example of questionable *in vivo* genotoxic significance is positive comet effects produced in lymphocytes of exercising humans that were not accompanied by micronucleus induction (Hartmann et al., 1998).

In the context of unique results for DNA damage systems, there are several specific examples of published studies considered in this review containing reported positive results

for DNA damage in contrast to negative or equivocal results for chromosomal effect endpoints for glyphosate and glyphosate salts in mammalian cells in the absence of S9 (Manas et al., 2009; Mladinic et al., 2009a; Sivikova & Dianovsky, 2006) and GBFs in fish species (Cavalcante et al., 2008; de Castilhos Ghisi & Cesari, 2012).

Concurrent assessment of cytotoxicity is recommended in *in vitro* and particularly in *in vivo* studies to assist in the interpretation of positive results. The reported "gold standard" for cytotoxicity in *in vivo* studies is the histopathological evaluation of the tissues or cells being evaluated (Burlinson et al., 2007). Other measures for evaluating cytotoxicity include neutral pH SCGE to detect double strand breaks associated with apoptosis or necrosis and measurement of "hedghogs" which are nuclei in which almost all of the DNA is in the tail (Tice et al., 2000). The latter are thought to represent dead or dying cells severely damaged by cytotoxicity. While "hedghogs" are usually not included in tabulation of comet effects, they may be used as an additional measure of toxic effects (Smith et al., 2008).

As noted earlier in the section "*In vitro* mammalian cell assays", several Comet studies of glyphosate and GBFs did not employ concurrent measures of cytotoxic effects that were optimally suitable for the interpretation of a relationship between comet DNA damage and cytotoxicity. Examination of different markers of toxicity in some studies indicated the possibility of association with some markers but not others. The development and routine use of cytotoxicity measurements with maximum relevance to comet effect mechanisms would greatly improve the ability to interpret the significance of this endpoint in both *in vitro* and *in vivo* mammalian systems.

Genotoxicity weight of evidence conclusions

The earlier review of Williams et al. (2000) applied a weight of evidence analysis to the available genotoxicity data. Various weighted components included assay system validation, test system species, relevance of the endpoint to heritable mutation, reproducibility and consistency of effects and dose-response, and relationship of effects to toxicity (Williams et al., 2000). The conclusion of that analysis was that glyphosate and RoundupTM-branded GBFs were not mutagenic or genotoxic as a consequence of direct chemical reaction with DNA. This was supported by a strong preponderance of results indicating no effects in *in vivo* mammalian assays for chromosomal effects and consistently negative results in gene mutation assays. Although some DNA damage responses were noted, these were judged likely to be secondary to toxicity rather than DNA reactivity.

Since this earlier review, several genotoxicity studies of glyphosate, glyphosate salt solutions and GBFs have been published. Additionally, a large number of unpublished regulatory studies of glyphosate and GBFs were available for this review. A weight of evidence approach was applied to these data that considers the same factors used by Williams et al. (2000) and which are consistent with recommendations for weight of evidence evaluations for genotoxicity data (EFSA, 2011; ICH S2(R1), 2011; UK COM, 2011; U.S. EPA, 1986; U.S. FDA, 2006). Additional considerations include the

robustness of the experimental protocols and more recent elaborated considerations relevant to whether genotoxic effects result from direct interaction with DNA or are secondary to other processes such as cytotoxicity (Kirkland et al., 2007; Thybaud et al., 2007).

In terms of composition, the genotoxicity studies of both glyphosate and glyphosate salts can reasonably be considered together to provide an overall evaluation for the glyphosate molecule. This is especially useful when numerous consistent results are observed for a particular endpoint. The fact that glyphosate is present in all GBFs should be considered in evaluating the genotoxicity of GBFs. It is unlikely that glyphosate or glyphosate salts would contribute novel genotoxic activity (i.e. different from when tested alone) as part of a GBF. Analysis of a weight of evidence of genotoxicity of GBFs should consider the fact that different formulations have different compositions. The weight of evidence, therefore, can allow some conclusions about genotoxicity typical of GBFs but the possibility always exists that individual components could lead to different toxic and genotoxic properties.

Apart from genotoxicity, the data indicate that GBFs are more toxic to the genotoxicity test systems than glyphosate or glyphosate salts, which is consistent with findings in aquatic systems (Folmar et al., 1979; Perkins et al., 2000; Tsui & Chu, 2003). In many cases a reasonable explanation for this difference is that surfactants in GBFs contribute more to toxicity than glyphosate or glyphosate salts *per se*.

Gene mutation is one of the two primary endpoints with direct relevance to heritable mutation and is considered to be one of the key drivers in the carcinogenic process. A large number of regulatory bacterial reverse gene mutation studies provide a very consistent pattern that glyphosate, glyphosate salts and numerous GBFs are negative in well-conducted GLP regulatory assays.

Additionally, there are two regulatory *in vitro* mammalian cell gene mutation (mouse lymphoma *tk* locus) studies which gave negative results for glyphosate. As noted earlier, these mouse lymphoma *tk* locus studies detect large deletions as well as gene mutational events that are also detected in the CHO/HGPRT locus assay. The earlier reported negative CHO/HGPRT result (Williams et al., 2000) and these negative *tk* mutation results support the conclusion that glyphosate and glyphosate salts do not induce gene mutations in mammalian cells.

The second primary endpoint with direct relevance to heritable mutation and the carcinogenic process is chromosomal effects, such as the induction of chromosomal aberrations or micronuclei in cultured mammalian cells. The earlier review (Williams et al., 2000) noted mixed results for three *in vitro* chromosomal aberration assays for glyphosate, but concluded that the most reliable result was the negative assay. No *in vitro* mammalian cell chromosomal aberration reports were noted for GBFs in the Williams et al. review.

A number of *in vitro* chromosomal aberration and micronucleus assay results for glyphosate or glyphosate salts have been subsequently published using bovine or human lymphocytes. Some technical limitations of these assays were discussed earlier and should be considered in the weight attributed to these studies. Both positive and negative results

were reported in these assays. In the absence of exogenous metabolic activation, the majority of studies were negative up to high (mM) dose levels that were toxic or close to toxic levels measured in parallel experiments. Two publications from a laboratory reported an increase in micronucleus frequencies for glyphosate in human lymphocytes in the presence of S9 mix but these studies have several limitations discussed earlier that complicate the interpretation of these effects.

A recent publication reported positive CB MN results for glyphosate in cultured human epithelial cells in the absence of metabolic activation at very low dose levels. The dose levels and exposure time reported as producing effects were much lower than dose levels and exposure times of many published and regulatory *in vitro* mammalian cell genotoxicity studies using different cell types that did not produce either genotoxic or toxic effects. Thus, the results of this study, especially the quantitative aspects, are quite unusual.

Three regulatory chromosomal aberration studies, which used upper dose levels of an estimated 3 mM to around 7 mM, gave negative results in both the presence and absence of S9. These results therefore agree with the majority of negative published data in the absence of S9 and support a weight of evidence that glyphosate is not active in *in vitro* mammalian cell gene mutation or chromosomal aberration assays in the presence of S9.

Overall, the weight of evidence indicates that glyphosate and glyphosate salts do not typically induce chromosomal effects *in vitro* in mammalian cells.

Two publications subsequent to the Williams et al. (2000) review reported positive results for chromosomal aberrations with two different GBFs in two different assay systems. The paucity of studies and study limitations discussed earlier precludes any general conclusion for GBFs for this endpoint. However, as discussed above, the weight of evidence is that glyphosate or glyphosate salts are not clastogenic in mammalian cells, so any positive results with GBFs do not appear to be due to glyphosate.

In vivo mammalian chromosomal effect studies are a particularly important class of studies because they are the pre-eminent core assays for *in vivo* mammalian genotoxicity. The Williams et al. (2000) review noted a predominance of negative results for glyphosate in these types of assays with only one study exhibiting a weak positive result.

Two subsequently published studies of glyphosate or glyphosate salt solutions in mouse bone marrow micronucleus assays gave discordant results with one study reporting positive results. However, eight out of 12 regulatory bone marrow micronucleus studies (seven mouse and one rat study) of glyphosate or glyphosate salts did not yield any statistically significant increases in the frequencies of micronucleated PCEs. Three other studies did give statistical increases in MN PCE frequency for high dose levels but these were judged not to be treatment-related because they were clearly within the historical negative control range. A fourth study exhibited a statistically significant increase in MN PCE only in females. This study had high vehicle control MN PCE frequencies and no historical control data were presented. In addition to the micronucleus results, a mouse bone marrow chromosomal aberration study was also negative. There did not appear to be

any data to suggest that, in the minority of studies that exhibited some statistical increases in MN PCE frequencies, the effects might be due to factors such as gender, route of exposure or dose level. The clearly negative results from the vast majority of studies, including a large number of robust regulatory studies conducted in accordance with good laboratory practices, indicate that, on weight of evidence, glyphosate and glyphosate salts are not genotoxic in rodent bone marrow micronucleus or chromosomal aberration studies.

A preponderance (4/5) of mouse bone marrow micronucleus assays on GBFs were indicated as negative in the earlier Williams et al. (2000) review. Mixed results were observed in subsequent published rodent bone marrow micronucleus or chromosomal aberration studies with a majority (4/6) being negative including 3/4 studies of Roundup™-branded GBFs. One rabbit drinking water study of a Roundup™-branded GBF was positive but there were some significant limitations of this study, and this is an unusual test model with little or no background data. Another GBF study reported positive results in spermatocytes with extended oral or i.p. treatments. No clear explanation exists for the discordant published mouse bone marrow results such as unique routes or dramatically different maximum dose levels.

The majority of regulatory rodent bone marrow micronucleus studies (11 mouse and one rat study) of various GBFs gave clearly negative results and the two that had statistical increases were also considered negative because the increases were well within historical control values.

The large number of negative regulatory studies, in combination with a majority of negative published studies, indicate that GBFs are generally negative for this important *in vivo* endpoint. The preponderance of negative results for GBFs is also consistent with a weight of evidence that glyphosate or glyphosate salt solutions are negative for chromosomal effects and suggests that formulation surfactant components are also negative for chromosomal effects *in vivo*.

The micronucleus test detects aneugenic as well as clastogenic (chromosomal breakage) events. The negative results for the large number of *in vivo* rodent micronucleus studies therefore support the conclusion that glyphosate, glyphosate salts and GBFs do not induce aneuploidy.

In addition to the rodent bone marrow studies, one regulatory rat dominant lethal study of glyphosate, albeit with some limitations, appears to confirm the earlier negative result for this type of assay, and reinforces the conclusion that glyphosate is not genotoxic for mammalian germ cells.

Although generally consistent negative results were observed for rodent micronucleus or chromosomal aberration assays of GBFs, discordant results were observed in *in vivo* erythrocyte micronucleus studies of fish, amphibians and reptiles. In addition to some technical limitations there is considerably less experience with these assay systems, and consequently these should have less influence in evaluating overall weight of evidence for chromosomal effects.

In general, induction of DNA damage is considered supplementary to induction of gene mutations and chromosomal effects because it does not directly measure heritable events or effects closely associated with heritable events. Regulatory genotoxicity testing focuses on gene mutation and

chromosomal effects for initial *in vitro* core testing (Cimino, 2006; Eastmond et al., 2009; EFSA, 2011; ICHS2(R1), 2011; UK COM, 2011).

The Williams et al. (2000) review noted negative DNA damage results for technical glyphosate in the *B. subtilis* *rec* assay and the primary hepatocyte UDS assay, but noted positive or equivocal results for SCE assays *in vitro* in human or bovine lymphocytes. The negative results for the *B. subtilis* *rec* and primary hepatocyte UDS assays have been confirmed in subsequent regulatory studies. The UDS result provides information on the lack of *in vitro* genotoxic activity when mammalian metabolic activation other than S9 is employed.

Subsequent literature publications indicated several positive responses for *in vitro* mammalian DNA damage endpoint assays of glyphosate or glyphosate salts. These include an SCE response in bovine lymphocytes and four positive Comet results in cultured mammalian cell lines or human lymphocytes. The positive Comet results were observed in the absence of mammalian metabolic activation and generally at concentrations in the mM range but one publication found positive results at much lower dose levels in human epithelial cells. As noted earlier, observations of differential responses in Comet and chromosomal aberration assays for some of these studies provide some support for the conclusion that the SCE or Comet responses observed may not be predictive of effects on other more relevant endpoints.

The Williams et al. (2000) review noted some equivocal or positive Roundup™-branded GBF results for the SCE endpoint in human lymphocytes and reports of DNA strand breakage in mouse tissues and induction of comets in tadpoles. An observation of mouse liver DNA adducts for a GBF were considered to be of questionable significance. Subsequent literature results for DNA damage in mammalian systems included induction of SCE in cultured mammalian cells and in mouse bone marrow for the uncharacterized herbazed formulation and induction of comets in cultured mammalian cells with a Roundup™ UltraMax formulation. There were a number of Comet assay reports for GBFs in a variety of aquatic organisms with a preponderance of positive results.

The fact that DNA damage is usually only seen at high, toxic concentrations *in vitro* (e.g. in the 1–10 mM concentration range) or *in vivo* where tissue damage might be induced, suggests that cytotoxic effects rather than DNA interaction may be responsible for the DNA damage reported for glyphosate, glyphosate salts and GBFs. In many Comet assay publications parallel data on toxic effects most directly relevant to comet mechanisms are lacking, and, in addition, many of the positive DNA damage results have been observed for GBFs in non-standard test systems. It is hoped that clarification of the mechanism and significance of comet effects can be improved by the more routine use of relevant markers such as quantitation of double-strand breaks and hedgehogs and histopathology, as appropriate, for *in vivo* studies. Studies with protocols for specifically identifying surfactant effects would also be useful in clarifying the significance of DNA damage effects of GBFs. However, it seems reasonably clear that GBFs are more toxic than the a.i. and a reasonable conclusion is that consistency of observations of DNA damage, particularly comets, with GBFs might be secondary to the toxicity of GBF surfactants.

As discussed extensively in the section "DNA damage" there are both general and specific reasons to consider DNA damage assays as subordinate in a weight of evidence for genotoxic risk, especially when they may arise from mechanisms secondary to toxicity. Whatever the precise causes of these DNA damage effects, they do not translate into gene mutations or chromosomal damage as demonstrated by the large preponderance of negative results for glyphosate, glyphosate salts and GBFs in well-conducted bacterial reversion and *in vivo* rodent bone marrow micronucleus assays.

In addition to considering the results relevant to genotoxicity hazard assessment, an important additional perspective on risk can be provided by comparing levels used in experimental studies with expected human levels. For example, estimated margins of exposure between the *in vivo* genotoxicity test systems (e.g. 1000 mg/kg body weight exposure) and calculated systemic doses from an exposure study of farmers (Acquavella et al., 2004: 0.004 mg/kg maximum systemic exposure, 0.0001 mg/kg geometric mean systemic exposure) are in the range of 250 000 for maximum systemic exposure and 10 million for geometric mean systemic exposure. The margins of exposure compared to *in vitro* mammalian cell exposures are also quite large. Assuming uniform distribution, the estimated systemic concentration of glyphosate from the Acquavella et al. (2004) farmer biomonitoring study would be of the order of 24 nM for the maximum and 0.59 nM for the geometric mean exposure. A typical maximum *in vitro* mammalian exposure of 5 mM represents margins of exposure of 208 000 for the maximum farmer systemic exposure and 8.5 million for the geometric mean farmer systemic exposure. Similarly, exposure levels evaluated in several published DNA damage and micronucleus assays in non-mammalian species were conducted at much higher glyphosate concentrations than anticipated under typical environmental conditions. Relevant environmental concentrations representing biologically available glyphosate are not equivalent to application rates. Sorption to soil and sediment occurs following glyphosate applications, significantly diminishing or eliminating glyphosate and POEA surfactant bioavailability to environmental species (Giesy, 2000).

This evaluation of the large volume of genotoxicity data available presents a convincing weight of evidence supporting the lack of genotoxic potential for both glyphosate and typical GBFs in core gene mutation and chromosomal effect endpoints. Given this conclusion, and for other reasons discussed, the observation of DNA damage effects seems likely to be secondary to cytotoxic effects. The lack of genotoxic hazard potential evidenced by core gene mutation and chromosomal effect studies, coupled with the very low human and environmental species systemic exposure potential discussed above, indicate that glyphosate and typical GBFs present negligible genotoxicity risk.

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Evaluating the potential carcinogenic hazard of glyphosate

Critical Reviews in Toxicology (CRT) has been a leader for more than four decades in publishing scientific reviews evaluating the health hazards of exposure to chemicals that are widely used around the globe. These reviews have been internationally recognized for their comprehensive coverage of contemporary topics ranging from novel testing and assessment strategies to the characterization of the potential hazards associated with chemicals. The reviews evaluating potential chemical hazards and risk typically cover and integrate evidence from multiple avenues of investigation, including molecular and cellular research, animal investigations and epidemiological studies. From its first issue in 1971 to the present, *CRT* has a well-earned reputation for scientific rigor and thoroughness of its external peer review.

This Special Issue of *CRT* contains five papers each addressing aspects of the evaluation of the potential carcinogenic hazard of glyphosate, a chemical discovered by a scientist at Monsanto Company in 1970. Glyphosate was rapidly commercialized and initially marketed in 1974 as Roundup. Since going off patent in 2000, glyphosate has been produced and marketed by a growing number of companies. It is one of the most widely used agricultural chemicals in the world and has been of great benefit in weed control and enhanced productivity of a number of crops.

Monsanto conducted the first safety evaluations on glyphosate prior to marketing of products containing the chemical. These in-house evaluations were followed by review and approval for marketing by the U.S. Environmental Protection Agency and then other government agencies around the world. Scientific information available on the potential health hazards of glyphosate continues to increase and is now voluminous.

The International Agency for Research on Cancer (IARC) announced in 2014 that it was going to review glyphosate along with four pesticides for their potential carcinogenic hazard. Four review papers, commissioned by Monsanto Company, addressing various aspects of the toxicity of glyphosate and glyphosate-based formulations, were submitted to *Critical Reviews in Toxicology*, subjected to rigorous external review, revised and published in *CRT* prior to the IARC meeting (Kimmel et al. 2013; Kier & Kirkland 2013; Kier 2015; Greim et al. 2015). Those papers were frequently accessed on-line and, most importantly, copies were provided to IARC prior to the meeting of the IARC review panel in Lyon, France in March 2015.

The IARC Panel classified glyphosate in Category 2a, probably carcinogenic to humans. At the conclusion of the review, IARC released a press announcement reporting key results of the review; this was followed by publication of a summary

paper (Guyton et al. 2015) and publication of a monograph (IARC 2015). The conclusions of the IARC Panel were a surprise to many scientists who had followed the literature on the potential health hazards of glyphosate over many decades. This was especially the case because the IARC classification of glyphosate as probably carcinogenic to humans ran counter to the conclusions of a number of previous carcinogenic hazard assessments conducted by multiple government agencies around the world.

Following the IARC carcinogenic hazard classification of glyphosate, the Monsanto Company engaged Intertek, a scientific and regulatory consulting firm, to convene an independent scientific panel to evaluate and synthesize the scientific evidence of the potential carcinogenic hazard of glyphosate. The activities and conclusions of the independent panel are reported in the five papers in this special issue. Each of the five papers was rigorously reviewed by 5–10 independent reviewers selected by the *CRT* Editor and anonymous to the authors. A total of 27 different reviewers participated with several of the individuals reviewing all five papers. The authors of each paper were provided the review comments on their paper and asked to make appropriate revisions. The final papers, published here, represented the work product of the authors. Each paper includes an Acknowledgements section and an extensive Declaration of Interest section.

In order to facilitate the broadest possible readership, Intertek requested that these five papers be published in a sponsored Open Access Supplement Issue in the 2016 volume of *Critical Reviews in Toxicology*. Negotiations for such sponsored supplements are customarily conducted between the sponsor and publisher, separate from the review process, thereby maintaining the journal's editorial independence. The Editor-in-Chief was not party to these negotiations.

It is anticipated that scientific discussions concerning the science of the potential carcinogenic hazards of glyphosate and its use will continue for some time along with related discussions of how this science informs policy decisions on the regulation of glyphosate-containing products. The contents of these five papers, the extensive listing of references in each paper and the Supplemental Material (available on-line for several of the papers), will contribute to and facilitate continued scientific discussions and policy decisions on this widely used chemical.

Acknowledgments

The Editor gratefully acknowledges the extensive review comments offered by the 27 external reviewers. Those comments enhanced the quality and completeness of the five papers.

Declaration of interest

Roger O. McClellan, the Editor-in-Chief of *Critical Reviews in Toxicology (CRT)*, since 1987, currently serves as an independent advisor to private and public entities on environmental and occupational health issues. Early in his career, his research focused on the health effects of radiation and internally-deposited radionuclides as an employee of General Electric Company and the U.S. Atomic Energy Commission (AEC). Later he provided leadership for the Lovelace Inhalation Toxicology Research Institute's extensive research program on airborne radionuclides and other toxicants with primary financial support from the AEC and the U.S. Department of Energy. From 1988 to 1999, he was the President and Chief Executive Officer of the Chemical Industry Institute of Toxicology (CIIT), a not-for-profit research institute whose extensive research program, focusing on mechanisms of action of chemicals, was supported by dues payments from member companies. The Monsanto Company was a founding member of the CIIT. The CIIT did not conduct any research on glyphosate. McClellan, during his career, has served on over 100 major advisory committees for private firms, academic institutions and U.S. government and international agencies, including IARC. None of these advisory assignments has directly involved review of the health hazards of glyphosate. McClellan, in his role as Editor-in-Chief of *CRT*, selected the 27 individuals who reviewed the five papers published in this Special Supplement. The reviewers represented a cross-section of scientists from around the globe employed by academic, government and private entities or working as sole proprietors. The review comments they provided were considered to represent their independent professional views.

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to Intertek by the Monsanto Company, which is a primary producer of glyphosate and products containing this active ingredient.

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A review of the carcinogenic potential of glyphosate by four independent expert panels and comparison to the IARC assessment

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ABSTRACT

The International Agency for Research on Cancer (IARC) published a monograph in 2015 concluding that glyphosate is “probably carcinogenic to humans” (Group 2A) based on limited evidence in humans and sufficient evidence in experimental animals. It was also concluded that there was strong evidence of genotoxicity and oxidative stress. Four Expert Panels have been convened for the purpose of conducting a detailed critique of the evidence in light of IARC’s assessment and to review all relevant information pertaining to glyphosate exposure, animal carcinogenicity, genotoxicity, and epidemiologic studies. Two of the Panels (animal bioassay and genetic toxicology) also provided a critique of the IARC position with respect to conclusions made in these areas. The incidences of neoplasms in the animal bioassays were found not to be associated with glyphosate exposure on the basis that they lacked statistical strength, were inconsistent across studies, lacked dose-response relationships, were not associated with preneoplasia, and/or were not plausible from a mechanistic perspective. The overall weight of evidence from the genetic toxicology data supports a conclusion that glyphosate (including GBFs and AMPA) does not pose a genotoxic hazard and therefore, should not be considered support for the classification of glyphosate as a genotoxic carcinogen. The assessment of the epidemiological data found that the data do not support a causal relationship between glyphosate exposure and non-Hodgkin’s lymphoma while the data were judged to be too sparse to assess a potential relationship between glyphosate exposure and multiple myeloma. As a result, following the review of the totality of the evidence, the Panels concluded that the data do not support IARC’s conclusion that glyphosate is a “probable human carcinogen” and, consistent with previous regulatory assessments, further concluded that glyphosate is unlikely to pose a carcinogenic risk to humans.

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Introduction

Background on glyphosate

Glyphosate, or N-(phosphonomethyl)glycine (CAS# 1071-83-6), is a widely used broad-spectrum, nonselective post-emergent herbicide that has been in use since 1974. Glyphosate 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 growth of plants such as weeds. Importantly, EPSPS is not present in mammals, which obtain their essential aromatic amino acids from the diet.

A wide variety of new uses have been developed for glyphosate in agricultural, industrial, and home & garden applications. Glyphosate accounts for approximately 25% of the global herbicide market (<http://www.glyphosate.eu>). Glyphosate is currently marketed under numerous trade names by more than 50 companies in several hundreds of crop protection products around the world. More than 160 countries have approved uses of glyphosate-based herbicide products (<http://www.monsanto.com>). 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.

Glyphosate is a relatively simple molecule which consists of the amino acid glycine and a phosphonomethyl moiety (Figure 1). As such, glyphosate has no structural alerts for chromosomal damage, genotoxicity, mutagenicity, or carcinogenicity when analyzed by DEREK (Deductive Estimation of Risk from Existing Knowledge) (Kier & Kirkland 2013). It is a polar molecule that is incompletely (15–36%) absorbed orally, undergoes very little biotransformation, and is rapidly excreted unmetabolized (Williams et al. 2000). A molecule with these characteristics would be expected to exhibit, if any, only a low order of toxicity. The results from toxicity studies and regulatory risk assessments have been consistent with that expectation (JMPR 1987, 2006; US EPA 1993; WHO 1994; Williams et al. 2000; European Commission 2002; EFSA 2015).

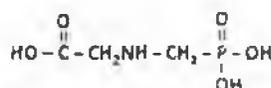


Figure 1. Structure of glyphosate.

Previous assessments of the carcinogenicity of glyphosate

The safety, including the potential carcinogenicity, of glyphosate has been reviewed by scientists and 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; EFSA 2015; Health Canada 2015; JMPR 2016). The conclusion of all these reviews is that proper use of glyphosate and glyphosate-based formulations (GBFs) does not pose a genotoxic or carcinogenic hazard/risk to humans.

The first assessment of glyphosate's carcinogenic potential was undertaken by the US EPA in 1985. This review was done by a US EPA panel that then was called the Toxicology Branch Ad Hoc Committee, which comprised members of the Toxicology Branch of the Hazard Evaluation Division. At that time, two chronic animal bioassays were available: a combined chronic toxicity/carcinogenicity study in Sprague-Dawley rats and a carcinogenicity study in CD-1 mice. The Agency concluded that the data did not demonstrate a carcinogenic response in rats. However, the US EPA also concluded that the dose levels used in that study were inadequate for assessing glyphosate's carcinogenic potential in this species. The US EPA concluded that there was limited evidence of an increased incidence of renal tubule adenomas in male mice at the high-dose level (4841 mg/kg/day), a dose that greatly exceeds the limit dose level (1000 mg/kg/day) for carcinogenicity testing with pesticides (OECD 2009). Based on this information, the Agency initially classified glyphosate as a Group C (Possibly Carcinogenic to Humans: Agents with limited animal evidence and little or no human data) carcinogen (see US EPA 1991a).

The kidney slides from the mouse study were subsequently reexamined by a consulting pathologist (Dr. Marvin Kuschner M.D., Dean, School of Medicine, State University of New York at Stony Brook), and three other scientists (Dr. Robert A. Squire, Robert A. Squire Associates Inc., Ruxton Maryland; Dr. Klaus L. Stemmer M.D., Kettering Laboratory, University of Cincinnati Medical Center; Dr. Robert E. Olson, M.D., Ph.D., Professor of Medicine and Pharmacological Sciences, State University of New York at Stony Brook) also reviewed the slides and/or the chronic toxicity data. All these scientists concluded that there was no relationship to treatment (US EPA, 1986a). In addition, a Pathology Working Group (PWG), consisting of 5 pathologists (Dr. RM Sauer, Dr. MR Anver, Dr. JD Strandberg, Dr. JM Ward, and Dr. DG Goodman), was also assembled and they issued the following conclusion: "This PWG firmly believes and unanimously concurs with the original pathologist and reviewing pathologist that the incidences of renal tubular cell neoplasms in this study are not compound related" (US EPA 1986a).

All available information was presented to an US EPA FIFRA Science Advisory Panel (SAP) in February 1986. The SAP determined that the carcinogenic potential of glyphosate could not be determined from the existing data and proposed that a chronic rat and/or mouse study be conducted

In order to clarify these unresolved questions, the panel also proposed that glyphosate be categorized as Group D or having "inadequate animal evidence of oncogenicity" (US EPA 1986b).

After considering the SAP's conclusions and recommendations, the US EPA requested that a new 2-year rat oncogenicity study be conducted. In 1991, after the new rat study was completed, the US EPA re-convened its Carcinogenicity Peer Review Committee to review the results of this study as well as all of the relevant scientific data on glyphosate (US EPA 1991a). The Committee concluded that glyphosate should be classified in Group E (evidence of non-carcinogenicity) based upon the lack of a carcinogenic response in two animal species. Subsequent reevaluations by US EPA (1993, 2012, 2013) have re-affirmed the Agency's earlier conclusion.

After Monsanto had marketed glyphosate-based herbicide products for a number of years, other companies entered the glyphosate market; as a result, some of them generated substantial, or even complete, additional toxicology databases. The first additional databases that became available were generated by Cheminova and Syngenta in the mid- to late 1990s timeframe. Additional data packages were subsequently generated by other companies (e.g. Arysta, Excel, Fenchemie, Nufarm) and became available in the mid- and late 2000s timeframe.

In addition to new studies conducted to meet regulatory guidelines and support various re-registration processes globally, new epidemiology and genotoxicity studies (testing glyphosate and glyphosate-based herbicide formulations) began to appear in the scientific literature in the late 1990s and early 2000s. One of the first epidemiological investigations of interest involving glyphosate published in the scientific literature was that of Hardell and Eriksson (1999), and other epidemiology studies were periodically published after 2000 up until the present. Genetic toxicology studies of glyphosate and GBFs began to appear in the literature in increasing numbers throughout the 1990s and were reviewed by Williams et al. (2000). The occurrence of such studies has increased during the 2001–2015 timeframe: approximately 125 such genotoxicity studies were reviewed by Kier and Kirkland (2013), and an additional 40 genotoxicity biomonitoring studies of GBFs were reviewed by Kier (2015).

As glyphosate underwent reregistration processes by major national regulatory authorities and additional reviews by other health agencies after 2000, these evaluations included more and more of the new toxicology, genotoxicity, and epidemiology information generated after the initial Monsanto animal bioassay studies. For example, a 2004 Joint Meeting of the FAO Panel of Experts on Pesticide Residues (JMPR) in Food and the Environment and the WHO Core Assessment Group concluded that there was an absence of carcinogenic potential in animals and a lack of genotoxicity in standard tests, thus, "the Meeting concluded that glyphosate is unlikely to pose a carcinogenic risk to humans" (JMPR 2006). The Australian Pesticides and Veterinary Medicines Authority (APVMA) evaluated the active ingredient and concluded that the evidence shows that glyphosate is not genotoxic or carcinogenic (APVMA 2013). The US EPA conducted a comprehensive Human Health Risk Assessment in 2012

(US EPA 2012). The Agency noted that "no evidence of carcinogenicity was found in mice or rats," and US EPA concluded that "glyphosate does not pose a cancer risk to humans" (US EPA 2013). Health Canada's Pesticide Management Regulatory Agency (PMRA) completed a comprehensive review of glyphosate as part of the reregistration process in that country. PMRA concluded that "the overall weight of evidence indicates that glyphosate is unlikely to pose a human cancer risk" (Health Canada 2015). The complete genotoxicity, carcinogenicity, and human epidemiology databases were evaluated by the German Federal Institute for Risk Assessment (BfR) for the European Commission on the Annex 1 renewal of glyphosate. The BfR concluded that glyphosate is unlikely to pose a carcinogenic risk to humans (Markard 2014). This conclusion was supported by the peer review evaluation conducted by the European Food Safety Authority (EFSA) both before and after a mandate from the European Commission to consider the findings from IARC regarding glyphosate's carcinogenic potential (EFSA 2015). Most recently, JMPR (2016) reviewed the data and concluded that: "glyphosate is unlikely to pose a carcinogenic risk to humans from exposure through the diet."

IARC assessment of the carcinogenicity of glyphosate

The International Agency for Research on Cancer (IARC) in 2015 undertook an evaluation of the oncogenic potential of glyphosate as part of its Monograph Programme. Glyphosate, along with four other pesticides (the insecticides diazinon, malathion, parathion, and tetrachlorvinphos), was considered by an IARC Working Group, which met in March 2015 at IARC in Lyon, France. A brief summary of IARC's conclusions was initially published in *The Lancet Oncology* on 20 March 2015 (Guyton et al. 2015), and the full IARC Monograph (Volume 112) was published online on 29 July 2015 (IARC 2015). IARC concluded that glyphosate is "probably carcinogenic to humans (Group 2A)" based on *limited evidence* in humans and *sufficient evidence* in experimental animals; it was also concluded that there was strong evidence of genotoxicity and oxidative stress (IARC 2015).

Expert Panel critique of the IARC assessment and review of relevant data

Since the IARC conclusions were found to be in such stark contrast to those from all other assessments of carcinogenic potential, it was decided that a thorough review should be conducted by scientists in the area of cancer risk assessment, critiquing IARC's processes where appropriate. Toward that end, Intertek Scientific & Regulatory Consultancy (Intertek, Mississauga, Ontario, Canada) was commissioned by the Monsanto Company to assemble panels of scientific experts in the four areas considered by IARC: exposure; epidemiology; cancer in experimental animals; mechanistic and other relevant data (focused on genotoxicity and oxidative stress).

Fifteen scientific experts were selected on the basis of their expertise and standing within the international scientific community (i.e. publication history, participation in scientific

Table 1. Composition of the four Expert Panels.

Expert panel group ^a	Name of participating scientist	Affiliation of scientist
Human exposures Carcinogen/Kity bioassays	Keith R. Solomon	Centre for Toxicology, University of Guelph, Guelph, ON Canada
	Gary M. Williams	Professor of Pathology, New York Medical College, Valhalla, NY
	Sir Colin Berry	Emeritus Professor of Pathology, Queen Mary, University of London, London, UK
	Michele M. Burns	Boston Children's Hospital, Boston, MA, USA
	Joao Laura Viana de Camargo	Professor of Pathology, Botucatu Medical School, São Paulo State Univ, UNESP, SP, Brazil
Genotoxicity	Helmut A. Greim	Emeritus Professor of Toxicology and Environmental Hygiene, Technical University of Munich, Germany
	David Brusick	Toxicology Consultant, Bumpass, VA, USA
	Marilyn Aardema	Marilyn Aardema Consulting, LLC, Fairfield, OH, USA
	Larry D. Kier	Private Consultant, Buena Vista, CO USA
	David J. Kirkland	Kirkland Consulting, Tadcaster, UK
Epidemiology	Gary M. Williams	Professor of Pathology, New York Medical College, Valhalla, NY
	John Acquavella	Professor, Department of Clinical Epidemiology, Aarhus University, Denmark
	David Garabrant	EpidStat Institute; Emeritus Professor of Occupational Medicine and Epidemiology, University of Michigan
	Gary Marsh	Professor of Biostatistics, Director and Founder, Center for Occupational Biostatistics & Epidemiology, University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA, USA
	Tom Sorahan	Professor of Occupational Epidemiology, University of Birmingham, Birmingham, UK
Douglas L. Weed	DLW Consulting Services, LLC, Adjunct Professor, University of New Mexico School of Medicine, Albuquerque, NM, USA	

^aAshley Roberts of Intertek Scientific & Regulatory Consultancy served as facilitator for each of the four panels.

and regulatory committees, and familiarity with regulatory authorities) and recruited by Intertek to participate on these Expert Panels. Panelists were recruited and assigned to one of the four areas considered by IARC (noted above) based on their areas of expertise; two panelists participated in two areas. A sixteenth scientific expert from Intertek participated on the Expert Panels and served as the overall organizer and facilitator for the panel meetings. A listing of the experts, their affiliations, and the specific "Panel" on which they served is presented in Table 1.

Prior to the meeting, all key studies/publications cited by IARC were made available to the panelists for their review; panelists were told to request any additional information they felt was necessary for them to conduct a thorough evaluation. The epidemiology panel conducted its own independent literature search. The scientists were asked to closely examine the studies/data that IARC used to come to their conclusions; panelists were also advised to examine any additional information needed to come to an overall conclusion in their respective areas.

Based on the scope of the information to be evaluated, it was decided that the panels would meet over a 2-day period to discuss all relevant information and make appropriate conclusions regarding the carcinogenic potential of glyphosate. As needed, the expert scientists held pre-meeting phone conferences and communicated *via* email to establish and plan how they would prepare for and conduct their review at the Expert Panels review meeting. Since the amount, nature, and quality of the data used by IARC varied considerably across the four areas, the evaluation approaches used by the expert panelists in their specialist areas varied somewhat as well. The Expert Panels Meeting was held on 27–28 August 2015 at Intertek in Mississauga, Canada. On the first day of the meeting, the discussions focused on the exposure and human epidemiology data. The second day of the meeting began with a summation of epidemiology and exposure discussions/conclusions and then focused on the animal bioassay and genotoxicity/oxidative stress data. After the Expert Panels met, the reports for the four individual areas were developed

by designated scientists; the content of these reports was finalized through additional phone conferences and email communications as necessary with the other panel members. As indicated previously, due to the large amount of data and information evaluated by the individual panels and the subsequent length of the individual reports, it was decided to prepare four separate specialist manuscripts covering the methodologies applied and their respective outcomes and conclusions. This report presents a summary of the deliberations, and conclusions reached, by the Expert Panels in the four areas of research. Prior to publishing the Expert Panels findings, they were presented at the Society for Risk Analysis Annual Meeting at Arlington, Virginia on 7 December 2015.

As a preface to the remainder of the document, the process by which IARC identifies and reviews data must be compared with that employed by the Expert Panel(s). IARC only reviews data included in: "reports that have been published or accepted for publication in the openly available scientific literature" or "data from governmental reports that are publicly available" (IARC 2006). In addition, IARC reviews and assesses these data in the context of hazard (i.e. inherent carcinogenic potential) not risk (i.e. the likelihood of carcinogenic effects at exposure levels humans may encounter). As a result, the conclusion of IARC is often solely associated with hazard. In contrast to IARC, toxicology, mechanism, and exposure Expert Panels evaluated all of the available scientific data, including the results of a number of unpublished reports, some of which have been submitted to and reviewed by regulatory authorities. These reports document GLP- and OECD/FDA Redbook guideline compliant studies, conducted to assess the genotoxic and carcinogenic potential of glyphosate. In essence, these studies provide the highest quality of documentation and verification; hence, a balanced assessment requires the inclusion of such studies in the review process. The third panel (epidemiology) took an approach consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews (Moher et al. 2009), standard approaches to critically evaluating epidemiologic studies (Aschengrau & Seage

2003a,b; Sanderson et al. 2007] and well-recognized interpretative methods – e.g. the criteria-based methods of causal inference (Hill 1965, 1971) – sometimes referred to as “weight of evidence” (WoE) methods (Weed 2005). In addition to the identification of hazard potential, the Expert Panels assessed exposure data to provide a perspective from which to comment on potential risk. In the absence of carcinogenic hazard, however, no risk is present regardless of exposure. The conclusions reached by the Expert Panels and IARC clearly differ. However, in the opinion of the Expert Panel(s) this is not due to differences in process (hazard versus risk assessment), but rather the result of the exclusion from the IARC review process of key data (animal bioassay and genotoxicity) or differences in the interpretation of the data that was assessed particularly in regard to the animal bioassay results. Given these differences, even without the data IARC did not include, there is no support for IARC’s conclusion that glyphosate is “probably carcinogenic to humans.” This critique is presented and discussed in the context of the Expert Panels’ assessment of the totality of the data.

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 (see Solomon 2016 for additional details and bibliography). 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% absorption of glyphosate from the air into the body of a 70 kg human breathing 8 m³ 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 in 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” (persons who are located within or directly adjacent to areas where pesticides are applied but who are not actively involved in the process) were reviewed and data extracted (Acquavella et al. 2004; Curwin et al. 2007; Mesnage et al. 2012; Hoppe 2013; Honeycutt & Rowlands 2014; Niemann et al. 2015). For those measurements,

publications that provided actual systemic dose calculations were used rather than estimates calculated from default exposure factors (e.g. body weight (bw), water consumption, breathing rate, etc.). 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 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). For studies using dosimetry, the normalization to systemic dose was conducted using the following assumptions: 70 kg adult, 2.1 m² surface area for a 70 kg male (US EPA 2009), 10% penetration through clothing if not actually measured, 1% 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 4 or 5 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.

Exposures via air

Based on the above assumptions, inhaling glyphosate in air at the maximum measured concentration would result in an exposure of 1.04×10^{-6} mg/kg body mass (bm)/day. This is about five orders of magnitude less than the systemic ADI proposed by EFSA (2015).

Exposures via water

The concentrations of glyphosate measured in US surface waters ranged from 0.02 to 73 µg/L. The 90th centile value was 0.79 µg/L (see Solomon (2016) for details of the calculations), more than four orders of magnitude less than the EFSA ADI.

Exposures from food and in 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 & Rowlands 2014; Krüger et al. 2014; Markard 2014). In these studies, the range for estimates of systemic doses was 0.000022–0.00063 mg/kg/day. These values are all less than the ADI suggested by EFSA.

Exposure of applicators

The 90th centile in the dosimetry studies was 0.021 mg/kg/day; about five-times less than the systemic EFSA ADI. The range of values for the systemic doses determined by biomonitoring was smaller than for the passive dosimeters. The 90th centile was 0.0014 mg/kg b.m./day; about 70-times less than the systemic EFSA ADI.

In summary, there is a robust dataset on glyphosate exposures to humans. Even when using worst-case assumptions, systemic exposures to applicators, bystanders, and the general public are very small. Based on current RfDs and ADIs and measured exposures, there is an extremely large margin of safety from exposure to glyphosate *via* normal uses.

Epidemiological data

The epidemiology Expert Panel 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) (see Acquavella et al. (2016) for additional details). 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. The relevant studies are listed in Table 2. Each study was then reviewed individually according to key validity considerations specified *a priori* and the results for NHL and MM were separately and systematically evaluated 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 factors, and evaluation of dose response (Table 3).

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 (prospective versus retrospective), was controlled comprehensively for confounding factors, and extensively considered RR 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 first-hand respondents reporting about pesticide use (*viz.* no proxy respondents), had minimal potential for selection bias, and included statistical analyses that controlled confounding factors 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 factors 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 reliable epidemiologic findings. As de Roos et al. (2005)

Table 2. Relevant studies for glyphosate review: non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM).

First author (year)	Study location(s)	Study design	More recent analysis	Outcome
Cantor et al. (1992)	Iowa + Minnesota	Case-control	de Roos et al. (2003)	NHL
Nordstrom et al. (1998)	Sweden	Case-control	Hardell et al. (2002)	HCL
Hardell and Eriksson (1999)	Sweden	Case-control	Hardell et al. (2002)	NHL excluding HCL
McDuffie et al. (2001)	Canada	Case-control	n/a	NHL
Hardell et al. (2002)	Sweden	Case-control (pooled)	n/a	NHL + HCL
de Roos et al. (2003)	Nebraska, Iowa/Minnesota, Kansas	Case-control (pooled)	n/a	NHL
de Roos et al. (2005)	Iowa, North Carolina	Cohort	n/a	NHL, MM
Eriksson et al. (2008)	Sweden	Case-control	n/a	NHL
Orsi et al. (2009)	France	Case-control	n/a	NHL, MM
Hohenadel et al. (2011)	Canada	Case-control	Extension of McDuffie et al. (2001)	NHL
Cocco et al. (2013)	Czech, France, Germany, Ireland, Italy, Spain	Case-control	n/a	B-cell lymphoma
Brown et al. (1993)	Iowa	Case-control	n/a	MM
Landgren et al. (2009)	Iowa	Prevalence	n/a	MGLS
	North Carolina	Case-control		
	Minnesota			
Pahwa et al. (2012)	Canada	Case-control	Kachuri et al. (2013)	MM
Kachuri et al. (2013)	Canada	Case-control	n/a	MM
Sorahan (2015)	Iowa, North Carolina	Cohort	Reanalysis of de Roos et al. (2005)	MM

n/a: not available.

Table 3. Key validity considerations in glyphosate epidemiological studies

First author (year)	Study design	Outcome	Recall bias	Selection bias	Proxy respondents	Adequate control for confounding	Exposure-response and 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. (2003)	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
Dro 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.

Whether recall bias, exposure misclassification, or selection bias was classified as likely or unlikely was based on a consensus after an in person discussion of each study by the authors.

concluded "... the available data provided evidence of no association between glyphosate exposure and NHL incidence." Results from this study were the basis for the Panel's conclusion of no epidemiologic support for a causal 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.

In summary, the epidemiology Expert Panel concluded that the glyphosate epidemiologic literature does not indicate a causal relationship between glyphosate exposure and NHL. For MM, the evidence was considered too sparse to judge a relationship between MM and reported glyphosate use. The panel's conclusion for NHL differed from that of the IARC working group primarily because the null findings from the AHS (cohort) study were the only epidemiologic findings considered likely to be valid.

Cancer bioassays

The carcinogenicity Expert Panel reviewed all listed cancer bioassays reviewed by Greim et al. (2015) and IARC (2015). 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 WoE approach (US EPA 1986c; ECHA 2010). 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. In any review, if certain studies are judged to be unreliable and thus not included, the reasons for this should be provided. The carcinogenicity 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. Additional details of the Expert Panel's considerations and conclusions are presented in Williams et al. (2016).

In contrast to the results of past reviews (see Table 4), IARC (2015) concluded that there is *sufficient evidence in experimental animals* for the carcinogenicity of glyphosate, based on the following:

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

Kidney tubular - cell neoplasia in mice

In regard to the rare renal tubular tumors in male CD-1 mice, the Expert Panel noted that the conclusions of the IARC were based on only one 2-year oral mouse carcinogenicity study, (Monsanto 1983) excluding two additional 18-month oral studies in CD-1 mice (Arysta Life Sciences 1997; Nufarm 2009)

Table 4. Regulatory agency reviews of three studies evaluated by IARC.

	Regulatory authorities	Conclusions of review – tumors related to treatment?		
		Mouse study (Monsanto 1983)	Rat study (Stout & Ruecker 1990)	Mouse study (Cheminova 1993)
2015	WHO/IARC	Yes	Yes	Yes
2016	WHO/JMPR	*	No	-
2016	US EPA Registration Review**	-	-	-
2016	Japan Food Safety Commission ADI Review**	No	No	-
2015	EU Annex I Renewal (BFR)**	No	No	No
2015	Canada PMRA Registration Review**	No	No	No
2013	Australia	No	No	No
2012	US EPA Human Health RA	No	No	-
2005	WHO/Water Sanitation Health	No	No	-
2004	WHO/JMPR	-	No	No
2002	EU Annex I	No	No	No
1999	Japan Food Safety Commission	No	No	-
1994	WHO/PCS	No	No	-
1993	US EPA RED	No	No	-
1991	Canada PMRA	No	No	-
1991	US EPA Cancer Classification	No	No	-
1987	WHO/JMPR	No	-	-

*The meeting could not exclude the possibility that glyphosate is carcinogenic in mice at very high doses.

**Evaluation not completed.

and one 18-month oral study in Swiss Albino mice (Feinchemie Schwabedda 2001). All of the studies were considered by authoritative bodies to have met the guidelines for a carcinogenicity bioassay in mice (US EPA 1990; ICH 1997).

In the study conducted by Monsanto (1983) considered by IARC (2015) to show evidence of renal tubular neoplasia associated with glyphosate dosing, male (M) and female (F) CD-1 mice received 0 (MO/FO mg/kg/day, control), 1000 (157/190, LD), 5000 (814/955, MD), or 30,000 (4841/5874, HD) ppm in the diet. The 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 (MD) group, followed by the control group, and the high-dose (HD) group. The low-dose (LD) group had no renal findings. Females had neither neoplasia nor hyperplasia. Absence of hyperplasia indicates that all renal proliferative and neoplastic lesions, which occurred in all experimental groups (including controls) occurred *de novo*, i.e. were spontaneous or background lesions and were not compound related.

Factors to assess whether an association between exposure and an effect (two variables) is causal include strength, consistency, and specificity of the association, the temporal (latency) and dose-response relationships present, plausibility of effect, and coherence of the available data. When applied to the study by Monsanto (1983), several conclusions were drawn, as follows.

1. The association was not strong because the incidence of rare renal neoplasms was not statistically significant in any exposed group when compared to the control group.
2. The association is not consistent, since four out of five mouse studies did not find similar renal neoplasms at similar doses.
3. The association is not specific, since females of this pivotal study, which were exposed to higher levels of glyphosate, did not develop renal neoplasms. Also, there

were no renal findings (hyperplasia, neoplasia) in the LD group, whereas the control group had four.

4. The time required between exposure and effect, i.e. the latency time, was not reduced; all tumors were observed only at termination. Also, no mouse with neoplasia had also hyperplasia.
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 (three of which were not considered in the IARC monograph), the mice did not develop similar neoplastic renal lesions.
8. The association does not demonstrate a dose-response pattern (see #5, 6), and furthermore 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 JMPR (1987, 2006), US EPA (1993), and EFSA (2015).

Hemangiosarcomas in mice

With respect to the common liver hemangiosarcoma in male mice, in the CD-1 mouse study reported by Cheminova (1993) there were no statistically significant increases in the incidence of any tumors when compared with the in-study and historical (for both sexes 2–12%) control groups and no dose response was apparent (Williams et al. 2016). IARC,

based on their own statistical analysis, indicated/reported that there was an increase in the incidence of hemangiosarcoma in males ($p < .001$, Cochran-Armitage trend test) based on the incidence of the HD group (Table 5). In addition, IARC (2015) did not comment on the lack of hemangiosarcomas in females which have received higher doses of glyphosate, and also of renal tumors in this mouse study.

It is clear that the association between glyphosate treatment and hemangiosarcoma in mice is weak since pairwise comparisons are not significant, there is no consistency (some mouse studies show no tumors of this type at all at comparable doses), and a dose response effect is not seen (some HD groups have a lower incidence than lower doses). In addition, the recorded incidences are within the historical control range.

Given the foregoing analysis, the Expert Panel concludes that overall the evidence does not support the conclusion that glyphosate exposure results in increased incidence of hemangiosarcoma in mice.

Pancreatic tumors in rats

In two of the seven carcinogenicity studies in rats that were 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 doses of 0, 30 (3), 100 (10), and 300 (31 mg/kg bw/day) ppm in the diet for 26 months. No pancreatic islet carcinomas were observed. Adenomas were found having a positive trend ($p < .05$) in the study. The level of significance for an increase in common tumors in the trend test should be $p < .005$. The tumor incidences for controls, low, mid, and high doses respectively were: 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. This incidence demonstrates no dose-response pattern, and an absence of pre-neoplastic effects. In addition, in the first study in males, the adenomas did not progress to carcinomas.

In the second 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 (2), 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, 0/59. 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 here again the level of significance 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) not evaluated by IARC, similarly did not show pancreatic islet cell tumors. Based on this information the Expert Panel concludes that there is no evidence that glyphosate induces islet cell tumors in the pancreas.

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

	Males				Females			
	0	100	300	1000	0	100	300	1000
Hemangiosarcoma	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).

Table 6. Sprague-Dawley male rats, hepatocellular tumor rates†, and Cochran-Armitage trend and Fisher's exact tests results (p values)

Tumors	Dose (ppm)			
	0	2000	8000	20,000
Carcinomas	3/34 (%)	2/45 (4)	1/49 (2)	2/48† (4)
p	0.324	0.489	0.269	0.458
Adenomas	2/44 (%)	2/45 (4)	3/49 (6)	7/48‡ (15)
p	0.16*	0.683	0.551	0.101
Adenoma + carcinoma	5/44 (%)	4/45 (9)	4/49 (8)	9/48 (19)
p	0.073	0.486	0.431	0.245
Hyperplasia only	0/44 (%)	0/45 (0)	1/49§ (2)	0/48 (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.

Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at dose level. If then $p < .05$.

Liver tumors in rats

Hepatocellular neoplasms are common for the SD rat (about 5% in males and 3% in female controls) (Williams et al. 2014).

The IARC evaluation indicated that there was "... a significant ($p = .016$) 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 6). 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: "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). 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 hepatocellular foci, etc. (Williams 1980; Bannasch et al. 2003; Maronpot et al. 2010). 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, which were not all included within the IARC monograph (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, the animals were exposed through the diet to 24 different doses distributed across a wide range (3.0–1290 mg/kg bw/day). In exposed males, the incidences of hepatocellular adenomas across the doses showed no dose-response relationship and varied within the same range as the controls. Similar rates were also seen for hepatocellular carcinomas. These observations confirm that glyphosate is not carcinogenic to the rat liver.

Thyroid tumors in rats

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

The incidence of thyroid C-cell adenoma was reported in the Monograph (IARC 2015), to have a significant positive trend ($p = .031$) in females. IARC based their opinion, again, on their interpretation of the Stout and Ruecker's (1990) study and the US EPA's Second Peer Review of Glyphosate (US EPA 1991a). In the Stout and Ruecker's study (1990), no statistically significant difference (group comparison) was reported in the incidence of thyroid C-cell neoplasms, as shown in Table 7. 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 MD and HD 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 a statistically significant positive trend in the incidence of thyroid, C-cell adenomas in females" ($p = .031$) but, because this is a common tumor type, the trend significance value should be $p < .005$ (US FDA 2001; Williams et al. 2014). Thus, this tumor is not significant.

Table 7. 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	8/60	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).

Therefore, in one of the two evaluated studies, the significant trend in the incidence of thyroid C-cell adenomas in female rats did not materialize, and there was no progression to carcinomas. The adenomas were within the historical ranges.

Genetic toxicity and oxidative stress data

The genetic toxicology Expert Panel (Brusick et al. 2016) considered published studies reviewed in the IARC monograph and additional published studies identified by literature searches or from review articles, 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 by the Expert Panel for which information was available from review publication supplements. These regulatory studies were not considered in the IARC monograph, but the Expert Panel concluded that sufficient test-related information was available to justify including these studies. In addition, some unpublished regulatory studies not reviewed previously were included in the Expert Panel evaluation.

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 items of evidence within a category influences the weight, and (iv) tests with greater potential to extrapolate results to humans carry greater weight. In general, human and *in vivo* mammalian systems have the highest test system weight, with a lower weight 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). Typically, the results of *in vivo* assays supersede the results of *in vitro* assays (EFSA 2011).

In contrast to the standard WoE approach used by the Expert Panel, IARC's process for evaluating/weighting the genotoxicity data for glyphosate, GBF and AMPA was not defined. IARC's process may be inferred by how the data were summarized and described, and indicate a number of differences from current standard procedures for WoE. For instance, it appears that IARC considered *in vitro* studies in human cells as carrying more weight than rodent *in vivo* studies as evidenced by the order of discussion topics in Section 4.2.1, and the inclusion of a separate table for human *in vitro* studies. Further, the IARC conclusion of

strong evidence of genotoxicity was stated as based on "studies in humans *in vitro* and studies in experimental animals." In contrast, the Expert Panel evaluation considered *in vitro* studies using cells of human origin to be weighted as equivalent to any other *in vitro* mammalian cell assay using the same endpoint. IARC also gave weight to publications in which glyphosate or GBFs have been tested for genotoxicity in a variety of nonstandard non-mammalian species (fish, insects). The Expert Panel did not consider data from these non-mammalian systems and nonstandard tests with glyphosate, GBF and AMPA to have weight in the overall genotoxicity evaluation, especially given the large number of standard core studies assessing the more relevant gene mutation and chromosomal effects categories available in mammalian systems. In addition, nonstandard tests lack internationally accepted guidelines for design and conduct, databases that document acceptable negative control data or positive control responses are absent, and validation with respect to concordance with rodent or human carcinogenicity has yet to be completed. OECD guidelines specifically state that use of any nonstandard tests require justification along with stringent validation including establishing adequate 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 sister chromatid exchange (SCE) studies. These tests are identified as indicators because the measured endpoint is reversible and does not always lead to mutation, a key event in cancer development. As stated by 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 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 suggests lack of genotoxicity and that genotoxic effects observed 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 (EFSA 2011; ICH 2011; Kirkland et al. 2011). Therefore, the endpoints given the greatest weight in Table 8 consist of gene mutation and chromosomal aberrations.

An evaluation of the studies in Table 8 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 (8 of 9) or from all studies combined (8 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 6 out of 15 studies identified as high weight being positive for the IARC evaluation, and only 8 out of 92 studies identified as high weight being positive for all studies combined.

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

- Glyphosate does not induce gene mutations *in vitro*. There are no *in vitro* mammalian cell gene mutation data for GBFs or AMPA, and no gene mutation data *in vivo*.
- Glyphosate, GBFs, and AMPA are not clastogenic *in vitro*. Glyphosate is also not clastogenic *in vivo*. Some positive *in vivo* chromosomal 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*. Although this could be a reflection of increased statistical power in the *in vitro* MN studies, the absence of clastogenic effects suggests 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 are likely to 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 more abundant.
- There is evidence that glyphosate and AMPA do not induce unscheduled DNA synthesis (UDS) in cultured hepatocytes.

Table 8. 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.

Source	Test category	Endpoint	Weight	Glyphosate (Pos/Neg)	GBFs (Pos/Neg)	AMPA (Pos/Neg)	Total (Pos/Neg)	
Kier and Kirkland (2013) and other published studies not included in IARC	Bacterial reverse mutation	Gene mutation	High	0/19	0/20	0/1	0/40	
	Mammalian <i>in vitro</i>	Gene mutation	Moderate	0/2	ND	ND	0/2	
		Chromosomal 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 <i>in vivo</i>	Chromosomal 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	
	IARC monograph 112	Bacterial reverse mutation	Gene mutation	High	0/1	0/0	ND	0/1
Mammalian <i>in vitro</i>		Gene mutation	Moderate	0/1	ND	ND	0/1	
		Chromosomal 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 <i>in vivo</i>	Chromosomal 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 <i>in vivo</i>		Chromosomal aberrations	High	ND	0/1	ND	0/1	
		Micronucleus	High	ND	0/3	ND	0/3	
High weight					2/37 (2/4)	5/45 (3/5)	1/1 (1/0)	8/84 (6/9)
Combined totals (IARC results only)								
Moderate weight					7/10 (4/3)	3/0 (1/0)	2/0 (2/0)	12/10 (7/3)
Combined totals (IARC results only)								
Low weight				5/2 (5/1)	2/0 (2/0)	1/1 (1/0)	8/3 (8/1)	
Combined totals (IARC results only)								

ND: no data

All responses based on study critiques and conclusions of Expert Panel members.

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.

Table 9. Summary of studies presented in Kier and Kirkland (2013) and of other publicly 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 <i>in vitro</i>	Gene mutation	0/2	ND	ND	0/2
	Chromosomal 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 <i>in vivo</i>	Chromosomal 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.

- Reports of the 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 regulatory genetic toxicology studies published in reviews such as Kier and Kirkland (2013) (Table 9) should be included in a WoE assessment. The rationale supporting the inclusion of these additional studies is that the supplementary tables presented in the Kier and Kirkland (2013) paper, contain

sufficient detail supporting the reliability 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.

Based on the results of the WoE critique detailed above and the wealth of regulatory studies reviewed by Kier and Kirkland (2013) and Williams et al. (2000), the Panel concluded that the available data do not support IARC's conclusion that there is strong evidence for genotoxicity across the glyphosate or GBFs database. In fact, the Panel's WoE assessment provides strong support for a lack of genotoxicity, particularly in the relevant mechanism

Table 10. 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, and 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 <i>in vitro</i> and <i>in vivo</i>	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 <i>in vitro</i> and <i>in vivo</i>	Conflicting and/or non-reproducible responses in the same test or test category both <i>in vitro</i> and <i>in vivo</i>
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 nontoxic exposure levels	Positive responses typically associated with evidence of overt toxicity

AMPA aminomethylphosphonic acid; GBF- glyphosate-based formulation.

categories (mutation, chromosomal effects) associated with carcinogen prediction. As additional support for the Panel's WoE conclusion, Table 10 provides a comparison between a set of characteristics associated with 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 chromosomal aberrations (Paz-y-Miño et al. 2011), and positive induction of MN (Bolognesi et al. 2009). These papers were critically reviewed by the Expert Panel and were found to be deficient as evidence for GBF genetic 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 MN found in exposed humans (Speit 2013; Kirsch-Volders et al. 2014). Importantly, for the Bolognesi study, increases in MN 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.

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 evidence 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 indirect response endpoints and the number of studies examining direct oxidative DNA damage are very few and presented 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/day, suggests that it is improbable that GBFs would induce levels of oxidative stress likely to exceed endogenous detoxication capacities.

The most appropriate conclusion supported by the oxidative stress data 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.

Discussion and conclusions

Four Expert Panels conducted detailed reviews of glyphosate exposure, animal carcinogenicity, genotoxicity, and epidemiologic studies. With respect to exposure, even when using a number of worst-case assumptions, systemic doses of glyphosate in human applicators, bystanders, and the general public are very small. Exposures of the general public are three or more orders of magnitude less than the US EPA's RfD (1.75 mg/kg/day) as well the ADIs established by JMPR (1 mg/kg/day) and EFSA (0.5 mg/kg/day). The RfD is the allowable limit of daily exposure derived from toxicity studies, and even in the most exposed applicators (90th centile) the systemic dose was estimated at 20-fold less than the RfD. Exposures to the public are in the range of 0.00001-0.001 mg/kg bw/day while occupational exposures can range up to 0.01 mg/kg

bw/day. Systemic exposures are even lower than the reported ranges since oral and dermal absorption of glyphosate is low.

With respect to the animal cancer bioassay data, the Expert Panel conducted a thorough overall WoE evaluation that considered a much wider range of studies than IARC, all of which met Good Laboratory Practice (GLP) guidelines and 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 would be expected to generate several numerical imbalances 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 US Food and Drug Administration has estimated that the overall rate can approach 10%.

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

- The mouse renal neoplastic effects are not associated with glyphosate exposure, because they lack statistical significance, consistency, specificity, a dose-response pattern, plausibility, and coherence;
- The association of hemangiosarcomas in the livers of mice is weak, lacks consistency, and there was no dose-response effect;
- The association of pancreatic islet-cell adenomas in male SD rats is weak, not seen in the majority of rat studies, lacks a dose-response pattern (the highest incidence is in the low dose followed by the high dose), plausibility and pre-neoplastic/malignant effects;
- In one study, 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;
- In one study, the significant positive trend in the incidence of thyroid C-cell adenomas in female rats did not materialize, the adenomas were only slightly increased in mid- and high doses, and there was no progression to malignancy.

Overall, extensive reviews of the genotoxicity of glyphosate, AMPA, and GBPs 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.

Lastly, the Expert Panel's review of the glyphosate epidemiologic literature and the application of commonly applied

causal criteria did 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.

In summary, the totality of the evidence, especially in light of the extensive testing that glyphosate has received, as judged by the Expert Panels, does not support the conclusion that glyphosate is a "probable human carcinogen" and, consistent with previous regulatory assessments, the Expert Panels conclude that glyphosate is unlikely to pose a carcinogenic risk to humans.

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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.

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Gary M. Williams, Sir Colin Berry, David Brusick, João Lauro Viana de Camargo, Helmut A. Steim, David J. Kirkland, Keith R. Solomon, and Tom Sorahan have previously served as independent consultants for the Monsanto Company on the European Glyphosate Task Force. John Acquavella and Larry D. Kier have also served as independent consultants and were previously employees of the Monsanto Company. John Acquavella was employed by Monsanto between the years 1989 and 2004 while Larry D. Kier was employed between 1979 and 2000. David Garabrant serves on a scientific advisory board to Dow Agro Sciences, which markets pesticides including glyphosate, and has consulted on behalf of Bayer Corp. on litigation matters concerning glyphosate and leukemia. Gary Williams and Tom Sorahan have consulted for Monsanto on litigation matters involving glyphosate. Tom Sorahan has received consultancy fees and travel grants from Monsanto Europe SA/NV as a member of the European Glyphosate Toxicology Advisory Panel and participated in the IARC Monograph Meeting for volume 112, as an Observer for the Monsanto Company. Douglas L. Weed has consulted on litigation matters concerning Monsanto that did not involve glyphosate. Marilyn Aardema, Michele M. Burns, Gary Marsh, and Ashley Roberts have not previously been employed by the

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Glyphosate in the general population and in applicators: a critical review of studies on exposures

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ABSTRACT

The recent classification of glyphosate as a probable human carcinogen by the International Agency for Research on Cancer (IARC) was arrived at without a detailed assessment of exposure. Glyphosate is widely used as an herbicide, which might result in exposures of the general public and applicators. Exposures were estimated from information in the open literature and unpublished reports provided by Monsanto Company. Based on the maximum measured concentration in air, an exposure dose of 1.04×10^{-8} mg/kg body mass (b.m.)/d was estimated. Assuming consumption of surface water without treatment, the 90th centile measured concentration would result in a consumed dose of 2.25×10^{-5} mg/kg b.m./d. Estimates by the Food and Agriculture Organization of the United Nations (FAO) of consumed doses in food provided a median exposure of 0.005 mg/kg b.m./d (range 0.002–0.013). Based on tolerance levels, the conservative estimate by the US Environmental Protection Agency (US EPA) for exposure of the general population via food and water was 0.088 mg/kg b.m./d (range 0.058–0.23). For applicators, 90th centiles for systemic exposures based on biomonitoring and dosimetry (normalized for penetration through the skin) were 0.0014 and 0.021 mg/kg b.m./d, respectively. All of these exposures are less than the reference dose and the acceptable daily intakes proposed by several regulatory agencies, thus supporting a conclusion that even for these highly exposed populations the exposures were within regulatory limits.

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particularly as the IARC classification was arrived at without a detailed assessment of risk to applicators and the general public. Glyphosate is widely used for control of weeds in agriculture, forestry, and in the management of public and private landscapes. These uses might result in exposures of the general public as well as applicators. Unfortunately, the IARC monograph merely focused on the potential hazards of glyphosate and not on the risks. Exposure is a critical component of risk assessment and, without measured values; it is difficult to provide guidance on the appropriate uses of glyphosate or, for that matter, any pesticide. It is also not possible to properly assess toxicity and hazard data for relevance to humans and the environment. As per their mandate, none of the IARC evaluations characterize exposures analytically or in the context of risk; the monograph on glyphosate (IARC 2015) summarizes several exposure studies from the open literature, but does not use these values to estimate risks. This is different from the approach used by most regulatory agencies such as the US EPA, the Food and Agricultural Agency (FAO) of the United Nations, and the European Food Safety Agency (EFSA) where exposures are compared to Reference Doses (RfDs) or Acceptable Daily Intake (ADIs).

There are several sources of exposure of humans to glyphosate in the environment. These are: air, water, application

Introduction

The recent classification of glyphosate as a probable human carcinogen by the International Agency for Research on Cancer (IARC 2015) has generated considerable interest.

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to crops and target weeds, and food. The following sections are an analysis of exposures of humans to glyphosate from these sources. Data for these exposures were obtained from papers published in the open literature and from unpublished reports provided by the Monsanto Company. These sources of information are listed in the references and summary data are provided in the Supplemental Information (SI).

Methods

Unpublished reports of studies on exposure to glyphosate in applicators were provided by the Monsanto Company and 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.

Air

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 degradation, aminomethylphosphonic acid (AMPA) were measured in air and precipitation (Chang et al. 2011). Detections of AMPA were infrequent and the concentrations were small. These are not discussed further. The frequency of detection of glyphosate ranged from 60 to 100% in air and rainwater. Concentrations in air ranged from <0.01 to 9.1 ng/m³, while those in rain were from <0.1 to 2.5 µg/L. Unless rainwater was collected as drinking water, this would be an incomplete pathway for exposure of humans. Once in contact with soil, exposures would be via surface waters (see below). Concentrations in air were seasonal and the sources were likely associated with application to crops in the growing season. For estimation of human exposure, it was assumed that there was total absorption of glyphosate from the air into the body of a 70 kg human breathing 8 m³ air (half a day for an adult, US EPA 2009). These values were then used to calculate the systemic dose, based on a worst-case assumption of 100% uptake via the respiratory tract.

Water

Glyphosate can enter surface waters through use on aquatic weeds, runoff from sprayed soils, and from drift of spray. Glyphosate is very soluble in water and, although it binds strongly to soils and sediments, small concentrations have been measured on surface waters in the United States. These measurements are part of the US Geological Survey (USGS) National Water-Quality Assessment (NAWQA) program (USGS 2015), which has been in place since the 1980s. Glyphosate was added to the large range of analytes measured in surface water in 2002. These data were downloaded from the NAWQA data warehouse (USGS 2015) 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". The values were ranked from the smallest to the largest and a cumulative frequency distribution was derived. These values were processed using the Weibull formula to estimate ranks and plotted on a log-probability scale (Solomon and Takacs 2002). The 90th centile values were calculated from the raw data using the Excel function $\langle =\text{percentile} \rangle$. Systemic dose was estimated from the assumption of consumption of 2 L of water per day by a 70 kg human with 20% absorption from the gastrointestinal (GI) tract (EFSA 2015). 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.

Food and bystanders

Several studies have measured concentration of glyphosate in "bystanders" and people not involved in application of glyphosate. Bystanders are presumable exposed via food, water, and air (see above). It is also assumed that bystanders are exposed on a daily basis through the environment and/or food and drinking water, and that these exposures are constant and not episodic as in an applicator. Here, a single daily sample of urine is a reasonable surrogate for daily exposures, although uncertainty would be reduced with more frequent samples and analysis of total daily urinary output. Several of these studies were critically reviewed in 2015 (Niemann et al. 2015). This review was thorough, but the strengths of the methods of the original studies were variable. In addition, the authors did not correct for incomplete excretion of glyphosate (95%) as has been done for the applicator studies. In a study of farm and non-farm households in Iowa (Curwin et al. 2007), urine samples were analyzed from 95 adults and 117 children. A study in Europe (Mesnage et al. 2012) measured exposures in a farm family (two adults and three children). A report on the analysis of urine of 182 people from 18 countries (Hoppe 2013) provided data on concentrations in urine. In another study, urine concentrations of 40 male and female German students were measured (Markard 2014). The original study was in German and the value used here for the systemic dose is from the review of Niemann et al. (2015). A study using enzyme linked immunosorbent assay (ELISA) analysis with an unstated level of quantitation (LOQ) was used to measure the concentrations of glyphosate in samples of urine from more than 300 individuals in the EU (most from Germany) (Krüger et al. 2014). A report of a study in the US on 35 individuals using an ELISA analysis (Honeycutt and Rowlands 2014) provided data from which a systemic dose of glyphosate was estimated.

Where the systemic dose was calculated, it was used. Where dietary exposures were provided, 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).

Under the auspices of the Food and Agricultural Organization of the United Nations, the Joint Meeting on Pesticide Residues (JMPR) conducts routine assessments of residues of pesticides in food (JMPR 2014). These are

evaluated in relation to diets in various regions of the world and exposure *via* food compared to an ADI. In 2013, the JMPR reviewed dietary exposures to glyphosate, its major metabolites, and breakdown products (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. These values were for a 60 kg person but were used without modification.

The US Environmental Protection Agency (US EPA) has calculated exposures to glyphosate using the Dietary Exposure Evaluation Model (DEEM, ver 7.81), which is 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).

There is some uncertainty in all of these studies and approaches. All of the monitoring studies used relatively few participants (<300), which increases uncertainty and lack of raw data in most studies does not allow variance to be fully characterized. Modeling approaches (US EPA and JMPR) based on maximum residue limits and assumptions of good agricultural practices are also subject to uncertainty; however, the assumptions used are more likely to result in overestimation. However, proportion of foods consumed is based on the statistical analyses of diets and this does incorporate, but not quantify, uncertainty.

Applicators

A relatively large number of studies on exposures of applicators to glyphosate have been conducted (see SI for a full list). Older studies tended to use passive dosimetry, either as whole-body dosimeters or patches. Some of the studies with dosimeters used tracers (dyes or other surrogates) and others analyzed dosimeters for glyphosate itself. Some more recent studies used biological monitoring and some a mixture of biological monitoring and dosimeter patches. For compounds, such as glyphosate, where the excretion kinetics is well understood, biological monitoring provides a measure of the actual amount of the chemical in the body. For this reason, data from these studies are most appropriate for risk assessment. However, data from dosimetry studies can be used to estimate systemic dose. This allows comparison of exposures from different studies to a benchmark for exposure i.e. the reference dose (RfD) or ADI.

For studies using dosimetry, the normalization to systemic dose was conducted using the procedure outlined in Table 1. This was done for the dosimetry studies listed in SI Table 1. The estimated systemic doses were ranked from smallest to

largest and a cumulative frequency distribution was derived. These values were plotted on a log-probability scale as above. The 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). Glyphosate is rapidly excreted and does not bioaccumulate. 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 appropriate for risk assessment.

The procedure of normalization for biomonitoring studies is complicated by the fact that many studies reported concentrations of glyphosate that are less than the LOQ, even on the day of application (d-0), when exposures would be expected to be greatest. Similarly, even if residues were detected on d-0, those on subsequent days might have values less than the LOQ. The common practice of using half the level of detection as a default value might be acceptable for the first observation day, but this fails to account for excretion that would reduce the amount in the body on each successive day. Use of half the LOQ on each day would grossly overestimate the systemic dose. Because of this, normalization of systemic doses was modeled using excretion kinetics and followed the steps outlined in Table 2.

If concentrations in urine are > LOQ for one or more days, the actual elimination rate for the individual can be used to correct for days where concentration is < LOQ. Unless already carried out in the study itself, these corrections were applied to the data in SI Table 2.

Because raw data were available for the studies on applicators, uncertainty could be considered. Total number of participants was large (249, See SI Table 2) and range of the values provided the upper and lower bounds of uncertainty. To be conservative, the 90th centiles of the data were used to characterize reasonable worst-case exposures.

Normalization of the RfD and ADI for systemic dose

Regulatory agencies set allowable limits for consumption of residues of glyphosate exposure based on toxicity studies. The US EPA RfD is 1.75 mg/kg body mass (b.m.)/day (US EPA 2012). The ADI for JMPR/WHO is 1 mg/kg b.m./d (JMPR 2014), while the ADI used by EFSA is 0.5 mg/kg b.m./d (EFSA 2015). In a recent review (summary published on 16 May 2016),

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

Step	From	To	Explanation
1	Total residue on patches (µg/cm ²)	to Potential body exposure (µg)	2.1 m ² surface area for a 70 kg male (US EPA 2009)
2	Potential body exposure (µg)	to Actual body exposure (µg)	Measured penetration through clothing or default of 10%
3	Actual body exposure (µg)	to Systemic body exposure (µg)	1% dermal penetration (from the value used by EFSA 2015)
4	Systemic body exposure (µg)	to Systemic dose (mg/kg body weight/day)	70 kg adult

Table 2. Procedure for normalization of biomonitoring data to estimate systemic dose of glyphosate.

Step	Data	Action
1	LOD = 10 µg/kg urine	Assume half the LOD = 5 µg/kg
2	Adjust estimated dose to amount of urine	Multiply kg urine produced on day by 1/2 LOD
3	D-0 value amount estimated	C ₀ amount
4	D-1 value estimated from remainder of d-0 concentration after excretion	Elimination rate constant (k) of 0.86 d ⁻¹ from (Acquaveila et al. 2004) use $C_t = C_0 \times e^{-kt}$
5	D-2 value estimated from remainder of d-1 concentration after excretion	
6	D-3 value estimated from remainder of d-2 concentration after excretion	
7	D-4 value estimated from remainder of d-3 concentration after excretion	
8	D-5 value estimated from remainder of d-4 concentration after excretion	
9	Sum of amounts for each day of urine collected	
10	Correction for monitoring period from elimination rate constant and number of days	For example, 99% for 5 d, divide by 0.99
11	Correction for incomplete excretion (95%)	Based on observations in TK studies in monkeys, which showed that 95% of total systemic dose was excreted via urine (Wester et al. 1991), divided by 0.95
12	Correction for dosimeters, if used	Increase dose by percentage of body area represented by the dosimeters
13	Correction for hand wash or gloves, if used	Increase dose by percentage of body area represented by hands
14	Calculate systemic dose	Divide total systemic dose by body mass

C₀: initial concentration, C_t: concentration at time t; LOD: level of detection, TK: toxicokinetic.

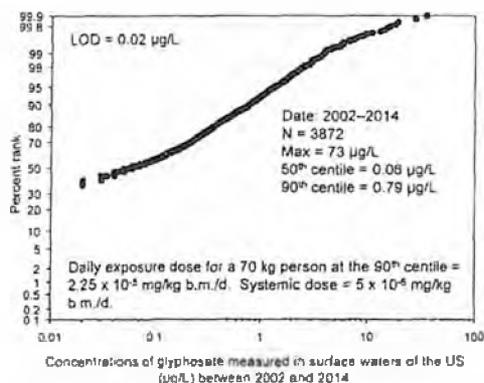


Figure 1. Distribution of concentrations of glyphosate measured in surface waters across the US.

JMPR (2016) has reaffirmed their ADI of 1 mg/kg b.m./d. These values are suitable for comparison to the dietary intake, but for comparison to systemic doses as estimated from biological monitoring (urinary excretion), the ADIs and RfD were divided by five to account for only 20% absorption from the GI tract (EFSA 2015). These normalized values are 0.35, 0.2, and 0.1 mg/kg b.m./d, for US EPA, JMPR, and EFSA, respectively.

Results

Air

Based on the above assumptions of respiratory volume and total absorption, inhaling glyphosate in air at the maximum measured concentration would result in an exposure dose of 1.04×10^{-6} mg/kg b.m./d. This is about five orders of magnitude less than the systemic ADI proposed by EFSA (2015).

Water

The cumulative frequency distribution of concentrations of glyphosate measured in surface waters of the US are shown in Figure 1. The 90th centile was 0.79 µg/L. The maximum concentration measured was 73 µg/L. Consumption of 2 L of drinking water by a 70 kg person at the 90th centile concentration is estimated to result in a consumed dose of 2.25×10^{-5} mg/kg b.m./d, more than four orders of magnitude less than the EFSA ADI.

Food and bystanders

Estimates of the systemic dose resulting from exposures of bystanders and the general public to glyphosate are shown in Table 3. All of these systemic doses are more than 150-times less than the EFSA ADI, normalized for reduced uptake from the gut.

Based on the estimates of daily intake from the FAO/JMPR, the minimum IEDI was 124 µg/person/d, the median was 301, and maximum was 762 (JMPR 2014). These values were normalized to a 60 kg person (0.002, 0.005, and 0.013 mg/kg b.m./d, respectively) for comparison to the ADI. Median exposures are 100-times less than the ADI suggested by EFSA.

The dietary exposure of the general population in the US was estimated by US EPA to be 0.088 mg/kg b.m./d and the range of values was from 0.058 to 0.23 mg/kg b.m./d across a range of age-groups from adults to toddlers. These values are all less than the ADI suggested by EFSA.

Applicators

For the applicator studies, the corrections were applied as in Table 1 or Table 2 and the results are presented graphically in Figure 2. Raw data are provided in SI Tables 1 and 2.

Table 3. Summary of exposures to glyphosate in bystanders and the general public.

Study	Source of exposure	Urinary concentration ($\mu\text{g/L}$)		Systemic dose (mg/kg b.m./d)		Comment
		Greatest mean	Maximum	Greatest mean	Maximum	
Table 2 from Curwin et al. 2007	Presumably food and water from non-farm households in Iowa	2.7	9.4	0.00009	0.00031	Highest mean and max was in non-farm children
Table 3 from Curwin et al. 2007	Bystanders from farm households in Iowa	2.1	-	0.00007	-	Highest median was in farm children. Max not reported
Mesnage et al. 2012	Bystander, farm family of five	-	2	-	0.00007	Maximum concentration in child
Hoppe 2013	Presumably food and water	0.82	1.82	0.000027	0.00061	Highest mean was in samples from Malta
Markard 2014	Presumably food and water	-	0.65	-	0.00022	Maximum concentration
Kruger et al. 2014	Presumably food and water	-	5	-	0.00017	Maximum concentration
Honeycutt and Rowlands 2014	Presumably food and water	-	18.8	-	0.00063	Maximum concentration

Systemic dose (mg/kg b.m./d): Urinary concentration ($\mu\text{g/L}$) \times 21 urine/day : 80 kg body mass \times 1000. b.m..

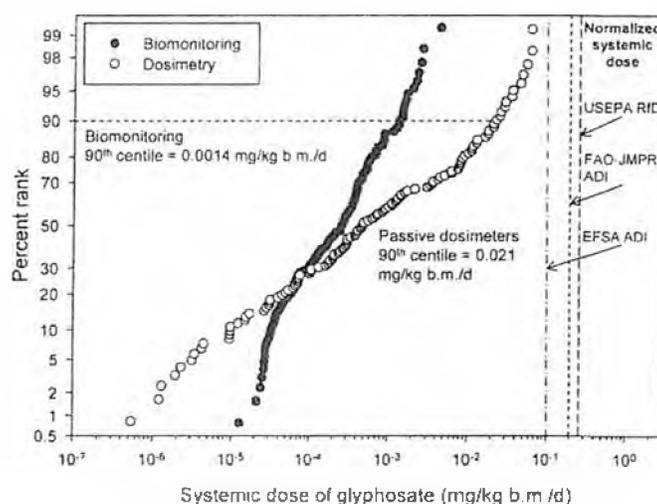


Figure 2. Systemic doses of glyphosate measured in exposure studies conducted in applicators.

The range of values for systemic doses measured in the dosimeter studies (90th centile = 0.021 mg/kg b.m./d) was greater than in the biomonitoring studies (90th centile = 0.0014 mg/kg b.m./d). Given the corrections applied to the data, this is surprising; however, there are a number of assumptions used in the normalization of the systemic doses that might result in overestimation of exposure. These are likely in the amount of absorption through skin and the penetration of clothing. The assumption of 1% penetration through the skin is greater than the value of 0.7% suggested from observations in an *in vitro* model with human skin (Bo Nielsen et al. 2009). The 90th centile in the dosimetry studies was 0.021 mg/kg b.m./d ; about five-times less than the systemic EFSA ADI.

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 90th centile was 0.0014 mg/kg b.m./d ; about 70-times less than the systemic EFSA ADI.

Conclusions

Even when using a number of reasonable worst-case assumptions, systemic doses of glyphosate in human applicators, bystanders, and the general public are small. Exposures to glyphosate in the general public are less than EFSA's ADI. The same conclusion applies to applicators. As an overall summary, exposures and ADIs are compared graphically in Figure 3. It should be noted that the ADIs and RfDs used in this assessment are derived from the most sensitive response in long-term feeding studies in the most sensitive laboratory test species and that an uncertainty factor is applied to these values. Furthermore, the biomonitoring exposures measured in applicators aggregate all sources of exposures (air, food, water, and dermal contact) and are still less than the most conservative ADI. Based on the current RfDs and ADIs, there is no hazard and no intolerable risk from exposure to glyphosate via its normal use in agriculture and management of weeds in landscapes.

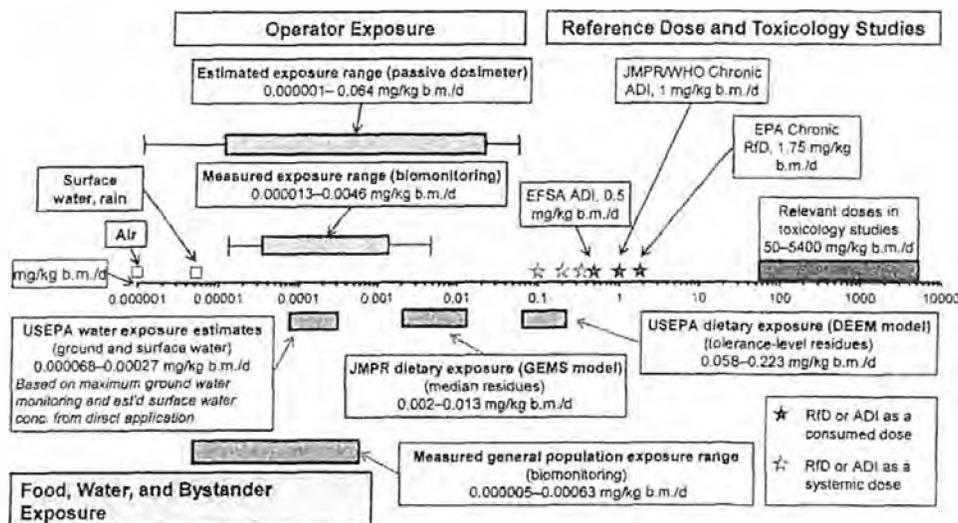


Figure 3. Illustration of measured and estimated exposures to glyphosate in applicators and the general public from various sources. Solid horizontal bars show 10–90th centiles, whiskers show minimum and maximum.

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Declaration of interest

The employment affiliation of the author is shown on the cover page. However, it should be recognized that the author participated in the review process and preparation of this paper as an independent professional and not as a representative of his employer. Keith R. Solomon previously served as an independent consultant for the Monsanto Company on the European Glyphosate Task Force. KS has not been involved in any litigation procedures involving Monsanto Company and glyphosate. KS's recruitment and evaluation of the data was organized and conducted by Intertek Scientific & Regulatory Consultancy (Intertek). KS acted as a consultant for Intertek. 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 Scientific & Regulatory Consultancy has not previously worked on glyphosate related matters for the Monsanto Company, previous employees of Cantox had worked in this capacity. Funding for this evaluation was provided by the Monsanto Company which is a primary producer of glyphosate and products containing this active ingredient. Neither any Monsanto company employees nor any attorney reviewed any of the Expert Panel's manuscripts prior to submission to the journal.

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Supplemental material

Supplemental material for this article is available online [here](#).

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Glyphosate epidemiology expert panel review: a weight of evidence systematic review of the relationship between glyphosate exposure and non-Hodgkin's lymphoma or multiple myeloma

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ABSTRACT

We conducted a systematic review of the epidemiologic literature for glyphosate focusing on non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) – two cancers that were the focus of a recent review by an International Agency for Research on Cancer Working Group. Our approach was consistent with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews. We evaluated each relevant study according to *a priori* criteria for study quality: adequacy of study size, likelihood of confounding, potential for other biases and adequacy of the statistical analyses. Our evaluation included seven unique studies for NHL and four for MM, all but one of which were case control studies for each cancer. For NHL, the case-control studies were all limited by the potential for recall bias and the lack of adequate multivariate adjustment for multiple pesticide and other farming exposures. Only the Agricultural Health (cohort) Study met our *a priori* quality standards and this study found no evidence of an association between glyphosate and NHL. For MM, the case control studies shared the same limitations as noted for the NHL case-control studies and, in aggregate, the data were too sparse to enable an informed causal judgment. Overall, our review did not find support in the epidemiologic literature for a causal association between glyphosate and NHL or MM.

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Introduction

The epidemiologic literature for glyphosate was reviewed recently as part of a multi-disciplinary scientific review by the International Agency for Research on Cancer (IARC 2015). In the aftermath of the IARC review and the designation of glyphosate as probably carcinogenic to humans, the Monsanto Company requested expert reviews of the glyphosate literature in several technical areas, including epidemiology. IARC's working group concluded that there was limited epidemiologic evidence¹ in human studies for the carcinogenicity of glyphosate, based on a positive association observed for non-Hodgkin's lymphoma (NHL). The panel also noted that excesses had been observed for multiple myeloma (MM) in three studies, but felt these results were less reliable because of small numbers of cases in the available studies and the

Table 1. Relevant studies for glyphosate review: non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM)

Author, year	Study location(s)	Study design	More recent analysis	Outcome
Cantor et al. 1992	Iowa – Minnesota	Case-control	De Roos et al. 2003	NHL
Nordstrom et al. 1998	Sweden	Case control	Hardell et al. 2002	HCL
Hardell & Eriksson 1999	Sweden	Case-Control	Hardell et al. 2002	NHL excluding HCL
McDuffie et al. 2001	Canada	Case-control	n/a	NHL
Hardell et al. 2002	Sweden	Case-control (pooled)	n/a	NHL – HCL
De Roos et al. 2003	Nebraska Iowa/Minnesota Kansas	Case-control (pooled)	n/a	NHL
De Roos et al. 2005	Iowa, North Carolina	Cohort	n/a	NHL, MM
Eriksson et al. 2008	Sweden	Case-control	n/a	NHL
Orli et al. 2009	France	Case-control	n/a	NHL, MM
Hoehnadel et al. 2011	Canada	Case control	Extension of McDuffie et al. 2001	NHL
Cocco et al. 2013	Czech Republic, France, Germany, Ireland, Italy, Spain	Case-control	n/a	B-cell lymphoma
Brown et al. 1993	Iowa	Case-control	n/a	MM
Landgren et al. 2009	Iowa North Carolina Minnesota	Prevalence Case-control	n/a	MGUS
Pahwa et al. 2012	Canada	Case-control	Kachuri et al. 2013	MM
Kachuri et al. 2013	Canada	Case-control	n/a	MM
Sorahan 2015	Iowa, North Carolina	Cohort	Reanalysis of De Roos et al. 2005	MM

HCL: hairy cell leukemia; MGUS: monoclonal gammopathy of undetermined significance

related inability to adjust findings for other pesticide and farming exposures. Lastly, the panel concluded that there was no epidemiologic evidence of a relationship for other cancer sites with respect to glyphosate exposure.

In this epidemiology expert panel review, we focused on the possible relationship between glyphosate exposure and two cancers that were the focus of the IARC epidemiology review: NHL and MM. The focus of our review was qualitative. That is, we evaluated the published evidence according to widely accepted validity considerations and criteria for causality. When there were two or more publications with overlapping populations, we concentrated on the most recent publication noting the relationship to a previous publication(s) (see Table 1). Herein, in succeeding sections, we have presented our evaluation approach, reviewed the key validity issues for epidemiologic studies of pesticides, detailed some statistical considerations pertinent to the glyphosate literature, critically evaluated published studies, and, lastly, provided an overall weight of evidence assessment of the epidemiologic evidence for causality between glyphosate and NHL or MM.

Methods

The approach we took was informed by and consistent with the PRISMA guidelines for systematic reviews (Moher et al. 2009), standard approaches to critically evaluating epidemiologic studies (Aschengrau & Seage 2003a,b; Sanderson et al. 2007) and well-recognized interpretative methods – e.g. the criteria-based methods of causal inference (Hill 1965, 1971) – sometimes referred to as “weight of evidence” methods (Weed 2005). With this approach in mind, we address the following questions:

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

Other types of scientific evidence are often evaluated when making causal determinations, including data on human exposure as well as animal studies and studies on mechanism. Since exposure assessment is critical for the validity of occupational epidemiologic studies and biologic plausibility is informed by presumed dose, the former were considered in our overall assessments.

Literature search and included/excluded published papers

A systematic search of the medical literature was performed to identify all analytic epidemiological studies that have examined the possible relationships between exposure to glyphosate and NHL and MM. The aim was to include all such publications – case control studies, cohort studies and pooled analyses – published to the present. In this process, other publications are typically identified, such as reviews, commentaries, methodological investigations, letters to the editor and case reports (or case series). Our primary concern here, however, was the evaluation of the published analytical epidemiological studies of glyphosate and either NHL or MM. To the extent that other types of publications inform our assessment, those papers will be cited in this report. The so-called “gray literature” was not reviewed.

Medline (PubMed) and TOXLINE were searched for English-language publications (with no time constraints) as follows:

- a. PubMed: (2 August 2015): search terms: “glyphosate” and “cancer” (n = 31);
- b. TOXLINE: (2 August 2015): search terms: “glyphosate” and “cancer” (n = 48);
- c. PubMed: (13 August 2015): search terms: “herbicide” and “cancer” and “lymphoma” and “epidemiology” (n = 153);
- d. PubMed: (24 August 2015): search terms: “herbicide” and “cancer” and “multiple myeloma” and “epidemiology” (n = 38);

Table 2 Results for glyphosate. Non-Hodgkin's lymphoma (NHL)

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

CI: confidence interval; HCL: hairy cell leukemia; OR: odds ratio; RR: relative risk

After removal of duplicates and examining the titles and abstracts, 11 publications were identified as relevant. Reasons for exclusions include: not analytical epidemiology, glyphosate not examined, and NHL and/or MM not examined.

An additional seven relevant analytic epidemiological studies were identified after examining reference lists from the publications above, the IARC Monograph 112 (2015) wherein glyphosate and cancer were evaluated, as well as personal collections of relevant papers by the expert panel. Upon further review, two of these references were excluded: Lee et al. (2005) because it did not focus on NHL or MM (only glioma) and the meta-analysis of Schinasi and Leon (2014) because our focus was on the primary literature. A meta-analysis by Chang and Delzell (2016) that was pending publication at the time of our review would have been excluded for the same reason.

The 16 relevant analytical epidemiological studies are listed in Table 1. Data collected from each study included the following: first author, year of publication, study design, number of cases and controls (for case-control studies), number of participants in cohort studies, results (typically in terms of an estimate of the relative risk [RR], e.g. an odds ratio [OR] with accompanying 95% confidence interval [95% CI]), exposure-response (if available), variables adjusted for in the

analyses, and outcome (e.g. NHL, MM). See Tables 2 and 3 for details.

Each study was evaluated by the panel for the following key features that relate to study validity: recall bias (likely/unlikely³), exposure misclassification (likely/unlikely), exposure-response analyses with a trend test (yes/no), selection bias (likely/unlikely), adjustment for confounding by other (non-glyphosate) pesticides (yes/no), adjustment for confounding from other variables (yes/no), pathological review of cases (yes/no), proxy respondents (%cases/%controls), bias from sparse data (possible/no), blinding of interviews (yes/no/unclear) and consideration of induction/latency (yes/no). See Table 4 for details.

Validity considerations

Selection bias and recall bias

With the exception of one notable cohort study (De Roos et al. 2005), epidemiologists have employed the case control design to investigate glyphosate. Case control and cohort studies are related designs. Both study designs, if conducted with high quality, can produce valid results. In fact, the case control design is best thought of as including the cases that would have been detected in a hypothetical cohort study

Table 3. Results for glyphosate: multiple myeloma (MM)

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

CI: confidence interval; HCL: hairy cell leukemia; OR: odds ratio, RR: relative risk.

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

along with a sample of the source population (Rothman et al. 2008). The purpose of the control group is to determine the relative size of the exposed and unexposed populations that gave rise to the cases, so as to enable valid risk estimates for exposed versus unexposed populations. At times in case control studies, the control population is selected for convenience or practicality in a way that does not allow determining the relative size of the exposed and unexposed populations. For example, hospital controls may be less likely to have strenuous occupations than the general population; hence farmers and/or others with pesticide exposures might be under-represented among hospital controls. Poor or selective participation by potential controls can produce the same result. Both scenarios are examples of selection bias that would almost certainly generate spurious positive associations between farming exposures and cancers.

A particularly important and well-known potential bias in case control studies of pesticides is recall bias. That is, cases tend to be more likely to remember or report exposures than are study participants who have not been diagnosed with cancer. This bias results from the natural self-examination by

cases of what might have caused their grievous illness. Recall bias is not a concern in the sole glyphosate cohort study (De Roos et al. 2005) because exposure was determined from study participants at study entry before follow-up began for health outcomes. Recall bias tends to produce spurious positive associations between exposure and disease.

Concern about recall bias also extends to next-of-kin who participate in epidemiologic studies in place of deceased or disabled family members. Analyses of next-of-kin or proxy respondents have been found to produce results similar to those of first-hand study subjects (e.g. Kachuri et al. 2013) or to show results quite different than those based on first-hand responders (e.g. Lee et al. 2005 – ORs for glyphosate and glioma were 0.4 based on primary respondents and 3.1 for proxy respondents); one never knows the impact of having appreciable numbers of next-of-kin respondents without a thorough analysis of data with/without proxy respondents (Johnson et al. 1993). This concern is noteworthy because the case-control studies for glyphosate frequently have a high proportion of next-of-kin participants and many studies did not evaluate the potential bias from next-of-kin responders.

Table 4. Validity considerations for glyphosate studies.

First author, year	Recall bias	Exposure misclassification	Exposure-response and trend test	Selection bias	Adjusted for confounding from other pesticides yes/no	Adjusted for confounding from other variables yes/no	Pathology review of cases	Proxies %cases/%controls	Bias from sparse data	Blinding of interviews	Consideration of latency
Brown et al. 1993	Likely	Moderate ever/never	No	Unlikely	No	Yes	Yes	42% for cases; 30% for controls	No	Unclear	No
McDuffie et al. 2003	Likely	Moderate ever/never; appreciable days of use	Yes, no trend test	Likely	No	Yes and no	Yes	21% cases; 15% controls	No	Unclear	No
Hardell et al. 2002	Likely	Moderate ever/never; appreciable in days of use analysis	No	Unlikely	Yes, but variables not specified	Unclear	Yes for NHL, unclear for HCL	43% NHL cases and controls, 0% for HCL	Possible	Yes	No
De Roos et al. 2003	Likely in original publications	Moderate ever/never	No	Likely, in original publications	Yes	Yes	Yes	31% for cases; 40% for controls	No	Yes	No
De Roos et al. 2005	No	Moderate ever/never; appreciable in days of use analysis	Yes, yes	Unlikely	Yes	Yes	Yes	No	Possible in some analyses	N/A	No
Eriksson et al. 2008	Likely	Moderate ever/never	Yes, no trend test	Unlikely	Yes	Age, sex, year of diagnosis	Yes	No	Possible in some analyses	Yes	Yes
Otsi et al. 2009	Likely	Moderate ever/never	No	Likely	No	Yes	Yes	No	Possible	Yes	No
Cocco et al. 2013	Likely	Likely	No	Likely	No	No	20%	No	Possible	Unclear	No
Kachuri et al. 2013	Likely	Moderate ever/never; appreciable in days of use analysis	Yes, no trend test	Likely	No	Yes	Yes	Excluded	No	Unclear	No

NHL: non-Hodgkin's lymphoma.

Exposure assessment and misclassification

With few exceptions, epidemiologic studies of pesticides assess exposure by questioning participants or their next-of-kin about the prior use of specific pesticides and associated work practices. This practice has limitations compared with other branches of occupational research where epidemiologists often have access to objective documentation about past industrial workplace conditions to aid in exposure assessment (e.g. engineering diagrams, process descriptions, job descriptions, area or personal exposure-monitoring data).

A number of publications provide insights about the validity or reliability of self-reported pesticide information used in epidemiologic studies. In one study, approximately 60% of farmers' self-reports agreed with suppliers' records of purchases for specific pesticides (Hoar et al. 1986), in another article, researchers evaluated the repeatability of self-reported pesticide information on enrollment questionnaires for 4188 licensed pesticide applicators, primarily farmers, who filled out questionnaires in successive years (Blair et al. 2002). The year-to-year reliability for reporting any lifetime use of 11 widely used pesticides varied from 79 to 87%; categorical agreement varied from 50 to 59% for typical days of use per year and from 50 to 77% for years of use. Based on this literature, it is apparent that perhaps 10–20% or more of participants in epidemiologic studies may report incorrectly that they have used a specific pesticide and that reporting on frequency of use and years of use is even less certain.

There seems to be considerable under-appreciation of the implications of the acknowledged degree of exposure misclassification in the pesticide literature. Many consider exposure misclassification to almost always be non-differential (e.g. similar for cases and controls) and, therefore, to bias analyses toward the null (or no association between an exposure and a disease). However, even assuming the misclassification is non-differential overall over multiple analyses, the direction of the resulting bias can be uncertain for any specific analysis. As Rothman and Greenland (1998) pointed out, in any given study, random fluctuations can lead to bias away from the null (towards a positive or negative association) even if the classification method satisfies all the conditions for being non-differential (viz. on average). Hence, in the studies considered in this review, with hundreds of comparisons per study, some fraction of results likely will be biased away from the null even if misclassification is non-differential.

Finally, unlike the five days per week, 50 weeks per year routine for exposures in industrial settings, glyphosate and other pesticide applications are not a frequent occurrence for farmers and applicators. In fact, for most, application of a specific pesticide, like glyphosate, is seasonal and happens only a few days per year. The high exposure category in the glyphosate literature is usually two or more days per year – reflecting extremely infrequent use for the great majority of study subjects and, annually, long periods without exposure. This implies that pesticide exposures are much less frequent than other occupational exposures for those who use pesticides in their occupations and that these other, daily exposures need to be addressed comprehensively in any analysis of infrequently used pesticides.

Biomonitoring studies, implications for exposure assessment

Epidemiologists recognize that there is a difference between exposure (viz. reported use) and dose (the quantity of a substance that is absorbed). In fact, dose is of more interest than exposure in studying potential causal associations. For some chemicals, exposure and dose correlate well. For other chemicals, the correlation is low. Understanding the correlation between exposure and dose is essential for exposure-response analyses – an important indicator for a causal relationship.

The properties of a chemical affect dose. Glyphosate is usually formulated as the isopropylamine salt, which has an extremely low vapor pressure of 1.6×10^{-8} mm Hg (Tomlin 2003). Inhalation of spray droplets was found to be a minor route of glyphosate exposure in a study of glyphosate applicators in Finland (Jauhainen et al. 1991), leaving dermal contact as the primary route of exposure. Dermal penetration experiments, where glyphosate was left undisturbed on skin surfaces of experimental animals and on human skin *in vitro*, indicate a percutaneous absorption of less than 2% (Wester et al. 1991).

Biomonitoring studies show results consistent with glyphosate's physical/chemical properties. In a study of 48 farmers in Minnesota and South Carolina during a normal day of glyphosate application on their farms, 60% of applicators were found to have quantifiable glyphosate in urine (the predominant route of excretion), while 40% of farmers did not (Acquavella et al. 2004). The distribution of urinary concentrations was highly skewed, with only a small percentage of values appreciably different than the one part per billion limit of detection. Nine farmers completed applications in excess of 100 acres and did not have detectable values for glyphosate in their urine. Evaluation of different approaches to exposure assessment used in epidemiologic studies has not shown good correlation with biomonitoring data for glyphosate (Acquavella et al. 2006), implying appreciable misclassification in studies that rely on traditional pesticide exposure assessment approaches.

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 Environmental Protection Agency (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 2 mg/kg/day (US EPA 1993). The geometric mean systemic glyphosate dose for applicators is 0.0001 mg/kg/day.

Statistical considerations

In addition to the potential study biases discussed above, other threats to validity arise from the statistical procedures used (or not used) in the epidemiology studies reviewed for glyphosate. First, glyphosate risk estimates in several studies were based on small numbers of events in the exposure sub-categories considered. For example, the case-control studies of NHL reported by Hardell et al. (2002), Cocco et al. (2013), and Eriksson et al. (2008) and of MM reported by Orsi et al. (2009) involved less than 10 exposed cases and/or controls

overall or in specific glyphosate exposure categories. Even the large cohort study of 57 311 pesticide applicators conducted by De Roos et al. (2005) and reanalyzed by Sorahan (2015) included sparse data (viz., 10 or fewer glyphosate-exposed MM cases in each of the three exposure categories considered).

Sparse data not only leads to imprecise risk estimates, but can decrease their validity when analyses are limited to asymptotic procedures (Greenland et al. 2000; Hirji 2006). The phenomenon of a bias away from the null due to small samples or sparse data is termed sparse data bias. It can occur if case-control or cohort studies are analyzed by conventional asymptotic methods such as logistic regression or Poisson regression rather than their counterparts based on exact estimation. For example, in the presence of sparse data, the estimated OR derived from asymptotic conditional logistic regression is substantially overestimated if the true OR is greater than one (Breslow & Day 1980). Sparse data bias also affects estimated CIs and *p* values (Greenland et al. 2000; Subbiah & Srinivasan 2008). It appears that all studies involving sparse data relied upon asymptotic procedures only, and were thus likely subject to sparse data bias and inflated risk estimates.

As shown in Table 4, with few exceptions, the statistical models used to evaluate NHL or MM risks among pesticide-exposed individuals were deficient at many levels. As all studies were exploratory (viz. not testing *a priori* hypotheses regarding specific pesticide exposures and NHL or MM risk), they produced a large number of risk estimates along with a high probability of some estimates being statistically significant simply due to chance alone. No attempt was made in any of the studies to adjust *p* values for these multiple comparisons, though one case control study (De Roos et al. 2003) used a two stage hierarchical modeling approach to adjust risk estimates based on pesticide class characteristics and extant carcinogenic classification to minimize false positives. Also, as shown in Table 4, most studies did not adjust glyphosate risk estimates for potential confounding by other pesticide exposures or relevant medical variables, and only one (Eriksson et al. 2008) considered latency period or the time between first (or last) glyphosate exposure and health outcome. Moreover, only one study (Hohenadel et al. 2011), considered the possible interaction or effect modification between pairs of commonly used pesticides.

Even among the few studies that incorporated potential confounding or effect modifying factors, little if any information was provided about the statistical model selection (e.g. asymptotic or exact), model building strategy (e.g. criteria for including/excluding co-variables) or the diagnostic procedures used to evaluate the fit or robustness of intermediate and final models. Thus, in most studies, reported glyphosate risk estimates remained relatively crude (viz. not fully adjusted) and likely biased due to residual confounding, poor model fit and in some cases, sparse data.

NHL studies

Cantor et al. (1992) conducted a NHL case control study in Iowa and Minnesota to evaluate possible causal factors,

including pesticides. The data from this study were pooled with two other US NHL case control studies and subsequently reported by De Roos et al. (2003). We defer consideration to that more recent analysis.

Nordstrom et al. (1998) conducted a population-based case control study in Sweden that included 121 cases of hairy cell leukemia (HCL) and 484 general population controls. The intent of the study was to evaluate occupational exposures and smoking as risk factors for HCL. The data from this study are included with data from the Hardell and Eriksson (1999) study in a later publication (Hardell et al. 2002). We defer consideration of both primary studies to that more recent analysis.

McDuffie et al. (2001) conducted a trans-Canada multi-center case control study to evaluate the relationship between pesticide exposures and NHL. Cases (*n* = 517) were identified from provincial Cancer Registries except in Quebec, for which hospital ascertainment was used. Controls (*n* = 1506) were selected at random from the provincial Health Insurance records (Alberta, Saskatchewan, Manitoba, Quebec), computerized telephone listings (Ontario) or voters' lists (British Columbia). Participation was much higher among invited cases (67%) than among invited controls (48%). Pesticide exposure was determined through telephone interviews of study participants or their proxies (21% of cases, 15% of controls). The authors used conditional logistic regression to estimate ORs. The OR for any reported glyphosate use was 1.2 (95% CI 0.8–1.7) controlling for age, province and medical variables associated with NHL. The strongest pesticide associations were with mecoprop (OR = 2.3) and dicamba (OR = 1.9). A subsequent analysis by reported days of use per year (none, ≤2 days/year, >2 days/year) showed glyphosate ORs of 1.0, 1.0 (95% CI 0.6–1.6), and 2.1 (95% CI 1.3–2.7), respectively. This latter analysis did not adjust for medical variables that were controlled in the analysis of any glyphosate use or for the effects of other pesticides.

Assessment: The strengths of this study are the relatively large number of NHL cases and the likelihood that almost all cases were confirmed histologically. The limitations are likely residual confounding in the analysis by days of use by the uncontrolled effects of medical variables and other pesticides, selection bias (differential participation by cases and more proxies for cases), and possible recall bias.

Hardell et al. (2002) reported a pooled analysis of two case control studies; one of NHL and the other of HCL. Both of these studies were previously reported as separate case-control studies (Nordstrom et al. 1998; Hardell & Eriksson 1999). HCL is rare, comprising 2% of lymphoid leukemias, and typically affects middle aged to elderly men (Foucar et al. 2008). It is regarded as a mature B cell neoplasm, as are a high proportion of NHLs. It appears that the authors pooled the two separate studies principally to achieve a larger study size under the assumption that the two neoplasms could be treated as a homogeneous entity for etiologic research. However, the pooled analysis is thereby heavily weighted by HCL cases and the results not representative of NHL more broadly. The 404 NHL cases were males aged 25 and older, diagnosed in 1987–1990, and living in mid- and northern Sweden, drawn from regional cancer registries (viz.

histologically verified). Each case was matched on age and sex to two controls drawn from the National Population Registry. The 111 HCL cases were males diagnosed in 1987-1990, identified from the Swedish Cancer Registry covering the whole country. Each HCL case was matched on age, sex and county to four controls drawn from the National Population Registry. A total of 515 cases and 1141 controls were included in pooled analyses of NHL and HCL. A questionnaire was completed by study subjects or next-of-kin regarding complete working history and exposure to various chemicals. Exposure to each chemical was dichotomized, with at least one working day a year before diagnosis being regarded as positive for exposure. Conditional logistic regression was used to estimate ORs and 95% CIs, adjusted for study (NHL versus HCL), study area, and vital status. In the analyses, only subjects with no pesticide exposure were regarded as unexposed⁴, whereas subjects who had not used glyphosate but had used other pesticides were excluded. Analysis for glyphosate, unadjusted for other pesticides, showed a positive association (OR = 3.0, 95% CI 1.1-8.5) based on eight exposed cases and eight exposed controls. Although multivariate analyses were done, it was not stated how variables were selected for inclusion or which variables were included in the multivariate models. The multivariate model for glyphosate indicated appreciable confounding in the unadjusted analysis and a reduced, statistically imprecise, positive association for glyphosate (OR = 1.9, 95% CI 0.6-6.2). Analyses based on increasing days of use were presented for some pesticides, but not for glyphosate.

Assessment: The strengths of this study were that cases were histologically confirmed and controls were population-based. The limitations of this publication were many. First, the investigators found a positive association for every class of pesticide and for every individual pesticide, suggesting a systematic bias in either the assessment of exposure (e.g. recall bias, interviewer or subject (inadvertent) unblinding), in the reporting of results, or due to selection bias. Second, the definition of unexposed (viz. no exposure to any pesticide) used in the analysis distorted the exposure prevalence for glyphosate and precluded being able to control for possible confounding by other pesticides and farming exposures. Third, there seems to be some inconsistency in exposure assessment between the two studies that were pooled in this publication. The prevalence of exposure to glyphosate was three times higher among HCL cases and controls (1.3%) than it was among NHL study subjects (0.4%), even though both studies were contemporaneous and would be expected to have similar exposure prevalences.

De Roos et al. (2003) reported a pooled analysis of three NHL case-control studies of pesticides and other potential causal factors (Hoar et al. 1986; Zahm et al. 1990; Cantor et al. 1992). This analysis was limited to men and excluded cases and controls with a history of living or working on a farm before (but not after) age 18. Cases from the Nebraska study by Zahm et al. (1990) were diagnosed between July 1983 and June 1986 and were identified using the Nebraska Lymphoma Study Group as well as data from area hospitals. Cases from the Kansas study by Hoar et al. (1986) represented a random sample of cases diagnosed between 1979 and 1981 and selected from the Kansas Cancer Data Service. Cases from the study in Iowa and Minnesota by Cantor et al. (1992) were diagnosed between 1981 and 1983 and were

identified from the Iowa State Health Registry along with a surveillance system established in Minnesota. Controls for these studies were randomly selected from population databases (e.g. Medicare, random digit dialing, and state mortality files for deceased cases) and frequency matched to cases on race, sex, age and vital status at time of interview. Cases and controls were interviewed (including next-of-kin when necessary) regarding use of pesticides and/or herbicides as well as other known or suspected risk factors for NHL. The final analysis dataset included 650 cases and 1933 controls, after exclusions of individuals for whom there was missing information. Forty-seven pesticides were included in the analysis after excluding pesticides for which there were not at least 20 persons exposed and data available from all three studies. The exposure metric in the analysis was restricted to any reported use of a specific pesticide, with no consideration of extent of use. Two types of statistical models were used to estimate ORs and 95% CIs: (1) standard logistic regression and (2) hierarchical regression, wherein logistic regression estimates were adjusted in a second stage based on expected similarities of effects within pesticide classes and the presumed *a priori* carcinogenic probability for specific pesticides as determined by external review bodies. For pesticides like glyphosate that were presumed to have a low probability of being carcinogenic, this second stage adjustment tended to draw positive associations toward the null. All analyses were adjusted for age and for the use of 46 other pesticides. Results for glyphosate showed an OR of 2.1 (95% CI: 1.1-4.0) in the logistic regression and a lesser association (OR = 1.6, 95% CI: 0.9-2.8) in the hierarchical regression.

Assessment: The strengths of this analysis were the histological confirmation of NHL cases and the large numbers of cases and controls that enabled simultaneous adjustment of the effects of 47 pesticides. The weaknesses of this study were the reliance on a relatively crude indicator of exposure (ever having used a pesticide with no consideration of the extent of use) and the limitations common to case control studies of pesticides - namely recall bias and, in this case, an appreciably higher proportion of proxy respondents for controls than cases (40% versus 31%).

De Roos et al. (2005) reported glyphosate findings from the Agricultural Health Study (AHS), a large prospective cohort study of health outcomes related to numerous pesticides among more than 53 000 licensed pesticide applicators in North Carolina and Iowa. Analyses for glyphosate considered potential exposure in a number of ways including: ever/never use, estimated cumulative exposure days (CED), and estimated intensity-weighted exposure days (IWED). The statistical approach was Poisson regression and effects were estimated as RRs with 95% CIs. After adjusting for age, findings for ever/never use of glyphosate showed a near null RR of 1.2 for NHL (95% CI 0.7-1.9), based on 92 cases. Further adjustment for education level, pack-years of smoking, alcohol use in last 12 months, family history of cancer, state of residence and 10 other pesticides that were correlated with glyphosate use, and excluding applicators who had missing data for any of these variables, had little effect on findings for NHL (RR 1.1 95% CI 0.7-1.9). Analyses of potential exposure-response effects using the first tertile of CEDs as a baseline category and with adjustments as described above, and

excluding the never-users from the analysis, found a slight non-significant negative trend (3–20 days: RR 1.0; 21–56 days: RR 0.7, 95% CI 0.4–1.4; 57–2678 days: RR 0.9, 95% CI 0.5–1.6). These categorical analyses were repeated for IWEDs and findings were little changed. De Roos et al. (2005) qualified their results as being based on small numbers, but concluded: "... the available data provided evidence of no association between glyphosate exposure and NHL incidence."

Assessment: The strengths of this study are the large size of the study cohort, the high quality assessment of cancer incidence based on statewide registries in Iowa and North Carolina, the lack of proxy respondents, the control for confounding by other pesticides, and the fact that collection of information about pesticide use could not be influenced by health status. The limitations of the study are the relatively short duration of follow-up for AHS cohort members, the relatively small number of NHL cases, and the likelihood of some degree of exposure misclassification in the various analyses.

Eriksson et al. (2008) reported a population based case control study of NHL in males and females aged 18–74 living in Sweden in 1999–2002. Cases were identified through physicians who diagnosed and treated NHL, and all cases were histologically verified. Controls were randomly chosen from population registries in the same health service regions as the cases, and were frequency matched in 10-year age and sex groups. A total of 910 NHL cases and 1016 controls were included in the analyses. The authors emphasized that, in contrast to their previous studies (Hardell et al. 1981; Hardell & Eriksson 1999), the analyses evaluated newer types of pesticides in relation to different histopathological subtypes of NHL. All subjects received a mailed questionnaire focusing on total work history and exposure to pesticides, solvents and other chemicals. For all pesticides, the number of years, number of days per year and length of exposure per day were questioned. Exposure to each chemical was dichotomized, with at least one working day at least a year before diagnosis being regarded as positive. In the analyses, only subjects with no pesticide exposure were regarded as unexposed³, whereas subjects with other pesticide exposures were excluded. Unconditional logistic regression was used to calculate ORs and 95% CIs, adjusted for age, sex, and year of diagnosis. Analyses for individual herbicides showed positive associations for every agent and ORs were elevated for every other pesticide (although not in every analysis by NHL subtype or category of duration of exposure). In the model for glyphosate and all NHL (not adjusted for other exposures), the OR was 2.0, 95% CI 1.1–3.7 for ever/never exposure, based on 29 exposed cases and 18 exposed controls. Exposure to glyphosate for >10 days showed OR = 2.4, 95% CI 1.0–5.4 (not adjusted for other exposures). Analyses of glyphosate exposure and NHL subtypes (not adjusted for other exposures) were positive for every subtype of NHL, and were statistically significant for lymphocytic lymphoma/B-CLL (OR = 3.4, 95% CI 1.4–7.9) and unspecified NHL (OR = 5.6, 95% CI 1.4–22.0). Results for other NHL subtypes were not statistically significant: all B-cell NHL (OR = 1.9, 95% CI 0.998–3.5); follicular NHL (OR = 1.9, 95% CI 0.6–5.8); DLBCL (OR = 1.2, 95% CI 0.4–3.4); other B-cell NHL (OR = 1.6, 95% CI 0.5–5.0); unspecified B-cell NHL (OR = 1.5, 95% CI 0.3–6.6) and

T-cell NHL (OR = 2.3, 95% CI 0.5–10.4). Multivariate analysis of glyphosate exposure was stated to include agents with statistically significant increased ORs or with an OR >1.5 and at least 10 exposed subjects. These models excluded subjects with exposure to pesticides that did not meet these conditions. The multivariate model for glyphosate and all NHL showed a non-significant positive association (OR = 1.5, 95% CI 0.8–2.9) for ever/never exposure, indicating substantial confounding in the analysis (not were not adjusted for other pesticides).

Assessment: Strengths of the study include histological verification of cases and use of population based controls. There were, however, a couple of major limitations. First, the investigators found a positive association for every herbicide and for every individual pesticide (although not in every sub-analysis), suggesting a systematic bias in either the assessment of exposure (e.g. recall bias, interviewer or subject [inadvertent] unblinding), in the reporting of results, or due to selection bias. Second, the definition of unexposed (viz. no exposure to any pesticide) used in the analysis distorted the exposure prevalence for glyphosate for cases and controls and precluded being able to control for possible confounding by other pesticides and farming exposures.

Hohenadel et al. (2011) conducted a reanalysis of data included in the McDuffie publication to evaluate the relationship between exposure to specific pesticide combinations and NHL. The authors used unconditional logistic regression to estimate ORs for the total number of pesticides used by type and carcinogenic potential and for pairwise pesticide combinations (neither, either only or both). Where the OR for joint exposure was higher than the OR for exposure to either pesticide alone, interaction on the additive scale was evaluated using an interaction contrast ratio (ICR). Exposure to glyphosate alone yielded an estimated 8% deficit in NHL risk (OR = 0.92, 95% CI 0.5–1.6), whereas use of malathion only was associated with an elevated NHL risk (OR = 2.0, 95% CI 1.3–2.9). The OR of 2.1 (95% CI 1.3–3.4) for joint exposure to glyphosate and malathion was similar to that for malathion alone and there was no indication of a super additive joint effect (ICR <0.5).

Assessment: The strengths and limitations of this study are similar to those outlined for the related study by McDuffie et al. (2001). The re-analysis was more an exploratory assessment of joint exposures than it was a study of specific pesticides *per se* and is of limited relevance for a possible association between glyphosate and risk of NHL.

Orsi et al. (2009) reported a hospital-based case-control study of occupational exposure to pesticides and lymphoid neoplasms (including but not limited to NHL and MM) undertaken in France. Incident cases of NHL (n = 244) were identified from six French hospital center catchment areas between 2000 and 2004. A panel of pathologists and hematologists confirmed pathology. Controls (n = 436) were selected from the same hospitals as cases; controls had no history of lymphoid neoplasms and were primarily patients from rheumatology and orthopedic departments. Patients admitted for occupation-related diseases or diseases related to smoking and/or alcohol abuse were not eligible as controls although a past history of such diseases/conditions did not eliminate the control. Controls were matched to cases by center, age (± 3 years) and gender. Information on cases and controls

involved a standardized self-administered questionnaire on socioeconomic status, family medical history, and lifelong residential and occupational histories. For additional information (on personal and family history), smoking, alcohol, tea and coffee consumption, use of pesticides (insecticides, fungicides, and herbicides) as well as detailed questions about work on farms, a trained interviewer performed a face-to-face interview with cases and controls. Two exposure definitions were used: definite or possible. Duration of exposure was estimated. ORs and 95% CIs were calculated using logistic regression. Results for any use of glyphosate and NHL showed no association (OR = 1.0, 95% CI 0.5–2.2) based on 12 exposed cases and 24 exposed controls.

Assessment: A strength of this study is that the NHL cases were confirmed histologically. The limitations are no assessment of potential confounding due to the uncontrolled effects of other pesticides/exposures, possible recall bias and selection bias (controls were primarily selected from orthopedic and rheumatological departments where general population prevalence of pesticide exposure would likely be under-represented). Scanning the ensemble of hundreds of effect estimates shows that the vast majority of estimates (though not for glyphosate) were greater than one, suggesting systematic error across the various analyses.

Cocco et al. (2013) reported results from the EPILYMPH case control study of NHL in six European countries, conducted in 1998–2004. The study included 2348 incident lymphoma cases and 2462 controls. Approximately 20% of the cases had their tissue slides reviewed by a central panel of pathologists. Controls were population-based in Germany and Italy, matched on gender, age (within five years) and residence area. Hospital controls were used in the Czech Republic, France, Ireland and Spain, excluding patients with diagnoses of cancer, infectious disease, and immunodeficiency. The participation rate was 88% in cases, 81% in hospital controls, but only 52% in population controls in Germany and Italy (Cocco et al. 2010). Trained interviewers conducted in-person interviews with a structured questionnaire regarding full time jobs held for a year or longer. Industrial hygienists coded the occupations to the ICSO, International Labour Office (1968) and the NACE, Statistical Office of the European Communities (1996) classifications. Subjects who reported having worked in agriculture were given a job-specific module inquiring in detail about tasks, kinds of crops, size of cultivated area, pests being treated, pesticides used, procedures of crop treatment, use of personal protective equipment, reentry after application and frequency of treatment in days/year. Hygienists reviewed the job modules to assess exposure to pesticides in categories. Exposure was scored in terms of confidence (probability and proportion of workers exposed), intensity and frequency. A cumulative exposure score was calculated. Subjects unexposed to any pesticide⁰ were the referent category for all analyses. Unconditional logistic regression was used to calculate ORs and 95% CIs, adjusted for age, gender, education and study center. The authors reported a moderate association between glyphosate (ever/never exposure) and B-cell NHL (OR = 3.1, 95% CI 0.6–17.1) in a univariate analysis that was statistically imprecise being based on only four exposed cases and two exposed controls. Clearly, there were too few

exposed cases and controls to estimate an OR for glyphosate controlling for other exposures.

Assessment: Glyphosate exposure was so infrequent in this study that it precluded an informative analysis. Were that not the case, there would have been obvious concerns about selection bias (esp. low participation for controls), confounding by other exposures (esp. solvent exposures found to be associated with NHL in a previous analysis of this data (Cocco et al. 2010), and recall bias. In addition, the definition of unexposed (viz no exposure to any pesticide) used in the analysis distorted the exposure prevalence for glyphosate and would have precluded being able to control for possible confounding by other pesticides and farming exposures had such analyses been attempted.

MM studies

Brown et al. (1993) conducted a re-analysis of the National Cancer Institute Iowa population-based case-control study (Brown et al. 1990, Cantor et al. 1992) to evaluate the relationship between exposure to specific pesticides and MM. Cases ($n = 173$) were identified from the Iowa Health Registry. Controls ($n = 650$) were frequency matched to cases by age group and vital status at interview and selected from three sources: random digit dialing (living cases under age 65), Medicare records (living cases aged 65+) and state death certificate files (for deceased cases). Participation was relatively high and similar among cases (84%) and controls (78%). Pesticide exposure for 34 crop insecticides, 38 herbicides (including glyphosate) and 16 fungicides was determined from in-person interviews with subjects or their proxies. The authors used unconditional logistic regression to estimate ORs for pesticides handled by at least five cases. Subjects who did not farm⁷ were the referent exposure category for these analyses. The OR for mixing, handling or applying glyphosate was 1.7 (95% CI 0.8–3.6) adjusted for vital status and age. Failure to use protective equipment (obtained from interviews) did not appreciably increase the risk for glyphosate (OR = 1.9, 95% CI not reported). None of the pesticides considered showed a statistically significant association with MM risk.

Assessment: Strengths of the study were the histological confirmation of cases and the high and similar participation for cases and controls. Study limitations were its exploratory nature (as noted by the authors), lack of control for potential confounding by possibly relevant personal characteristics or by exposure to other pesticides, and possible recall bias. In addition, the definition of unexposed (viz non-farmers) used in the analysis excluded 64% of cases and 58% of controls, distorted the exposure prevalence for glyphosate, and would have precluded being able to control for possible confounding by other pesticides and farming exposures had the investigators sought to control potential confounding.

De Roos et al. (2005), based on data from the AHS cohort study described previously, estimated the age-adjusted RR for glyphosate and MM to be 1.1 (95% CI 0.5–2.4), based on 32 cases. Further adjustment for education level, pack-years of smoking, alcohol use in the last 12 months, family history of cancer and state of residence, together with the use of 10 other pesticides that were correlated with glyphosate use, and excluding approximately 14 000 applicators and 13 MM cases with missing data for any of these variables, markedly

increased the RR for MM (RR=2.6, 95% CI 0.7-9.4). Analyses of exposure-response effects using the first tertile of CEDs as a baseline category and with adjustments as described above, and excluding the never-users from the analysis, produced a non-significant positive trend (1-20 days: RR=1.0; 21-56 days: RR=1.1, 95% CI 0.4-3.5; 57-2678 days: RR=1.9, 95% CI 0.6-6.3; *p* values for trend 0.27). This MM CED analysis was based on 19 (of 32) cases, the other 41% of cases being excluded for any missing covariate information. These analyses were repeated for IWED categories and findings were little changed (RRs 1.0, 1.2, and 2.1; *p* values for trend = 0.17). The authors also repeated the exposure-response analyses for MM, using the never-use group as the baseline category and found a monotonic positive trend (tertile 1: RR=2.3; 95% CI 0.6-8.9, tertile 2: RR=2.6; 95% CI, 0.6-11.5; tertile 3: RR=4.4; 95% CI 1.0-20.2; *p* values for trend = 0.09). The authors noted that the marked difference between the age adjusted MM findings and the more fully adjusted findings (viz. RR=1.1 versus 2.6) could have been due to selection bias related to the 14 000 AHS cohort members who were dropped from the more fully adjusted analysis due to missing values for one or more variables.

Assessment: The strengths of this study are the large size of the study cohort, the high quality assessment of cancer incidence based on statewide registries in Iowa and North Carolina, the lack of proxy respondents, the control for confounding by other pesticides, and the fact that collection of information about pesticide use could not be influenced by health status. The limitations of the study are the short duration of follow-up for AHS cohort members, the relatively small number of MM cases, the likelihood of some degree of exposure misclassification in the various analyses, and the indications of selection bias affecting RR estimates due to the exclusion of so many cohort members and MM cases from the more fully adjusted analyses (addressed in a subsequent publication by Sorahan 2015).

Orsi et al. (2009) reported a French hospital-based case-control study of occupational exposure to pesticides and lymphoid neoplasms (including but not limited to NHL and MM), described previously, included were 56 incident cases of MM and 313 controls matched to cases by center, age (± 3 years) and gender. ORs and 95% CIs were calculated using logistic regression. Results for glyphosate and MM showed a moderate, but statistically imprecise, association (OR=2.4, 95% CI, 0.8-7.3) based on five exposed cases and 18 exposed controls.

Assessment: A strength of this study is that the MM cases were confirmed histologically. The limitations are likely residual confounding due to the uncontrolled effects of other pesticides/exposures in the assessment of the OR for glyphosate, possible recall bias, and selection bias (controls were primarily selected from orthopedic and rheumatological departments where general population prevalence of pesticide exposure would likely be under-represented). Scanning the ensemble of hundreds of ORs shows that the vast majority was greater than 1.0, suggesting systematic error across the various analyses.

Landgren et al. (2009) estimated the age-specific prevalence of monoclonal gammopathy of undetermined significance (MGUS) (a medical condition that is sometimes a precursor to multiple myeloma) among a stratified random sample of 678 AHS participants selected based on lifetime organophosphate use. Subjects in the sample had completed

all three phases of the AHS questionnaires, were enrolled into a neurobehavioral study nested within the AHS cohort, and had provided serum for analysis. The authors compared MGUS prevalence for this sample to that for the general population of Olmsted County, Minnesota (due to availability of Mayo Clinic MGUS screening data) and found higher prevalence for AHS participants. Within the AHS sample, associations between MGUS prevalence and pesticide exposures and subject characteristics were assessed in logistic regression models adjusted for age and education level. The prevalence OR for MGUS for glyphosate users versus non-users, adjusted for age and education level, was 0.5 (95% CI 0.2-1.0). None of the herbicides studied showed a strong association with MGUS.

Assessment: This is a small exploratory study of pesticide effects on a medical condition that is sometimes a precursor to MM. Taken at face value, the results provide evidence of a weak inverse association between risk of MGUS and glyphosate, though the exploratory nature of this study, the lack of adjustment for other pesticides in pesticide-specific analyses, the cross-sectional nature of the study, and the implied speculative hypothesis underlying the analysis (that pesticides might cause MM by causing MGUS first) limit conclusions that can be drawn from this work.

Pahwa et al. (2012) reported a trans-Canada, multi-center case control study regarding the relationship between pesticide exposures and MM. The publication is related to the trans-Canada NHL study reported initially by McDuffie et al. (2001) wherein there was a common control group for the study of several lymphopoietic cancers. Pahwa et al. (2012) was updated by Kachuri et al. (2013) and we defer consideration to that more recent publication.

Kachuri et al. (2013) presented a reanalysis and extension of Pahwa et al. (2012) in which they excluded 149 (of 1506) controls who did not have an age match with the MM cases. Kachuri et al. utilized unconditional logistic regression to estimate ORs and presented analyses including and excluding proxy respondents (15% of controls and 30% of cases) and adjusting for smoking, which was associated with MM. They also presented analyses by days of use for individual pesticides. Approximately 9% of cases and controls reported use of glyphosate. ORs adjusted for smoking were 1.2 (95% CI 0.8-1.9) including all cases and controls and 1.1 (95% CI 0.7-1.9) excluding cases and controls who had proxy respondents. ORs excluding proxy respondents for one and two days/year of glyphosate use and for two or more days/year were 0.7 (95% CI 0.4-1.3) in the lower use category and 2.0 (95% CI 0.98-4.2) in the higher use category. However, these results for days of use per year were not adjusted for the potential confounding effects of other pesticides or farm exposures.

Assessment: The strengths of this study are the relatively large number of MM cases, the likelihood that almost all cases were confirmed histologically, and the explicit consideration of proxy respondents in the analysis. The limitations are likely residual confounding in the days of use per year analysis by the uncontrolled effects of other pesticides/exposures, selection bias (58% participation for cases and 48% participation for controls), and possible recall bias.

Sorahan (2015) conducted a re-analysis of data from the AHS to assess the basis for the disparate age-adjusted and

more fully adjusted glyphosate MM findings reported by De Roos et al. (2005). The author used Poisson regression to estimate RRs for MM in relation to glyphosate exposure categorized as ever versus never exposed and by levels of CEDs and IWEDs. Applicators who had missing covariate data were included in the analysis in a "not known" category so that the entire AHS cohort could be maintained. The RR for any glyphosate use adjusted for age and gender was 1.1 (95% CI 0.5–2.5); further adjusting for lifestyle factors and use of 10 other pesticides yielded a similar RR of 1.2 (95% CI 0.5–2.9). RRs for MM tended to increase with increasing CED and IWED reaching a peak RR of 1.9 (95% CI 0.7–5.3; p values for trend = 0.2) in the highest category of IWED in the fully adjusted model; however, none of the trend tests or category-specific RRs was statistically significant. This reanalysis showed that selection bias was associated with inflated MM risk estimates in the paper by De Roos et al. (2005). Those excluded from the analysis included five of eight MM cases in the glyphosate never use category. Sorahan's secondary analysis of this AHS data does not support the hypothesis that glyphosate use is a risk factor for MM and indicates that the practice of restricting analyses to subjects with complete data for all variables can produce appreciable bias.

Assessment: This reanalysis answers some of the questions about the impact of selection bias in the MM analysis by De Roos et al. (2005). Given that there were only 32 MM cases in the original publication, there are obvious limitations to analyses by estimated extent of exposure that can only be addressed with analyses of the AHS cohort using more recent follow-up data.

A special consideration: selection bias in the analysis

According to accepted case control theory (Rothman et al. 2008), the validity of case control studies depends on accurately estimating the exposure prevalence in the population that gave rise to the cases. Exposure prevalence cannot be estimated accurately by excluding from the analysis cases and controls with farm exposures other than glyphosate as was done in several studies. This practice distorts the glyphosate exposure prevalence for cases and controls and biases OR estimates. We illustrate this bias using data from such a glyphosate analysis by Brown et al. (1993).

Brown et al. (1993) analyzed a case control study that had 173 MM cases and 650 controls. Of these, 11 of 173 cases (6%) and 40 of 650 controls (6%) reported use of glyphosate. Hence, there was no difference in exposure prevalence for cases and controls. However, the authors calculated ORs using non-farmers as the referent population with the rationale that they were not exposed to any farm activities. This seemingly well-intentioned modification of the referent population violates a fundamental premise that underlies the validity of case control studies – that controls should be drawn from the population that gave rise to the cases, which, of course, includes individuals with exposure to farm activities. With these exclusions 100 of 173 cases (58%) and 338 of 650 controls (52%), the glyphosate exposure prevalence for cases was increased to 15% (11 of 73 cases) and the glyphosate

Table 5. Results as presented by Brown et al. (1993) for glyphosate exposure.

	Case	Control	Total
Exposed	11	40	51
Unexposed	62	272	334
Total	73	312	385

OR_{unadjusted} = 1.2, 95% CI 0.5, 2.6

Table 6. Results for glyphosate exposure using all the cases and controls from Brown et al. (1993).

	Case	Control	Total
Exposed	11	40	51
Unexposed	162	610	772
Total	173	650	823

OR_{unadjusted} = 1.0, 95% CI 0.5, 2.1

exposure prevalence for controls was increased a lesser amount to 13% (40 of 312 controls). This created a bias away from the null as illustrated in Tables 5 and 6 in our OR analysis of the Brown et al. data with and without restriction of the referent group to those not exposed to any farm related activities (using Stata version 14).

Ironically, the reason for the clear bias away from the null is that those with exposure to farm related activities and who did not use glyphosate had higher MM risks than farmers who used glyphosate. In addition, by excluding those without exposure to glyphosate and exposure to other farm exposures, the authors would have precluded being able to control fully for confounding had they attempted multivariate analyses of pesticide exposures. Hardell et al. (2002), Eriksson et al. (2008) and Cocco et al. (2013) made similar exclusions, defining their referent population as those not exposed to pesticides (other than glyphosate). The limited data presented in those papers did not permit us to address statistically the direction and extent of the bias as we have for Brown et al. (1993).

In a similar vein, Sorahan's reanalysis of the MM data from the cohort analysis by De Roos et al. (2005) provides another example of selection bias in the analysis that produced an appreciable bias away from the null. In this case, Sorahan (2015) showed that excluding those with any missing covariate data increased the adjusted RR from 1.1 to 2.6, largely by excluding five of eight MM cases from the glyphosate unexposed population.

Weight of evidence evaluation

Descriptive summary

We systematically collected, summarized and critiqued 16 analytical epidemiological publications examining aspects of the possible relationship between reported use of glyphosate and two cancer types: NHL and MM. We excluded redundant publications (Cantor et al. 1992; Nordstrom et al. 1998; Hardell & Eriksson 1999; Pahwa et al. 2012) in favor of more recent published analyses of the same subjects. This resulted in a final evaluative dataset of seven studies of glyphosate exposure and NHL (see Table 2) and four studies of glyphosate exposure and MM (see Table 3), considering the Sorahan publication (2015) as an extension of De Roos et al. (2005).

The descriptive characteristics of each of these studies were examined for the likely presence or absence of validity concerns (see Table 4). It is clear from Table 4 that only one study in the glyphosate literature (highlighted in Table 4) – the AHS cohort study (De Roos et al. 2005) – was designed to minimize selection bias and recall bias, had only firsthand respondents reporting about exposures (viz. no proxy respondents), and conducted analyses that controlled comprehensively for confounding by personal characteristics and occupational exposures. In addition, the AHS cohort study was the only study that attempted to look at exposure–response relationships while controlling for confounding exposures. As such, it deserves the highest weight in our assessment of the literature. The other studies have so many validity concerns that they cannot be interpreted at face value. Indeed, there is evidence in many of these studies that virtually every exposure studied was associated with NHL or MM – a clear indication of widespread systematic bias and the unreliability of any of the reported exposure–disease associations.

We note one potential limitation to our systematic review. Although we were careful to systematically search the existing literature using search terms and secondary sources to identify relevant studies, it is possible that some relevant studies were not identified. Given the focus on glyphosate epidemiology by IARC and the authors of two recent meta-analyses, included among our secondary sources, we think this potential limitation is unlikely to be consequential.

Assessment of causality

The assessment of causality is a complex process that relies upon a family of well-recognized methods: the general scientific method (familiar to all scientists), study design and statistical methods, and research synthesis methods (e.g. the systematic narrative review, meta-analysis and pooled analysis, and the so-called criteria-based methods of causal inference). Of these, the criteria-based methods are often described and considered in causal assessments, with the most familiar having been proposed by Hill (1965) and utilized extensively in the 1964 Surgeon General's Committee on Smoking and Health and the many publications on the topic that dotted the scientific landscape in the late 1950s and early 1960s (Surgeon General 1964; Weed 2005). These "criteria" or "considerations" are substantive components of the stated methodologies of agencies such as the US EPA (2005) and IARC (2015).

At the center of these methods is the fundamental scientific aim of selecting the best explanation from the alternative explanations that exist for any body of scientific observations, however carefully they were obtained. In epidemiological terms, those alternative explanations typically are defined as cause, bias, confounding (a type of bias) and chance. Some studies are better at excluding alternative explanations than others; cohort studies, for example, are typically better at avoiding recall bias than interview based case-control studies, and recall bias affects not only the exposure of interest (here, glyphosate) but also potential confounding factors (e.g. exposure to other pesticides). Similarly, any and all epidemiologic study designs can – and should – control statistically for

factors believed to be potential alternative explanations, (e. known and putative confounders. For example, studying glyphosate and any lymphohematopoietic cancer without controlling for the potential confounding effects of other pesticides and herbicides, as was widely the case for almost all of the case control studies, does not permit one to exclude those confounders as an alternative explanation. And finally, if the results of an epidemiologic study (whether case-control or cohort) fail to achieve conventional levels of statistical significance – whether defined in terms of "p values" or "95% CIs" – then the alternative explanation of chance cannot be excluded. Notably, however, as Greenland (1990) pointed out, interpretation of p values and CIs at face value requires the assumption that a particular OR or RR has been estimated without bias (e.g. recall bias, selection bias, or confounding), elevating the importance of concerns about study validity in the interpretation of results.

In essence, all the causal frameworks in epidemiology focus on whether the observed associations are strong (viz. the size of the OR or RR is appreciably different than 1.0), whether the associations appear to have been estimated without bias, whether the OR or RR increases or decreases with increasing exposure (viz. exposure–response), whether the temporal relationship between exposure and effect is considered appropriate, and whether the results are statistically robust enough to rule out chance as an explanation (Hill 1965; Bhopal 2002; Aschengrau & Seage 2003a, 2003b; Sanderson et al. 2007).

Assessment of the NHL studies

With these considerations in mind, for NHL, it is justified scientifically to rely most on the results of the De Roos et al. (2005) cohort study as those best suited to reveal the existence (or not) of an association between exposure to glyphosate and NHL. This cohort study was the only study where information about pesticide use was collected independently of the participants' knowledge of cancer status, where there were no proxies providing information about pesticide use, where exposure–response was evaluated extensively, and where there was statistical adjustment for other pesticide exposures and personal factors in estimating RRs for glyphosate. As De Roos et al. (2005) concluded "... the available data provided evidence of no association between glyphosate exposure and NHL incidence." On the other hand, all the case control studies had the potential limitation of recall bias, many had clear indications of selection bias (either in terms of subject participation or in the analysis), most had very small numbers of glyphosate exposed cases and controls, none showed evidence of an exposure–response relationship, and most did not control for the potential confounding effects of personal factors or other occupational exposures in their glyphosate risk estimates. We consider the case control studies to be inadequate for the assessment of a relationship between glyphosate and NHL and consider the AHS cohort study as the one reliable evaluation of NHL risk from glyphosate. The two limitations of the AHS study are the relatively small number of NHL cases (n = 92) and that the length of follow-up after enrollment was less than

a decade. Those limitations speak to statistical robustness, not validity.

Assessment for MM

The glyphosate literature for MM is appreciably sparser than the literature for NHL. Again, the AHS cohort study (De Roos et al. 2005) is the best source of evidence when compared with the three available case control studies. The AHS data indicate that glyphosate users had about the same rate of MM as non-users adjusting for confounding factors (factoring in Sorahan's (2015) reanalysis of the fully adjusted MM results from De Roos et al. (2005) to correct the inadvertent selection bias discussed previously). Exposure-response analyses by De Roos et al. (2005) and Sorahan (2015) were relatively uninformative in light of the few MM cases split among exposure categories. More informative analyses await additional follow-up of the AHS cohort to increase the number of MM cases. The three MM case control studies are based on very small numbers, have concerns about recall bias and selection bias, and did not control for confounding by other exposures. Overall, then, we consider this literature inadequate to make an informed judgment about a potential relationship between glyphosate and MM.

Conclusions

The purpose of this literature review was to address two questions:

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

Our review of the glyphosate epidemiologic literature and the application of commonly applied causal criteria do not indicate a relationship with glyphosate exposure and NHL. In addition, we consider the evidence for MM to be inadequate to judge a relationship with glyphosate. Our conclusion for NHL differs from that of the IARC workgroup seemingly because we considered the null NHL findings from the AHS to be more convincing than the case control studies, in aggregate, with their major limitations. We utilized a structured systematic review approach, we formally addressed pre-specified validity criteria for each study, and our weight of evidence assessment employed widely utilized criteria for causal inference.

Notes

1. A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.
2. Grey literature publications may include, but are not limited to the following types of materials: reports (pre-prints, preliminary progress and advanced reports, technical reports, statistical reports, memoranda, state-of-the-art reports, market research reports, etc.), theses, dissertations, conference proceedings, technical

specifications and standards, non-commercial translations, bibliographies, technical and commercial documentation, and official documents not published commercially (primarily government reports and documents) (Alberani et al. 1996).

3. Whether recall bias, exposure misclassification or selection bias was classified as likely or unlikely was based on a consensus after an in person discussion of each study by the authors.
4. According to accepted case control theory (see Rothman et al. 2008), the validity of case control studies depends on accurately estimating the exposure prevalence in the population that gave rise to the cases. Exposure prevalence cannot be estimated accurately by excluding from the analysis cases and controls with farm exposures other than glyphosate. This practice distorts the glyphosate exposure prevalence for cases and controls and biases OR estimates. We illustrate this in the section on selection bias in the analysis using data from such an analysis by Brown et al. (1993). In addition, excluding those with exposure to other pesticides hinders controlling for confounding by other farming exposures and pesticides in multivariate models.
5. Per footnote 2, defining the referent in this way distorts the glyphosate exposure prevalence for cases and controls, biases OR estimates, and precludes adequate control for confounding in multivariate models. See the section on selection bias in the analysis for additional details.
6. Per footnote 2, defining the referent in this way distorts the glyphosate exposure prevalence for cases and controls, biases OR estimates, and precludes adequate control for confounding in multivariate models. See the section on selection bias in the analysis for additional details.
7. Per footnote 2, defining the referent in this way distorts the glyphosate exposure prevalence for cases and controls, biases OR estimates, and precludes adequate control for confounding in multivariate models. See the section on selection bias in the analysis for additional details.

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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. This expert panel evaluation was organized and conducted by Intertek Scientific & Regulatory Consultancy. Funding for this evaluation was provided by Monsanto Company, which is a primary producer of glyphosate and products containing this active ingredient. The authors had sole responsibility for the content of the paper, and the interpretations and opinions expressed in the paper are those of the authors.

JA worked for Monsanto from 1989 through 2004 and is a consultant on a legal case unrelated to glyphosate that involves a former Monsanto industrial chemical plant. DG serves on a scientific advisory board to Dow Agro Sciences, which markets pesticides including glyphosate, and has consulted on behalf of Bayer Corp. on litigation matters concerning glyphosate and leukemia. GM has no additional declarations. TS has received consultancy fees and travel grants from Monsanto Europe SA/NV as a member of the European Glyphosate Toxicology Advisory Panel and participated in the IARC Monograph Meeting for volume 112, as an Observer for the Monsanto Company. In addition, TS has consulted for Monsanto on litigation matters involving glyphosate. DW has consulted on litigation matters concerning Monsanto that did not involve glyphosate.

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Supplemental material

Supplemental material for this article is available online here.

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Glyphosate rodent carcinogenicity bioassay expert panel review

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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

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		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	

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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 G8Fs 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*

Select neoplasm	Tumor incidence/number of animals examined by dose in mg/kg bw/day (ppm diet)													
	Controls — 0 [range in %]	31 (30)	7.45 (100)	10† [100]	10% (adjust)¶¶	31† (300)	73.9% (1000)	861† (1500)	891 (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	41/51	5/58	1/17	10/74	81/63		
Hepatocellular adenoma	30/351 [0–48]	NF	2/50	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		

Select neoplasm	Tumor incidence/number of animals examined by dose mg/kg bw/day (ppm diet)													
	150† (3000)	285†† (5000)	300% (adjust)¶¶	354# (10000)	361** (6000)	362† (8000)	740.65 (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	0/50	NF	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	410/51	2/21	5/79	411/63	8/58	1/50	NF	7/60	8/49	413/51	6/78	140/64	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	2/78	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 (Chemnova) SD rats.

§Study 4 (Fenchem Schweda) 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 Crj: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 ($\leq 1\%$ 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 ($p = .037$) of renal tubule carcinomas and of adenomas and carcinomas ($p = .034$) 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 ($p = .016$) in the incidence of hepatocellular adenomas occurred in males.
5. In the first dietary study in SD rats, a significant positive trend ($p = .031$) 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 Goldman) 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 (MD/FO, 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 x 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 x 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 McConnell (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 $p = .034$, 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 Bowman's 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 $p = .037$ (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 $p = .034$ (in the Cochran-Armitage trend test). While both these p values ($p = .037$ and $p = .034$) 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 (JMPRI) 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).

mg/kg bw/d (ppm)	Males				Females			
	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 (2%), 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 $p < 0.05$ (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 ($p = .016$) 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 ($p = .101$, 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 ($p = .016$) 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).

Tumors	Dose mg/kg bw/d (ppm)			
	0 (0)	89 (2000)	367 (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 + 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 hepatocellular 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

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

malignancy and no compound-associated pre-neoplastic lesions were induced.

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 ($p = .031$). 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 ($p = .031$)." 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

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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.

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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 Lairto 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.

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Genotoxicity Expert Panel review: weight of evidence evaluation of the genotoxicity of glyphosate, glyphosate-based formulations, and aminomethylphosphonic acid

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ABSTRACT

In 2015, the International Agency for Research on Cancer (IARC) published a monograph concluding there was strong evidence for genotoxicity of glyphosate and glyphosate formulations and moderate evidence for genotoxicity of the metabolite aminomethylphosphonic acid (AMPA). These conclusions contradicted earlier extensive reviews supporting the lack of genotoxicity of glyphosate and glyphosate formulations. The IARC Monograph concluded there was strong evidence of induction of oxidative stress by glyphosate, glyphosate formulations, and AMPA. The Expert Panel reviewed the genotoxicity and oxidative stress data considered in the IARC Monograph, together with other available data not considered by IARC. The Expert Panel defined and used a weight of evidence (WoE) approach that included ranking of studies and endpoints by the strength of their linkage to events associated with carcinogenic mechanisms. Importantly, the Expert Panel concluded that there was sufficient information available from a very large number of regulatory genotoxicity studies that should have been considered by IARC. The WoE approach, the inclusion of all relevant regulatory studies, and some differences in interpretation of individual studies led to significantly different conclusions by the Expert Panel compared with the IARC Monograph. The Expert Panel concluded that glyphosate, glyphosate formulations, and AMPA do not pose a genotoxic hazard and the data do not support the IARC Monograph genotoxicity evaluation. With respect to carcinogenicity classification and mechanism, the Expert Panel concluded that evidence relating to an oxidative stress mechanism of carcinogenicity was largely unconvincing and that the data profiles were not consistent with the characteristics of genotoxic carcinogens.

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Executive summary

Overall, extensive reviews of the genotoxicity of glyphosate, aminomethylphosphonic acid (AMPA) and glyphosate based formulations (GBFs) that were available prior to the development of the International Agency for Research on Cancer (IARC) Glyphosate Monograph all support a conclusion that glyphosate (and related materials) is inherently not genotoxic. Further, evidence indicative of an oxidative stress mechanism of carcinogenicity is largely unconvincing. The Expert Panel concluded that there is no new, valid evidence presented in the IARC Monograph that would provide a basis for altering these conclusions.

The differences between the conclusions of the IARC review and the Expert Panel review were in large part due to IARC exclusion of numerous available studies and in some cases differences in interpretation of study results reported in the IARC Monograph. Another significant source of difference was the Expert 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 weight of evidence (WoE) assessment.

The IARC review process does not allow for use of data from reports that are not published or accepted for publication in the open scientific literature or data from government reports that are not publicly available. However, detailed primary data were extracted and published in reviews such as Kier and Kirkland (2013), although the study reports themselves are unpublished. The Expert Panel concluded that these data along with regulatory studies of GBFs and AMPA summarized in Williams et al. (2000) should have been considered by IARC, and should be considered by all stakeholders going forward in evaluating the genetic toxicology of glyphosate and GBFs. A critical review of the complete dataset by the Expert Panel supports a conclusion that glyphosate (including GBFs and AMPA) does not pose a genotoxic hazard and therefore, should not be considered support for the classification of glyphosate as a genotoxic carcinogen.

Introduction

In 2015, IARC published the Glyphosate Monograph of Volume 112 (IARC 2015) which concluded that there was strong evidence supporting that "glyphosate can operate through two key characteristics of known human carcinogens" including genotoxicity and induction of oxidative stress. This was viewed as providing strong support for

IARC classifying glyphosate as probably carcinogenic to humans, Group 2A. A number of published and regulatory approval reviews of the carcinogenic and genotoxic potential of glyphosate, AMPA and GBFs were available prior to the development of the IARC Monograph (Health and Welfare Canada 1991; US EPA 1993; WHO 1994; Williams et al. 2000; European Commission 2002; Kier & Kirkland 2013; US EPA 2013). The consensus among these reviews was that proper use of glyphosate and GBFs does not pose a genotoxic or carcinogenic hazard/risk with hazard indicating potential for adverse effects and risk indicating potential for adverse effects under actual conditions and amounts of exposure. As a result, glyphosate based herbicides have been approved for use in over 160 countries. The recent IARC conclusion was therefore inconsistent with these other reviews. Consequently, the Monsanto Company commissioned Intertek Scientific & Regulatory Consultancy to assemble a panel of experts to conduct a thorough review in the four areas considered by IARC including mechanistic data (focused on genotoxicity and oxidative stress). This review section reports the views of the Expert Panel of genetic toxicologists on the genotoxicity of glyphosate, GBFs and AMPA and discusses how they relate to the IARC opinions. The views and conclusions represent those of the Expert Panel of genetic toxicologists as independent scientific consultants and neither employees of the Monsanto Company nor attorneys reviewed this manuscript prior to submission.

Proper methods to accurately evaluate and interpret complex sets of genetic toxicology data

Characteristics of genetic toxicology tests and genetic testing data sets

Due to interest in understanding the potential to produce adverse effects, chemicals such as glyphosate, for which there is widespread human exposure, are typically subjected to extensive testing for genotoxic activity. The resultant database will contain studies that encompass diverse phylogenetic boundaries, types of genetic alterations, and exposure methods. Some of the more common test methods are often represented by multiple entries in the database. Proper evaluation of such data sets requires an approach that is both systematic and critical.

In large datasets, there are always likely to be some positive responses that are described as "false" or "misleading" positives from the standpoint of predicting carcinogenicity or relevance to carcinogenic mechanism (Waters et al. 1988; Mendelsohn et al. 1992; Jackson et al. 1993). False or misleading responses generally fall into one of three types:

1. Non-predictive – positive responses produced by non-carcinogenic agents. It is well documented that misleading positive responses are more frequent in certain genotoxicity tests (particularly in *in vitro* mammalian cells) due to their inherent lack of specificity (Kirkland et al. 2005; Pfuhrer et al. 2011; Walmsley & Billinton 2011) and artifacts resulting from *in vitro* treatment conditions (Halliwell 2003).

2. Secondary response – the positive response is not associated with direct DNA-reactivity of the agent or metabolites of the agent but is a downstream or indirect consequence of high levels of cytotoxicity (Kirsch-Volders et al. 2003; Pratt & Barron 2003) or extreme treatment conditions such as high osmotic conditions or significant variations in pH (Scott et al. 1991). Such responses may not be relevant to *in vivo* prediction because they involve effects generated by exposures that exceed potential *in vivo* exposures.
3. Technical deficiencies – positive responses may be produced by inadequate study designs, mistakes made during the conduct of a test or inappropriate evaluation of data. This type includes cases where there is reason to question whether a positive experimental result has actually been obtained.

An understanding of possible actions leading to false or misleading responses with respect to carcinogenicity prediction or carcinogenic mechanism must be incorporated into the design, conduct, evaluation, and interpretation of genotoxicity assays. As a consequence, new standard test guidelines for *in vitro* mammalian assays published by the Organization for Economic Cooperation and Development (OECD) and other organizations indicate that treatment conditions must be monitored for maintenance of normal physiological parameters.

Therefore, it is expected that a chemical as heavily tested as glyphosate would exhibit some positive responses in its genotoxicity database that would be considered “misleading” and therefore not predictive of its true genotoxic or carcinogenic hazard/risk potential.

Methods applicable to evaluation and interpretation of complex data sets

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 2005; Dearfield et al. 2011). Many of the principles of the WoE analysis indicated here are consistent with and included in the very recently issued endpoint specific guidance document of the European Chemicals Agency (ECHA 2015).

While numerous attempts to develop a standard WoE method to evaluate large, complex data sets have not found universal acceptance, some critical performance requirements for WoE approaches have been identified by the US EPA (Suter & Cormier 2011). One of the most important requirements is that individual test methods should be assigned a weight that is consistent with their contribution to the overall evidence, and different types of evidence or evidence categories must be weighted before they are combined into a WoE.

The weight of a category of evidence used in the Expert Panel evaluation is based on four considerations:

1. **Different categories of evidence (i.e. assay types) have different weights.** Genotoxicity tests measuring mutations and chromosome damage have greater

weight than “indicator” assays that measure DNA damage. For example, for human pharmaceuticals, ICH S2 (R1) (ICH 2011) states that “fixation of damage to DNA in the form of gene mutations, larger scale chromosomal damage or recombination is generally considered to be essential for heritable effects and in the multi-step process of malignancy” The following comments are taken from the “Overview of the Set of OECD Genetic Toxicology Test Guidelines and Updates Performed in 2014–2015” (OECD 2015): “There are tests that detect primary DNA damage (i.e. the first in the chain of events leading to a mutation), but not the consequences of this genetic damage. The endpoint measured in these tests does not always lead to a mutation, a change that can be passed on to subsequent generations (of cells or organisms). The DNA damage measured in the comet assay, or the unscheduled DNA synthesis (UDS) test, may lead to cell death, or it may initiate DNA repair, which can return the DNA either to its original state or result in mutation. When evaluating the mutagenic potential of a test chemical, more weight should be given to the measurement of permanent DNA changes (i.e. mutations) than to DNA damage events that are reversible.”

2. **The aggregate strength (robustness of protocols and reproducibility) and quality of evidence in the category also influence the weight.** It is generally acknowledged that studies conducted in compliance with Good Laboratory Practice (GLP) Regulations and studies conducted according to OECD guidelines have greater weight than studies lacking these attributes. These are fundamental features of the Klimisch scoring system, which is widely used to assess the reliability of study data, particularly for regulatory purposes (Klimisch et al. 1997).
3. **The number of pieces of evidence within a category influences the weight.** A single (or few) divergent responses (positive or negative) within a majority of studies exhibiting concordant findings would be insufficient to alter the direction and strength of the WoE. This component of the overall WoE is an aggregate of the weights of all the pieces of evidence within a single test category (e.g. tests for gene mutation).
4. **Tests with greater ability to extrapolate results to humans carry greater weight.** Test responses able to more accurately predict potential hazard in humans, such as *in vivo* tests, will generally be weighted more heavily than evidence developed from tests conducted *in vitro* or in non-mammalian models.

Human versus non-human test results

Using a variety of different methods, genotoxicity test data can be derived from human populations exposed under typical use conditions. Human population monitoring studies, if performed with sufficient sample sizes, knowledge of exposure levels and adjusted appropriately for confounding variables, can offer highly relevant information. Poorly controlled human biomonitoring studies, however, can lead to erroneous conclusions (Schmid & Speit 2007; Dusinska & Collins

2008). Adjustments that need to be considered in human biomonitoring studies for genotoxicity must extend beyond age, gender, smoking, alcohol, tobacco use, and medicines used. Diet, disease status (e.g. presence of inflammatory diseases), seasonal variation, and physical stress are all important confounding factors that influence an individual's background level for any parameter under consideration (Moller 2005; Battershill et al. 2008; Bonassi et al. 2011; Fenech et al. 2011; Tenorio et al. 2013; Collins et al. 2014). There is evidence that different factors may have different impact depending on the specific genotoxic endpoints (e.g. Fenech et al. 2011 for the cytokinesis block MN endpoint; Collins et al. 2014 for the comet endpoint).

It is worth noting that there is currently considerable debate concerning the relevance of increased levels of micronuclei in human biomonitoring studies. Speit (2013) suggested that micronuclei induced in the cytochalasin B micronucleus assay used in human biomonitoring studies, do not represent micronuclei that were induced during exposure, but rather represent DNA damage that generates micronuclei during the *in vitro* culturing required for the assay. As such, this bioassay could be classified as an "indicator test" of DNA damage with lower relevance for genotoxic risk. Kirsch-Volders et al. (2014), however, considered gaps in the knowledge regarding the source of micronuclei observed in human biomonitoring studies, but considers the assay, especially with modifications, to have utility for human genotoxic hazard/risk measurements. For the purposes of this review, the Expert Panel adopted a conservative approach and the measurement of micronuclei detected in studies of exposed humans was assigned a high weight.

It is also possible to conduct genetic tests using human derived cell lines or in primary lymphocyte cultures. With respect to results from cell lines of different origin, the benefits of using human rather than rodent derived cell lines are not as compelling as one might presume. Cell lines (human or rodent origin) with mutations affecting how cells handle initial DNA damage (e.g. p53 mutations) are typically more susceptible to genetic damage. Consequently, human cell lines with altered responsiveness to DNA damaging mechanisms may be expected to generate results not dissimilar to those produced in rodent cell lines. At this time there are not enough data available to reliably determine if the use of p53-competent cell lines of human origin (as opposed to p53-competent rodent derived lines) or other human cells confer greater accuracy (Walmsley & Billinton 2011; Fowler et al. 2014).

The most current OECD *in vitro* mammalian cell chromosomal aberration and micronucleus test guidelines indicate that either human or rodent cell lines or primary cultures may be used (OECD 2014a, 2014d). These guidelines also state that: "At the present time, the available data do not allow firm recommendations to be made but suggest it is important, when evaluating chemical hazards to consider the p53 status, genetic (karyotype) stability, DNA repair capacity and origin (rodent versus human) of the cells chosen for testing."

Thus, any *in vitro* mammalian cell results should be interpreted with caution, and the weight they contribute to an

overall assessment of genotoxic activity should take account of the potential limitations.

A summary of assumptions, results, and conclusions regarding the IARC genotoxicity evaluation of glyphosate, GBFs, and AMPA

The Expert Panel used the considerations discussed above when assigning weights to genotoxicity endpoints and to the responses present in the glyphosate (and related materials) dataset. The results of this review indicate some areas of agreement with IARC, but also identified some major differences between the conclusions of the two assessments.

An evaluation of IARC and expert panel review processes

The Expert Panel agreed that there was sufficient evidence to conclude that glyphosate and GBFs appeared to induce DNA strand breaks and possibly micronuclei in *in vitro* mammalian and non-mammalian systems and sister chromatid exchanges (SCEs) in *in vitro* mammalian systems. These results provide some evidence of genotoxicity, but it is not possible to accurately characterize or classify genotoxic hazard/risk or carcinogenesis mechanisms based on these results alone. As noted earlier and further stated in the OECD overview comments (OECD 2015) regarding test weights, "When evaluating the mutagenic potential of a test chemical, more weight should be given to the measurement of permanent DNA changes (i.e. mutations) than to DNA damage events that are reversible." Consequently, positive responses in genotoxic endpoints identified above as "indicator tests" (i.e. DNA strand breaks, SCEs) are evidence of compound exposure but not sufficient to determine compound effect. In order to determine compound effect, consideration must be given to available evidence clearly demonstrating the induction of gene mutations or stable chromosomal alterations, particularly *in vivo* in mammalian systems.

Evidence weighting

Weights assigned to individual assays represent the strength of evidence assigned to an endpoint or category and may be derived from validation studies supporting the endpoint's involvement in carcinogen prediction as well as its relevance to mechanisms involved with initiation of malignancy (ICH 2011). 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" tests using mammalian metabolic activation). Other considerations, such as response reproducibility or GLP compliance, may influence the weight of a particular study result. GLP compliance indicates a high degree of, and standard for, detailed documentation of experimental conditions and data.

Section 4.2.1 of the IARC Monograph does not provide sufficient information to its readers regarding the strategy

employed by IARC reviewers in assessing the WoE; therefore, it is not possible to know if, for example, studies were assigned variable weights in accordance with the criteria discussed above. While the Expert Panel agrees that data from a well conducted human population biomonitoring study might carry more weight in a WoE assessment, it appears that IARC considered *in vitro* studies in human cells as carrying more weight than rodent *in vivo* studies as evidenced by the order of discussion topics in Section 4.2.1, and the inclusion of a separate table for human *in vitro* studies. The overall IARC Monograph evaluation (Section 6.0) and rationale (Section 6.4) indicate that the conclusion of strong evidence of genotoxicity is based on "studies in humans *in vitro* and studies in experimental animals." As discussed above, the Expert Panel evaluation considered *in vitro* studies using cells of human origin to be weighted as equivalent to any other *in vitro* mammalian cell assay using the same endpoint.

There did not, however, appear to be additional weight assigned by IARC to other criteria such as relevance of the endpoint to neoplastic initiation, quality of study performance, *in vitro* versus *in vivo* or reproducibility of responses.

Table 1 summarizes the Expert Panel's endpoint weighting assumptions. Weights represent strength, relevance and reliability of evidence and are based on a compilation of information regarding the endpoint's reversibility and susceptibility to false or misleading positive responses with respect to carcinogenicity prediction or relevance to mechanisms involved in initiation of malignancy (Solomon et al. 1991; Pierotti et al. 2003; Petkov et al. 2015).

The endpoint and test system weighting categories are defined as follows:

- **Negligible weight** – the endpoint is not linked to any adverse effect relevant to genetic or carcinogenic hazard/risk and as such is not given weight as evidence of genotoxicity.

- **Low weight** – the end point is indicative of primary DNA damage, is not unequivocally linked to mechanisms of tumorigenicity, and the test system has low specificity.
- **Moderate weight** – the endpoint is potentially relevant to tumorigenicity or may be subject to secondary, threshold-dependent mechanisms of induction (e.g. cytotoxic clastogens, aneugens) or the test system exhibits a high rate of misleading positives with respect to carcinogenicity predictivity or carcinogenic mechanism.
- **High weight** – the endpoint is one that has been demonstrated with a high level of confidence to play a critical role in the process of tumorigenicity.

Chemical structure and chemistry of GBFs

Chemical structures of glyphosate and AMPA are presented in Figure 1. IARC did not consider the chemical structure of glyphosate in its mechanistic section; however, IARC Monograph Section 5.3 states that glyphosate is not electrophilic. Many guidelines recommend that the presence of structural alerts be considered in evaluation of or testing for genotoxicity (Cimino 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. Analysis of structural alerts for genotoxicity inherently includes consideration of potential

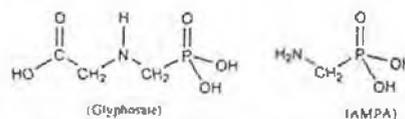


Figure 1. Chemical structures of glyphosate and AMPA. Glyphosate: N-(phosphonomethyl)glycine, acid form, CAS 1071-83-6; AMPA: aminomethylphosphonic acid; CAS 1066-51-9.

Table 1. Expert Panel's evidence weighting assumptions for mammalian (plus selected microbial test) endpoints.

Endpoint*	Negligible weight	Low weight	Moderate weight	High weight
DNA binding (adduct formation) <i>in vitro</i>				
DNA binding (adduct formation) <i>in vivo</i>				
SSB/DSB <i>in vitro</i> (including comet)				
SSB/DSB <i>in vivo</i> (including comet)				
SCEs <i>in vitro</i>				
SCEs <i>in vivo</i>				
Oxidative DNA				
Damage <i>in vitro</i>				
Oxidative DNA				
Damage <i>in vivo</i> (detection of 8-OHdG adducts)				
DNA repair effects <i>in vitro</i>				
DNA repair effects <i>in vivo</i>				
Micronuclei <i>in vitro</i>				
Micronuclei <i>in vivo</i>				
Chromosomal aberrations <i>in vitro</i>				
Chromosomal aberrations <i>in vivo</i>				
Gene mutation in bacteria (Ames Test)				
Gene mutation mammalian <i>in vitro</i>				
Gene mutation <i>in vivo</i>				

*Shaded box indicates weight for the endpoint. SSB: single strand breaks; DSB: double strand breaks; SCE: sister chromatid exchange.

metabolites. Although formal analysis is not available, it does not appear likely that the metabolite AMPA (glyphosate without a carboxymethyl group) has structural alerts. While structural alerts are not as definitive as experimental data, they serve as part of a WoE (Dearfield et al. 2011). The lack of structural alerts in the glyphosate molecular structure suggests lack of genotoxicity or that genotoxic effects might well be secondary to toxicity or resulting from mechanisms other than DNA-reactivity.

Another aspect of chemistry that should be recognized is the fact that GBFs, while containing glyphosate (often present as a sodium or potassium salt) also contain other components which frequently include surfactants. Specific formulations differ in composition and differences may exist between GBFs identified with a common brand name. Frequently, GBFs are observed to have greater toxicities than glyphosate. Evaluation of genotoxicity results for glyphosate and GBFs should always consider the possibility that effects observed with GBFs may be due to GBF components other than glyphosate and that there may be chemical differences between various GBFs.

The case for including other published results in the IARC genotoxicity evaluation

Although IARC policies and Working Group decisions excluded consideration of additional data from unpublished studies or publicly unavailable governmental reports, it was the Expert Panel's conclusion that the genetic toxicology studies published in reviews such as Kier and Kirkland (2013), in particular the supplementary primary data submitted with the paper, should have been considered by IARC in evaluating the genetic toxicology of glyphosate and GBFs. Though the primary study reports from which the data were extracted were not available to IARC, detailed data were provided in the Kier and Kirkland (2013) review and exceed the weight of data in most published reports that were considered by IARC. Regulatory studies of GBFs and AMPA summarized in Williams et al. (2000) should also have been considered and information on these studies is presented in Appendices A and B.

Inclusion of the studies in these publications would have filled data gaps, supplemented study categories for which there were limited numbers of test responses and would have added a very high level of confirmation to other core assay results. Table 2 summarizes an additional 90 studies

covering a range of test categories that were available for review if the regulatory studies in the Kier and Kirkland (2013) publication and other published or publicly available studies had been included. Among the 90 studies not included in the IARC Monograph, only nine were reported as positive. Inclusion of these studies in a WoE produces a much clearer, more reliable and balanced assessment of the genotoxicity of glyphosate, GBFs and AMPA.

The rationale supporting the inclusion of these 90 additional studies is that the supplementary tables presented in the Kier and Kirkland (2013) paper, and presented in Supplemental Information, Appendix A of this publication, do contain sufficient detail concerning the robustness of the studies. For the regulatory studies, which were the key studies not reviewed by IARC, the Kier and Kirkland (2013) paper clearly states:

Each study examined was stated to have been conducted in accordance with GLP standards with almost all studies citing the OECD Principles of Good Laboratory Practice (OECD GLP 1982, 1997) Reports also cited compliance with various national and regional GLP Guidelines (e.g. European Commission GLP Directives 87/18/EEC or 88/320/EEC; U.S. Environmental Protection Agency GLP Standards, 40 CFR Part 160; Japanese Ministry of Agriculture, Forestry, and Fisheries (MAFF) GLP Standards, 11 Nonsan No. 6283). Variations from GLPs were considered not to have significantly impacted the study results.

Almost all of the studies were reported to have been conducted in accordance with the relevant OECD test guidelines applicable at the time of the study. Study reports were examined to determine that the protocols and experimental methods for the report were consistent with the OECD guidelines and any deviations were noted and considered. Report data were examined to confirm the conclusion of the report regarding whether treatment-related activity had been observed.

Thus, the methods used were generally as specified in OECD guidelines, or any deviations were noted. Moreover, the studies were performed under GLP conditions, which would ensure protocol compliance and high quality data. The key aspects of each test method were detailed in the first few pages of the supplementary material in Kier and Kirkland (2013) so it is easy to see how top concentrations were chosen, what measures of cytotoxicity were used, how many cells were scored etc. Links to the guidelines were provided.

The rationale given by IARC for not including the regulatory studies in Kier and Kirkland (2013) was that the primary study reports were not available, and that the information provided in the supplementary tables was insufficient regarding topics such as details of statistical methods, choice of

Table 2. Summary of test categories, number of studies, and study responses available from Kier and Kirkland (2013) and other publicly available studies not included in the IARC Monograph (details for all studies provided in Supplemental Information, Appendix A).

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 <i>In Vitro</i>	Gene mutation	0/2	ND	ND	0/2
	Chromosomal 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 <i>In Vivo</i>	Chromosomal 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, AMPA: aminomethylphosphonic acid, GBFs: glyphosate based formulations, ND: not done

highest dose tested, and verification of the target tissue exposure.

This rationale for exclusion is unjustified for the following reasons.

For bacterial reverse mutation assays the concentrations tested were detailed in every table, as were critical aspects of the methods (e.g. plate incorporation or pre-incubation for the Ames tests, inducing agent for the S9 and its final concentration, and number of replicate cultures). Thus, it is clear what top concentrations were used, whether they complied with the maximum concentration/dose as recommended in OECD guidelines, or whether they were defined by toxicity.

Almost all of the many Ames tests on glyphosate used a top concentration of the maximum required, 5000 µg/plate unless contraindicated by toxicity. All of the required strains, including either TA102 or *Escherichia coli*, have been used in the regulatory studies included in Kier and Kirkland (2013). The Ames tests on GBFs used quite variable top concentrations. Some went as high as the maximum required (5000 µg/plate) but others only reached <100 µg/plate, seemingly limited by toxicity. Since we know glyphosate *per se* is not very toxic in the bacterial tests, the toxicity is presumably caused by the other components of the formulations, which were more toxic in some GBFs than in others.

The mammalian cell assays on glyphosate generally reached top concentrations in the range 500–5000 µg/mL, even when prolonged (48 h) treatments were performed in the chromosomal aberration studies. Thus, many of these studies exceeded 10 mM (1690 µg/mL for glyphosate), the top concentration currently recommended in OECD guidelines for nontoxic substances. There were no regulatory mammalian cell tests on GBFs.

All except one of the regulatory *in vivo* micronucleus (MN) tests on glyphosate that used oral dosing achieved a top dose of at least 2000 mg/kg, which is the top dose for a nontoxic substance recommended in OECD guidelines. One oral study achieved a top dose of only 30 mg/kg, seemingly because severe toxicity and lethality was seen at higher doses. It is unclear why such lethal effects were seen in this study when much higher doses were tolerated in other studies using the same acute dosing regimen. Several studies using intraperitoneal (i.p.) injection had lower top doses because of greater toxicity when using the intraperitoneal route. Thus, all of the regulatory MN studies on glyphosate met or exceeded the required top dose.

The *in vivo* bone marrow MN and chromosomal aberration regulatory studies of Kier and Kirkland (2013) generally did not report evidence of target organ toxicity (e.g. %PCE, which would be a measure of bone marrow toxicity) or include analyses to demonstrate presence of glyphosate in plasma. Therefore, the issue of whether the bone marrow was exposed needs verification by evidence other than target organ toxicity.

The IARC Monograph states that about 1/3 of glyphosate administered orally to rodents is absorbed and excreted, largely unchanged, in urine. This provides evidence that it is likely that the bone marrow, a well-perfused tissue, is exposed to glyphosate in rodents treated orally. Definitive evidence of absorption and systemic distribution of

glyphosate in rodents is also contained in a summary of regulatory toxicokinetic studies (JMPPR 2006). These studies demonstrated absorption of glyphosate and systemic distribution, including distribution in bone marrow, in rats dosed intraperitoneally or orally. Published reports have also indicated absorption and systemic distribution of glyphosate administered by the intravenous (i.v.) or oral route in rats (Brewster et al. 1991; Anadon et al. 2009) and by the oral (dietary) route in mice (Chan & Mahler 1992). Thus, in the regulatory rodent *in vivo* MN and chromosomal aberration tests, target organ exposure would have been achieved.

If statistical analysis was performed (not commonly performed or required for Ames tests) this is given as a footnote to the supplementary tables (Kier & Kirkland 2013, supplementary tables; Appendix B, this report), together with the statistical method used, and whether the results were significant.

Thus, in view of the Expert Panel, the exclusion of these studies was not justified. 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, resulted in an inaccurate assessment of glyphosate, GBFs and AMPA's genotoxic hazard/risk potential.

Expert panel's critique of selected studies: impact on IARC evaluation

Genetic toxicology tests relied upon by most regulatory bodies to support decisions focus on a set of core endpoints that are known to be involved either in direct activation of genes responsible for neoplastic initiation in somatic cells or alteration of the genetic information in germ cells (EFSA 2011; ICH 2011; Kirkland et al. 2011). Therefore, the endpoints given the greatest weight in Table 1 include gene mutation and chromosomal aberrations.

MN formation *in vivo* was also assigned a high weight (Table 1), as it is considered an indication of chromosome breakage but could also result from aneuploidy (Kirsch-Volders et al. 2003). However, aneugenic effects are usually thresholded (Parry et al. 1994). For instance, MN may be induced by alterations in normal mitosis produced by various kinases. It was demonstrated that GBFs activate mitotic kinase CDK-1 (Marc et al. 2002) which could possibly play a role in MN induction through a separate mechanism believed to be threshold based (Terasawa et al. 2014). Although a thresholded mechanism may be considered of less weight than a non-thresholded mechanism, most *in vivo* MN studies did not investigate this. In the absence of information on clastogenic or aneugenic mode of action, the panel considered that a high weight should be applied to all *in vivo* MN studies.

Human genotoxicity biomonitoring studies

The results provided for GBFs in Table 4.1 (human studies) of the IARC Monograph concluded positive evidence of DNA breakage as determined by results in humans using the comet assay Paz-y-Miño et al. (2007), negative induction of

chromosomal aberrations (Paz-y-Miño et al. 2011), and positive induction of MN (Bolognesi et al. 2009). Due to the importance of these studies in the IARC review, these papers were critically reviewed by the Expert Panel as described in detail below.

Paz-y-Miño et al. (2007) reported increased DNA damage (comet assay) in individuals recently exposed to GBF spraying, but only "suggested" this implied a genotoxic risk. The comet assay, as discussed earlier is an "indicator" endpoint and primary DNA damage does not accumulate, so the consequences of the observed DNA breaks remain unknown (Faust et al. 2004).

The Expert Panel review of this study identified a number of issues that questioned the validity of the interpretation of results. For example, it is not clear which blood cells were scored for comets, or if it was all cells in the blood. Also, the observation of a median comet tail length of exactly 25.0 μm for 20/21 unexposed control individuals in this publication questions the quality of data collection. This unusual observation was not noted in the IARC Monograph. The Paz-y-Miño et al. (2007) publication indicated that signs of clinical toxicity were reported in the population and that the GBF application rate was reported to be some 20 times higher than recommended. The clinical signs were consistent with acute intoxication associated with severe exposures (Menkes et al. 1991) and these factors suggest that comet effects might have been secondary to toxicity from very high exposure to GBF. The Paz-y-Miño et al. (2007) report seems to qualify the conclusiveness of the results by indicating that the results "suggest" a genotoxic effect. Due to uncertainties regarding the negative control data, and particularly because of uncertainties regarding the mechanistic role of cytotoxicity in generating the effects the Panel regarded this study as inconclusive evidence for *in vivo* human genotoxic effects relevant to induction of mutations or carcinogenesis.

In a follow-up study, Paz-y-Miño et al. (2011) reported negative results for induction of chromosomal changes in individuals from areas where GBF spraying had occurred two years previously. The absence of chromosomal aberrations supports the presumption that the DNA strand breaks identified in the Paz-y-Miño et al. (2007) study were either repaired or lethal and did not persist as lesions which could be expressed as chromosomal aberrations in cultured lymphocytes in the follow-up study.

Bolognesi et al. (2009) reported a significant but small, transient and inconsistent effect of glyphosate spraying on MN induction in individuals living in areas where aerial spray application of glyphosate occurred (Figure 1 in Bolognesi et al. 2009), but concluded that any risk was "low". Of greater importance however, is the observation that no statistically significant increase in the frequency of micronucleated binucleated cells (BNMN) was observed in individuals that actually reported direct exposure to the spray compared to individuals who lived in the spray area but were not present during spraying (Bolognesi et al. 2009, Table 4). These results are shown graphically in Figure 2 (graph provided by K. Solomon). As indicated in Table 4 of Bolognesi et al. (2009), statistical analysis did not indicate a significant difference ($p < 0.05$, ANOVA) in post-spray BNMN frequency between

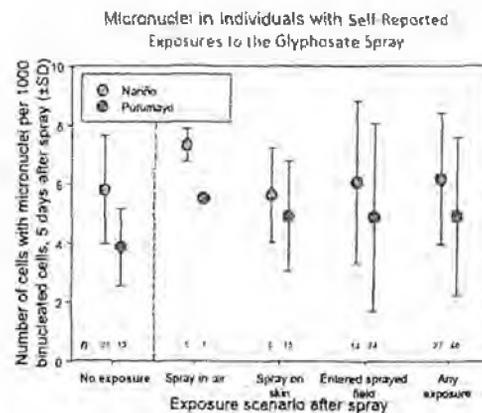


Figure 2. Mean frequency of binucleated cells with micronuclei (BNMN) in self-reported exposures to glyphosate spray in areas where aerial application occurred. From Bolognesi et al. (2009), Table 4. Data from Valle del Cauca not shown in graph since only one individual reported exposure. Graph provided by K. Solomon.

different categories of self-reported spray exposure and there was no statistically significant difference ($p < .05$) between no exposure and any self-reported spray exposure for any of the three regions. The Valle del Cauca region, which exhibited the highest post-spraying increase, only had 1/26 persons self-reporting spray exposure and the GBF spray application rate was substantially lower than the application rates in the other two regions.

Although results were temporally consistent with GBF spraying, the lack of significant correlation between increased post-spraying BNMN frequencies and self-reported spray exposure, and inconsistency with application rates, indicate that the MN effects observed in this study cannot be associated with GBF exposure (Figure 2) and therefore the Expert Panel concluded the results to be negative. The panel agrees with the statement made in the discussion section of Bolognesi et al. (2009) that based on the Bradford Hill criteria (Hill 1965) it is not possible to assign causality to the BNMN increases observed in their study and notes that elsewhere in this publication the authors seemed to qualify their conclusions with terms like "suggest" and "potentially". Lack of clear evidence of causality indicates that it is inappropriate to conclude that GBF induces MN in humans. The Bolognesi et al. (2009) results were considered negative by the Expert Panel because there were no statistically significant increases in MN frequency associated with self-reported spray exposure. This conclusion is subject to the limitation of the use of self-reporting as a measure of exposure.

The Expert Panel conclusion for the Bolognesi et al. (2009) results seems to be quite different from the IARC Monograph. The qualifications about lack of consistency with exposure rates or statistically significant association with self-reported spray exposure are noted in the discussion of this study in IARC Monograph Section 4.2.1(a)(i). However, these qualifications are not evident in IARC Monograph Section 5.4 which presents these results as positive without qualification. IARC Monograph Section 6.4 not only presents the results as

positive without qualification but seems to give this study a high weight in arriving at their conclusion of a genotoxic mode of action.

Due to the deficiencies cited in the biomonitoring studies above, along with the lack of scientific consensus regarding the relevance of MN found in exposed humans, the Expert Panel concluded that there was little or no reliable evidence produced in these studies that would support a conclusion that GBFs, at levels experienced across a broad range of end-user exposures, poses any human genotoxic hazard/risk.

Studies in mammalian *in vitro* and *in vivo* assays

The number of studies conducted in mammalian models both *in vitro* and *in vivo* was relatively extensive but with some notable data deficiencies and gaps. However, looking for evidence consistent with a concern for genotoxic hazard finds little or no compelling support among test methods that assess relevant endpoints.

Gene mutation

IARC noted one negative *in vitro* mammalian gene mutation result for glyphosate (IARC Monograph Table 4.4). Additionally there are two negative results for glyphosate in the mouse lymphoma tk locus assay (Kier & Kirkland 2013). These provide a clear WoE that glyphosate does not induce gene mutation in mammalian cell systems. There are no *in vitro* mammalian cell gene mutation results for GBFs or AMPA.

Chromosomal effects *in vitro*

In *in vitro* mammalian cell chromosomal aberration assays (IARC Monograph Tables 4.2 and 4.4) glyphosate was reported positive in one study and negative in two other studies. Regulatory studies and published studies, not considered by IARC, provide one additional positive result and five additional negative results (see Supplemental Information, Appendix A, Table 2 of this paper). One of the positive studies (Lioi et al. 1998a) is not considered valid due to the fact that there was excessive cytotoxicity (>50% reductions in mitotic index at all concentrations tested, exceeding current regulatory guidelines for a valid assay). Several of the published studies did not include exogenous mammalian metabolic activation. Most importantly, the negative studies tested glyphosate at dose levels well in excess of those reported positive by Lioi et al. (1998a, 1998b) and included several human and bovine lymphocyte studies. In addition to the negative chromosomal aberration assays the two negative results in the mouse lymphoma tk locus assay also add weight to a conclusion that glyphosate is not clastogenic in *in vitro* mammalian cell assays. Overall these results provide sufficient evidence that glyphosate is not clastogenic in mammalian cells when studied under appropriate *in vitro* treatment conditions.

No *in vitro* mammalian chromosomal aberration studies of GBFs and one positive *in vitro* mammalian chromosomal

aberration study with AMPA were reported by IARC. The latter study by Sivikova and Dianovsky (2006), reported as a GBF study in IARC, is considered to be a study of a manufacturing batch of an isopropyl salt of glyphosate from a Monsanto source (Kier & Kirkland 2013). An additional positive *in vitro* mammalian chromosomal aberration study was not considered by IARC (Amer et al. 2006; see Supplemental Information, Appendix A, Table 2 of this paper). The positive GBF study tested an unusual GBF and employed very high dose levels. These single studies do not provide a strong WoE for induction of chromosomal aberrations for GBFs or AMPA in mammalian cells *in vitro*.

IARC reported two positive *in vitro* mammalian cell MN studies of glyphosate. However, another four positive or equivocal *in vitro* mammalian cell MN studies of glyphosate were identified in the literature that were not reported in IARC but were summarized in Kier and Kirkland (2013). Several of the studies had weak or inconsistent responses. Piesova (2004, 2005), not in IARC, reported statistically significant increases in MN in bovine lymphocytes only with 48-h incubation without S9 metabolic activation but the responses were not consistent between donors. Two papers by Mladinic et al. (2009a, 2009b) reported weak responses in human lymphocytes at the highest dose tested in the presence of S9 metabolic activation. MN results for Mladinic et al. (2009a) were not reported in IARC. One of these studies (Mladinic et al. 2009a) had a very high control MN frequency and in both publications it appears that cells were treated prior to mitogen stimulation which would mean cells would have been exposed in G0 cell stage. This treatment regimen is not considered appropriate according to current test guidelines. The MN induced at high doses were predominantly centromere positive suggesting the possibility of an aneugenic effect. These responses were considered of limited quality by IARC and the publication authors indicated that the high dose effects might have been at a dose level exceeding a threshold and possibly associated with high toxicity. Koller et al. (2012). MN results not evaluated by IARC, reported positive *in vitro* MN results in human-derived buccal epithelial cells for glyphosate in the absence of S9 metabolic activation. An unusual feature of this paper was indication of significant cytotoxicity at very low dose levels (20 µg/mL) and with very short exposure times (20 min). Although the authors speculated their epithelial cells might be more sensitive than cells of the hematopoietic system such as lymphocytes, a large number of other studies using non-hematopoietic cells used much higher doses and longer exposure times. A study by Roustan et al. (2014) reported increases in MN frequency in CHO-K1 cells only in the presence of S9 activation. There was very little dose response observed over an order of magnitude of concentrations (10–100 µg/mL). Thus, although positive (or equivocally positive) responses were observed for glyphosate in several studies these responses were not consistent in terms of dose levels or requirement for an S9 metabolic activation system. The possibility of a threshold aneugenic effect in the presence of S9 metabolic activation might be suggested by the results of Mladinic et al. (2009a, 2009b) but other studies cannot confirm this possibility because presence or absence of centromeres was not

measured. It should be noted that there is a report that glyphosate is essentially unchanged by incubation with rat liver homogenate which would indicate that S9 activation dependent responses might not be due to metabolites of glyphosate (Gohre et al. 1987).

Overall these studies provide only very limited evidence of the possibility of MN induction by glyphosate in *in vitro* mammalian cell assays and this observation, coupled with the negative profile for clastogenicity in *in vitro* mammalian cell assays, would suggest this low possibility is limited to aneugenic effects that are likely to be indirect and thresholded.

Although IARC reports one negative *in vitro* mammalian cell assay with a GBF (Sivikova & Dianovsky 2006), as noted above this assay is likely to have been performed with a technical glyphosate preparation rather than a formulation. Koller et al. (2012) report a positive *in vitro* MN result for a GBF (result not included in IARC) in buccal epithelial cells derived from a human-neck metastatic tumor. The authors noted that these cells have not been used for genotoxicity assessments and the Expert Panel considered the results in this non-validated system to be of unknown relevance. IARC reported one positive result for AMPA in an *in vitro* mammalian cell MN assay in CHO-K1 cells (Roustan et al. 2014). An unusual feature of the Roustan et al. (2014) study was that AMPA apparently exhibited much higher cytotoxicity than glyphosate. Although complete cytotoxicity data are not presented, the maximum AMPA concentrations evaluated for MN, appearing to produce less than 50% reduction in cytokinesis blocked proliferation index, were 1000-fold lower than glyphosate concentrations in the absence of S9 metabolic activation, 20-fold lower in the presence of S9 metabolic activation and 100,000-fold lower with light activation. These very large cytotoxicity differences are dramatically different from the relative toxicities of AMPA and glyphosate observed in other mammalian cell studies, e.g. Chaufan et al. (2014); Manas et al. (2009a, 2009b); Li et al. (2013); Kwiatkowska et al. (2014). These individual studies, particularly the Roustan et al. (2014) study, appear to exhibit technical problems and do not present a convincing WoE for *in vitro* mammalian cell MN effects of GBFs or AMPA.

Chromosomal effects *in vivo*

As a general point, it was noted earlier that there is adequate evidence available from toxicology studies demonstrating absorption and distribution of glyphosate to bone marrow in the rat (i.p., i.v., and oral routes) and absorption and distribution of glyphosate in blood by the oral route in the mouse. This information provides evidence for target organ exposure in the rodent bone marrow studies discussed below, which is particularly important when negative results are obtained.

Table 4.3 in the IARC Monograph reported one negative *in vivo* rat bone marrow chromosomal aberration result and one negative mouse dominant lethal result for glyphosate. In addition there is one negative regulatory *in vivo* mouse bone marrow chromosomal aberration study of glyphosate not evaluated by IARC (Suresh 1994; see Supplemental Information, Appendix A, Table 3). These studies provide *in vivo* evidence complementing the larger number of *in vitro*

studies (discussed above) indicating glyphosate is not clastogenic when tested in mammalian assays.

IARC reported two positive results and one negative result for glyphosate in *in vivo* MN assays. In one of the positive studies reported by IARC (Bolognesi et al. 1997), relatively low increases in MN frequency were observed which might well be within the historical range of many laboratories (Salamone & Mavournin 1994). The other positive study (Manas et al. 2009a) had an unusual feature in that it is reported that erythrocytes were scored for MN, but in the bone marrow and at an early sampling time. Historical control data were not reported in the publication so the relevance of this result cannot be determined. By contrast, there are an additional 13 published, publicly available or regulatory *in vivo* MN studies with glyphosate in the mouse (12 studies) or rat (one study), all of which gave negative results (see Supplemental Information, Appendix A, Table 3 of this paper). These negative results were obtained in multiple studies at dose levels that exceeded those at which positive results had been reported in the IARC reviewed studies mentioned above using the same (i.p.) route of administration. With respect to a route of exposure, the negative MN results in a glyphosate mouse feeding study (Chan & Mahler 1992) that was not reported in IARC are of particular relevance to carcinogenic potential. The Expert Panel's conclusion is that there is a strong WoE that glyphosate does not induce MN *in vivo* in mammals.

IARC reported one positive and one negative rodent bone marrow chromosomal aberration study for GBFs. An additional two published positive rodent chromosomal aberration studies on GBFs were identified that were not reported in IARC. One mouse study with positive results (Prasad et al. 2009) employed sampling times for a chromosomal aberration assay quite different from those currently recommended (OECD 2014c). Moreover, the GBF was administered i.p. using dimethylsulfoxide (DMSO) as a vehicle and the use of this vehicle and route has unusual toxicity properties (Heydens et al. 2008). This assay was also unusual in that dose-responsive increases were observed at multiple sampling times, which is difficult to explain since cells damaged at early sampling times have usually died and disappeared from the bone marrow by later sampling times. Another positive publication (Amei et al. 2006), not reported in IARC, found positive chromosomal aberration results in mouse bone marrow and spermatocytes with treatments that included repeated oral and i.p. dosing. The test material was reported to be a formulation containing 84% glyphosate which is very unusual and raises the possibility that observed effects were due to some unusual or unique component of this formulation. Another published positive GBF study (Helal & Moussa 2005) uniquely involved rabbits exposed to GBF (750 ppm) in drinking water for 60 days. Using extended repeat dosing for a bone marrow chromosomal aberration assay is questionable because cells with chromosome breaks usually do not accumulate and any cytogenetic effects would likely be due to the final one or two doses. Total aberrations reported for this study included some nonstandard and questionable categories such as gaps and centromeric attenuations. Thus, most of the positive *in vivo* chromosomal aberration studies with

GBFs are all subject to concerns regarding the reliability or biological relevance of the results. While they cannot be ignored, they do not warrant undue weight, and do not support a conclusion of strong evidence of genotoxicity.

IARC reported two positive and three negative *in vivo* rodent bone marrow MN results for GBFs. One of the two positive studies (Bolognesi et al. 1997) had low negative control MN frequencies and the MN frequencies in treated groups were within historical control ranges for many laboratories (Salamone & Mavournin 1994) although historical control ranges for the laboratory were not reported in the publication. The other positive study (Prasad et al. 2009) was unusual in using DMSO as a vehicle by the i.p. route which, as noted above, may have led to unusual toxicity. However, there are an additional 17 rodent bone marrow studies with GBFs that were not considered by IARC, and all were negative (see Supplemental Information, Appendix A, Table 3 of this paper). The negative studies included use of both oral and i.p. routes and maximum dose levels frequently were limit doses of 2000 mg/kg (OECD 2014b). The overwhelming majority of *in vivo* MN studies on GBFs, therefore, gave negative results. In the studies reported positive, there are indications that the results may not be biologically meaningful, or that artifacts may have resulted from use of DMSO as vehicle.

For AMPA, IARC reported one positive mouse bone marrow MN study. There was one negative regulatory mouse bone marrow MN study of AMPA not reported in IARC. Both studies used the i.p. route. The positive study used a top dose of 200 mg/kg administered on two occasions, 24 h apart. The negative study used a single top dose of 1000 mg/kg which produced signs of toxicity. There is no obvious explanation for these conflicting results and the limited data do not allow reasonable WoE conclusions for AMPA in terms of the *in vivo* MN endpoint.

DNA damage *in vitro*

As noted above, the Expert Panel is in agreement with IARC reviewers that there are several *in vitro* mammalian cell studies of glyphosate which show DNA strand break effects (more specifically the alkaline single cell gel electrophoresis or comet endpoint). However, as also noted above, these studies should be assigned low weights compared to other more relevant endpoints in evaluating genotoxic risk, particularly when the results for relevant endpoints are more abundant. An assumption that the DNA damage observed *in vitro* might be secondary to toxicity rather than leading to DNA-reactive or persistent genotoxicity is underscored by cases where the same publication reports DNA damage effects but not chromosomal alterations, e.g. Sivikova and Dianovsky (2005); Manas et al. (2009a); Mladinic et al. (2009a) without metabolic activation. Other publications reported both DNA damage and chromosomal effects, e.g. Lioi et al. (1998a); Koller et al. (2012).

For GBFs there are only two positive *in vitro* mammalian cell comet results reported by IARC. These provide limited evidence for GBF-induced DNA damage effects *in vitro* in mammalian cells.

There are a few positive *in vitro* mammalian cell SCE reports for glyphosate and GBFs reported in IARC. Since the

OECD guideline for the SCE test has recently been deleted because of a lack of understanding of the mechanism(s) detected by the test, the biological relevance of SCE is unclear, and these studies have not been further considered by the Expert Panel for a WoE evaluation.

One negative primary hepatocyte UDS result is reported by IARC for glyphosate, but there are also negative primary hepatocyte UDS results for glyphosate and AMPA (one each) not reported by IARC.

DNA damage/adducts *in vivo*

One *in vivo* mammalian DNA damage and one *in vivo* mammalian DNA adduct study of glyphosate were reported by IARC. No additional regulatory or published studies were identified. Results for 8-hydroxydeoxyguanosine (8-OHdG) measurements are considered in the oxidative stress section (Section IIIB).

Bolognesi et al. (1997) reported transient (4 h after dosing) increases in alkali-labile DNA strand breaks in liver and kidneys of mice treated i.p. with glyphosate. Interpretation of the genotoxic significance of these observations is difficult because such effects might be due to arrest of cells in S-phase or secondary to cytotoxicity (Williams et al. 2000). Peluso et al. (1998) reported no induction of adducts in mouse liver or kidney detectable by ³²P-postlabelling methodology after i.p. administration of glyphosate.

There is one positive *in vivo* SCE report for a GBF by Amer et al. (2006) which was not evaluated by IARC. For reasons of relevancy noted above, this study has not been further considered by the Expert Panel in a WoE evaluation.

One *in vivo* mammalian DNA damage and one *in vivo* mammalian DNA adduct studies of GBFs were reported by IARC. No additional regulatory or published studies were identified.

Bolognesi et al. (1997) reported transient (4 h after dosing) increases in alkali-labile DNA strand breaks in liver and kidneys of mice treated i.p. with a GBF. Similar conclusions about interpretation of these results apply as for the glyphosate results by the same authors discussed above. Peluso et al. (1998) observed ³²P-postlabelling adducts in liver and kidneys of mice dosed with a GBF. The source or identity of the adducts were not characterized although such adducts were not observed in studies with glyphosate in their publication.

No *in vivo* mammalian DNA damage studies of AMPA were reported in IARC or identified.

The paucity of data as well as the limited significance of the primary DNA damage endpoints on tumor initiation did not warrant that these observations should have a significant WoE impact.

Weight of evidence (WoE) for genotoxic effects in mammalian systems

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* chromosomal aberration studies with GBFs are all subject to concerns regarding their reliability or biological relevance.
- There is limited evidence that glyphosate induces MN *in vitro*. Although this could be a reflection of increased statistical power in the *in vitro* MN studies, the absence of clastogenic effects in a large majority of *in vitro* chromosomal studies suggests 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.

Studies in non-mammalian test systems

With the exception of the bacterial reverse mutation test, global genotoxicity testing guidelines such as those issued by OECD (2015) and other regulatory bodies do not recommend routine use of non-mammalian assays. Recently, OECD guidelines for two non-mammalian tests have been deleted because mammalian cell tests are considered more biologically relevant, and non-mammalian tests (with the exception of the bacterial reverse mutation test) are rarely used for regulatory test batteries.

Table 4.6 in the IARC Monograph summarized results from two bacterial reverse mutation test publications. One publication (Li & Long 1988) reviewed by IARC reported no mutagenic activity associated with glyphosate in a bacterial reverse mutation test but a publication by Rank et al. (1993) indicated a positive finding with a glyphosate formulation.

Rank et al. (1993) reported positive mutagenicity in TA98 only without S9 and positive mutagenicity in TA100 only with S9. At the outset this combination of responses is problematic as it is an unlikely combination and suggests that either

one or both strain/S9 responses would be in error. The study data shown in Table 2 of the Rank et al. (1993) publication indicates that the positive responses reported for TA98 and TA100 were neither dose related nor were they reproduced in repeat data sets. The authors called the results indicative of gene mutation capabilities for a GBF; however, the data should never have been accepted for publication without additional testing over a narrower range of doses and as they currently stand, do not meet commonly used criteria for declaring Ames test results positive. The data from this one publication are not in agreement with 19 bacterial reverse mutation assays of GBFs presented in Supplemental Information, Appendix A, Table 1 that were not included in the IARC Monograph. The Expert Panel considered the results of this study to be inconclusive.

A large number (20) of negative bacterial reverse mutation assays of GBFs are presented in Supplemental Information, Appendix A, Table 1. None of these were included in the IARC Monograph. There is also one negative regulatory study of AMPA.

In contrast to the two bacterial reverse studies considered in the IARC Monograph there are actually abundant data from 40 additional studies (Supplemental Information, Appendix A, Table 1) that glyphosate and GBFs are negative in the one genetic test for gene mutation considered overall to be the best non-mammalian predictor of mammalian carcinogenesis.

Publications in which glyphosate or GBFs have been tested for genotoxicity in a variety of non-mammalian species other than bacterial reverse mutation appear to be included in the IARC Monograph, with only a few regulatory or published studies not included. With the exception of two positive and one negative chromosomal aberration assays in plants for glyphosate, chromosomal effect assay results have mainly been published for GBFs and showed predominantly positive results for MN in fish and amphibians.

A larger number of DNA damage comet assays in fish and other non-mammalian species *in vitro* are reported as exhibiting predominantly positive results for glyphosate. Larger numbers of positive comet results are available for GBFs in fish and amphibian/reptile studies. One positive fish comet study is reported for AMPA.

Some general features of these non-mammalian tests should be noted. First, both major endpoints measured in the majority of non-mammalian tests (i.e. MN and comet) might well be secondary to toxic effects. Second, many of these tests involve exposure by immersion in or surface contact with the test material in water. This is certainly not a standard or relevant route of exposure for *in vivo* mammalian systems and may introduce route-specific unique toxicity and genotoxic effects. This is particularly a concern for GBFs which commonly contain surfactants.

As a consequence, the Expert Panel did not consider data from a majority of the non-mammalian systems and nonstandard tests with glyphosate, GBF, and AMPA to have significant weight in the overall genotoxicity evaluation, especially given the large number of standard core studies in the gene mutation and chromosomal effects categories available in mammalian systems. Rationale supporting this consideration

is the absence of internationally accepted guidelines for such non-mammalian test systems, lack of databases of acceptable negative control data or positive control responses, and no results from validation studies suggesting concordance with carcinogenicity. OECD guidelines specifically state that use of any nonstandard test requires justification along with stringent validation including establishing robust historical negative and positive control databases. Therefore, results in these tests, when conflicting with findings obtained in well validated test systems for which OECD guidelines exist, and where the biological relevance of the results can be evaluated, do not carry a significant WoE.

Critique of the classifications and mode of action (MoA) proposed in the IARC monograph for glyphosate and related agents

Genotoxicity classification and MoA

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

In order to demonstrate how the evidence from all sources was used to develop the Expert Panel's WoE conclusions for glyphosate, GBFs, and AMPA, the results from all study types were compiled in Table 3. Wherever possible, positive or negative responses were assigned to the individual studies in Table 3 according to the conclusions given in the original publication or report. In a small number of studies the Expert Panel concluded that there were significant issues regarding data analysis and interpretation of results and either changed the positive call given by IARC, e.g. Bolognesi et al. (2009) or, if the impact of the issues on the overall conclusions of the study was considered inconclusive, the data from that paper were excluded from Table 3, e.g. Paz-y-Miño et al. (2007) and Rank et al. (1993).

It should also be noted that the weight indicated in this table primarily reflects the endpoint of the publication or report. As noted above, there are significant test system (experimental protocol and data interpretation) considerations for some specific studies that significantly lowered the weight of these studies independently of the endpoint measured.

An evaluation of the studies in Table 3 according to their relative contributions to a WoE produced the following results:

- Test methods identified as providing low contribution (Low Weight) to the WoE 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 with respect to carcinogenicity prediction or carcinogenic mechanism 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 Expert Panel 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 by the Expert Panel.

Contrary to IARC's conclusion that there is strong evidence of genotoxicity, the Expert Panel's WoE analysis of the complete database (or the IARC subset alone) using the weighting categories proposed in Suter and Cormier (2011) indicates that glyphosate and GBFs should not be classified as genotoxic. The panel does not agree with IARC's conclusion of moderate evidence for genotoxicity of AMPA. The data needed to make an assessment of the genetic hazard of AMPA are too limited and conflicting to reliably support such a classification.

To provide greater emphasis to the Expert Panel's WoE conclusion, Table 4 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.

Oxidative stress classification and MoA

Oxidative stress was the second characteristic considered by IARC as operative in human carcinogens and thus supporting their classifying glyphosate as probably carcinogenic to humans. Publications investigating the relationship between oxidative DNA damage and cancer (Wu et al. 2004; Klaunig et al. 2010) have demonstrated that following exposure to oxidative stress-inducing agents, a common adaptive response induced in mammalian cells is the up-regulation of stress-response genes. The resultant toxic response is threshold dependent.

It has been shown that reactive oxygen species (ROS) are genotoxic in principle, and the question arises as to whether GBFs that increase ROS production will add to an endogenously produced background level of DNA lesions or whether compensatory mechanisms may result in non-linear dose-effects. Halliwell (2003) reported that alteration to DNA molecules triggers repair, and frequent activation may increase the general repair capacity, irrespective of the cause of the damage. Thus, repeated exposure to ROS may lead to an adaptive response, mitigating the mutagenicity of oxidative DNA lesions. Moreover, as suggested by Deferme et al. (2015) oxidative stress is not uniquely associated with a genotoxic carcinogen and simple measurements of ROS are insufficient

Table 3. Summary of Expert Panel's evaluation of human, non-human mammalian, and selected microbial genotoxicity studies from IARC Section 4.2.1 and other published sources.

Source	Test category	Endpoint	Weight	Glyphosate (Pos/Neg)	GBFs (Pos/Neg)	AMPA (Pos/Neg)	Total (Pos/Neg)	
Kier and Kirkland (2013) and other published studies not included in IARC	Bacterial Reverse Mutation	Gene mutation	High	0/19	0/20	0/1	0/40	
	Mammalian <i>In Vitro</i>	Gene mutation	Moderate	0/2	ND	ND	0/2	
		Chromosomal 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 <i>In Vivo</i>	Chromosomal 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	
	IARC Monograph 112	Bacterial Reverse Mutation	Gene mutation	High	0/1	0/0	ND	0/1
Mammalian <i>In Vitro</i>		Gene mutation	Moderate	0/1	ND	ND	0/1	
		Chromosomal 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 <i>In Vivo</i>	Chromosomal 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 <i>In Vivo</i>		Chromosomal 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	5/45	1/2	8/84	
Moderate Weight Combined Totals (IARC results only)				12/4	13/5	1/0	16/9	
Low Weight Combined Totals (IARC results only)				7/10	3/0	2/0	12/10	
High Weight Combined Totals (IARC results only)				4/3	11/0	2/0	17/3	
Moderate Weight Combined Totals (IARC results only)				5/2	2/0	1/1	8/3	
Low Weight Combined Totals (IARC results only)				15/1	2/0	1/0	18/1	

AMPA aminomethylphosphonic acid; GBFs: glyphosate based formulations; ND: no data.

All responses based on study critiques and conclusions of Expert Panel members.

Non-mammalian responses from IARC monograph in this table did not include four positive studies measuring DNA strand breaks in bacteria and one negative Rec assay in bacteria from IARC monograph Table 4.6

Table 4. 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 in Section 4.2.1
Profile of test responses in genetic assays	Positive effects across multiple key predictive endpoints (i.e. gene mutation, chromosomal aberrations, aneuploidy) both <i>in vitro</i> and <i>in vivo</i>	No valid evidence for gene mutation in any test; no evidence for chromosomal 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 <i>in vitro</i> and <i>in vivo</i>	Conflicting and/or non-reproducible responses in the same test or test category both <i>in vitro</i> and <i>in vivo</i>
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 nontoxic exposure levels	Positive responses typically associated with evidence of overt toxicity

evidence supporting a genotoxic causal MoA for carcinogenicity (Aral et al. 2006).

The evidence for oxidative stress induction summarized by IARC comes from studies employing a variety of endpoints and test systems, but in the IARC Monograph the data on oxidative stress are comingled with data from other endpoints, and data on glyphosate and GBFs are also comingled. It is therefore difficult to obtain a clear picture of the oxidative stress effects.

Indirect measures of oxidative stress vs. measures of oxidative damage

In some respects, measures (endpoints) of oxidative effects can be weighted in a manner similar to that applied to

measures of genotoxicity. For example, in the majority of the studies reviewed by IARC, the endpoints assessed were only indirect measures of oxidative stress, in the form of antioxidant suppressive effects, changes in endogenous levels of protective molecules or enzymes (e.g. glutathione, superoxide dismutase) or changes in ROS (e.g. H₂O₂). The experiments *in vitro* in mammalian cells produced conflicting results and some positive results were observed only at very high dose levels which could be problematic for reliable evaluation of the potential for *in vivo* oxidative stress (Halliwell 2003). Long et al. (2007) demonstrated that reactive oxygen can be produced as an artifact by chemical reactions with components of the culture media, a possibility not evaluated in the studies reviewed by IARC. Overall, IARC's assessment did not appear to consider the relative importance of different

biomarkers of oxidative stress with the exception of noting limitations of using dihydrofluorescein acetate as a marker of oxidative stress.

A more meaningful endpoint for identification of oxidative damage, particularly as it pertains to identification of a possible genotoxic mechanism of cancer, would be the identification and application of a biomarker relevant to oxidative stress-induced damage to DNA. While a number of biochemical and physiological changes in cells can be produced during oxidative stress, the most extensively studied oxidative DNA lesion produced is 8-OHdG. This adduct has been widely used as a biomarker of oxidative DNA damage, and determination of 8-OHdG levels may be useful in defining a chemical's MoA.

Oxidative damage studies evaluated in the IARC monograph

Peluso et al. (1998) reported ³²P-postlabelling adducts in rats treated with GBFs (but not glyphosate). The nature or source of the adducts was not identified but Williams et al. (2000) noted that the solvent system used by Peluso et al. (1998) could not detect oxidative DNA damage. Evidence for increased DNA damage in Bolognesi et al. (1997) as measured by 8-OHdG DNA adducts was both limited and contradictory. Glyphosate was reported to induce 8-OHdG adducts in liver but not kidney tissues whereas a GBF (with an equivalent level of glyphosate) was reported to induce 8-OHdG adducts in kidney but not in liver tissue. Results of the Bolognesi et al. (1997) study are contradicted by another published study (Heydens et al. 2008) that was not considered by IARC. In this study no statistically significant increases in 8-OHdG were observed in liver or kidneys of mice 24 h after treatment by i.p. injection with 600 and 900 mg/kg of a GBF of the same composition as those used by Peluso et al. (1998) and Bolognesi et al. (1997).

The only other cited mammalian study examining oxidative DNA damage was a measurement of the effect of human 8-oxoguanine DNA N-glycosylase 1 (hOGG1) on the comet endpoint in human lymphocytes exposed to glyphosate (Mladinic et al. 2009a). This study showed a small but statistically significant effect on comet tail intensity at only a low mid-dose level in the absence of an S9 metabolic activation system and at the highest dose level tested (580 µg/mL) in the presence of S9. The observation of an effect at the highest dose level only in the presence of S9 is unusual because statistically significant increases in other markers of oxidative stress were observed at the high dose levels in either the presence or absence of S9. The authors indicated that their results were not considered an unequivocal indication of the oxidative potential of glyphosate. As noted above there does not appear to be any significant *in vitro* metabolism of glyphosate with rat liver homogenate (Gohre et al. 1987).

A series of studies in eels examined oxidative DNA damage of glyphosate, GBF, and AMPA by measurement of comet endpoints with and without treatment of samples with endonucleases that cleave at sites of oxidative damage (Guilherme et al. 2012a, 2012b; Guilherme et al. 2014a, 2014b; Marques

et al. 2014a, 2014b). When considering net effects of endonuclease treatment there were varied responses in different conditions, tissues, and treatments ranging from no statistically significant effect to relatively small but statistically significant effects. These studies did not provide consistent strong evidence of oxidative DNA damage in a non-mammalian system.

In addition there was a human biomonitoring study measuring blood 8-OHdG which did not indicate a statistically significant association between previous GBF exposure and high 8-OHdG levels (Koureas et al. 2014, not evaluated in IARC). There are concerns with this study, particularly the relationship between the timing of exposure and a presumably transient marker of exposure. While some other agents did show associations, the lack of a statistically significant association between 8-OHdG and past GBF exposure does not provide support for GBF-related oxidative DNA damage in humans.

Many more oxidative stress studies are available for GBFs than for glyphosate or AMPA. Unlike glyphosate, most of the GBF studies show evidence of oxidative stress suggesting that GBFs contain compounds that are likely to be toxic under some treatment conditions leading to ROS followed by normal cellular protective responses. Comparison of GBF oxidative stress study results with predicted human exposure levels (e.g. calculated 90th percentile for applicators of 0.064 mg/kg body weight/day and much lower for other exposures), suggests that it is not likely that GBFs would induce oxidative stress likely to exceed endogenous detoxification capacities.

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

Research on oxidative stress induced genotoxicity suggests that it is often a secondary response to toxicity and characterized by a threshold (Pratt & Barron 2003). Therefore the most appropriate conclusion supported by the oxidative stress data presented in IARC Monograph Section 4.2 is that there is not a strong WoE 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.

Summary and conclusions

Detection of genotoxic activity or induction of oxidative stress/damage in any test conducted with a chemical does

not, *a priori*, mean that the agent has a carcinogenic potential, induces key events leading to tumor development or represents an *in vivo* genotoxic risk. A systematic and critical assessment of the WoE is required before genotoxic hazard and MoA conclusions can be reached. The IARC process leading to conclusions suggesting modes of action involving genotoxicity and oxidative stress was incomplete (excluding valuable data) and did not appear to critically evaluate some of the key studies it relied upon. A meaningful WoE evaluation depends on an assessment of all available data using an appropriate weighting process.

A number of reviews of the carcinogenicity, genotoxicity, and oxidative stress/damage for glyphosate, AMPA, and GBFs were available prior to the development of the IARC Glyphosate Monograph (see Introduction). These prior reviews included much of the data available to IARC reviewers involved in the evaluation presented in the IARC Monograph. In general, genetic toxicology data evaluated in these prior reviews all support a conclusion that glyphosate (and related materials) is inherently not genotoxic. 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 and that including the study results reviewed by Kier and Kirkland (2013) would provide considerable additional support to the conclusion of absence of inherent genotoxic potential.

- The Expert Panel concluded that glyphosate, GBFs, and AMPA genotoxicity response profiles are not consistent with characteristics of genotoxic carcinogens (Table 4).
- There is substantial evidence, particularly in bacterial reverse mutation assays, demonstrating that glyphosate, GBFs, or AMPA do not induce gene mutation from either direct or oxidative induced mechanisms.
- The evidence indicating that glyphosate can produce chromosomal aberrations in mammalian systems is very limited, conflicting, and potentially due to secondary mechanisms.
- The absence of evidence indicating that glyphosate or GBFs induced lesions characteristic of genotoxic carcinogens, in well-validated test systems with robust experimental protocols, invalidates conclusions that glyphosate or GBFs might act via a genotoxic MoA.
- The evidence for oxidative stress/damage as a mechanism or predictor of carcinogenesis is unconvincing. Repeated exposure to ROS most likely leads to adaptive responses, mitigating the mutagenicity of oxidative DNA lesions. Studies directed toward a better understanding of this relationship for glyphosate or GBF related exposures have not been reported.
- There is little or no reliable evidence that GBFs, at levels experienced across a broad range of end-user exposures, poses any human genotoxic hazard/risk.

The Expert Panel concluded that the IARC assessment of classifications regarding strong evidence of genotoxicity and oxidative stress capabilities of glyphosate, GBFs, and AMPA is not supported by the available data. A critical review of the complete dataset by the Expert Panel supports a conclusion

that glyphosate (including GBFs and AMPA) does not pose a genotoxic hazard and therefore, should not be considered support for the classification of glyphosate as a genotoxic carcinogen. These conclusions are supportive of recent reviews that have occurred during the preparation of this review. A European Food Safety Authority peer review concluded that glyphosate is unlikely to pose a carcinogenic hazard to humans (EFSA 2015) and a Joint FAO/WHO Meeting on Pesticide Residues concluded that glyphosate is unlikely to be genotoxic at anticipated dietary exposures and unlikely to cause a carcinogenic risk to humans from dietary exposure (JMPR 2016).

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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. Gary Williams, David Brusick, and David Kirkland have previously served as independent consultants for the Monsanto Company on the European Glyphosate Task Force. Gary Williams has consulted for Monsanto on litigation matters involving glyphosate. Larry Kier was previously an employee of the Monsanto Company. Marilyn Aardema has not previously been employed in the Monsanto Company or previously been involved in any activity involving glyphosate and as such declares no potential conflicts of interest. Furthermore, other than Gary Williams, none of the aforementioned authors have been involved in any litigation procedures involving glyphosate.

The Expert Panel Members recruitment and evaluation of the data were organized and conducted by Intertek Scientific & Regulatory Consultancy (Intertek). The Expert Panelists acted as consultants for Intertek. 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 Scientific & Regulatory Consultancy has not previously worked on glyphosate related matters for the Monsanto Company, previous employees of Cantox had worked in this capacity.

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Supplemental material

Supplemental material for this article is available online [here](#).

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Expression of Concern

Critical Reviews in Toxicology, 46(S1): 'An Independent Review of the Carcinogenic Potential of Glyphosate'

We, the Editor-in-Chief and Publisher of the journal, have been informed of concerns over the completeness of acknowledged contributions to the above supplement, and in the declarations of interest provided by the named contributors, for the following articles:

Williams, G. M., Aardema, M., Acquavella, J., Berry, C., Brusick, D., Burns, M. M., de Camargo, J. L. V., Garabrant, D., Greim, H. A., Kier, L. D., Kirkland, D. J., Marsh, G., Solomon, K. R., Sorahan, T., Roberts, A., & Weed, D. L. (2016). A review of the carcinogenic potential of glyphosate by four independent expert panels and comparison to the IARC assessment. *Critical Reviews in Toxicology*, 46(S1), pp. 3–20.

Solomon, K. R. (2016). Glyphosate in the general population and in applicators: a critical review of studies on exposures. *Critical Reviews in Toxicology*, 46(S1), pp. 21–27.

Acquavella, J., Garabrant, D., Marsh, G., Solomon, K. R., Sorahan, T., & Weed, D. L. (2016). Glyphosate epidemiology expert panel review: a weight of evidence systematic review of the relationship between glyphosate exposure and non-

Hodgkin's lymphoma or multiple myeloma. *Critical Reviews in Toxicology*, 46(S1), pp. 28–43.

Williams, G. M., Berry, C., Burns, M. M., de Camargo, J. L. V., & Greim, H. A. (2016). Glyphosate rodent carcinogenicity bioassay expert panel review. *Critical Reviews in Toxicology*, 46(S1), pp. 44–55.

Brusick, D., Aardema, M., Kier, L. D., Kirkland, D. J., & Williams, G. (2016). Genotoxicity Expert Panel review: weight of evidence evaluation of the genotoxicity of glyphosate, glyphosate-based formulations, and aminomethylphosphonic acid. *Critical Reviews in Toxicology*, 46(S1), pp. 56–74.

We have requested corrigenda from the authors to provide additional disclosure as to contributions to the articles. To date, we have only received corrigenda for three of the five articles that have been agreed by all authors. We have not received an adequate explanation as to why the necessary level of transparency was not met on first submission. We thank those who brought this matter to our attention. When reading the articles, we recommend that readers take this context into account. We will continue to work to update these articles and ensure full disclosure of all contributions to them.

Expression of Concern

Critical Reviews in Toxicology, 46(51): 'An Independent Review of the Carcinogenic Potential of Glyphosate'

With the cooperation of the authors, we, the Editor-in-Chief and Publisher of the journal, have published corrigenda for each of the following articles:

Williams GM, Aardema M, Acquavella J, Berry C, Brusick D, Burns MM, de Camargo JLV, Garabrant D, Greim HA, Kier LD, 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.* 46(51):3–20.

Solomon KR. 2016. Glyphosate in the general population and in applicators: a critical review of studies on exposures. *Crit Rev Toxicol.* 46(51):21–27.

Acquavella J, Garabrant D, Marsh G, Solomon KR, Sorahan T, Weed DL. 2016. Glyphosate epidemiology expert panel review: a weight of evidence systematic review of the relationship between glyphosate exposure and non-Hodgkin's lymphoma or multiple myeloma. *Crit Rev Toxicol.* 46(51):28–43.

Williams GM, Berry C, Burns MM, de Camargo JLV, Greim HA. 2016. Glyphosate rodent carcinogenicity bioassay expert panel review. *Crit Rev Toxicol.* 46(51):44–55.

Brusick D, Aardema M, Kier LD, Kirkland DJ, Williams G. 2016. Genotoxicity Expert Panel review: weight of evidence evaluation of the genotoxicity of glyphosate, glyphosate-based formulations, and aminomethylphosphonic acid. *Crit Rev Toxicol.* 46(51):56–74.

After investigation into the completeness of the original declarations of interest provided by the authors, it was found that these did not fully represent the involvement of Monsanto or its employees or contractors in the authorship of the articles.

These corrigenda provide additional disclosure as to contributions to the articles, in some places in contradiction to the statements originally supplied.

We have not received an adequate explanation as to why the necessary level of transparency was not met on first submission and welcome the opportunity to address this. We regret that these corrections were necessary and thank those who brought this matter to our attention.

To the best of our knowledge, the scholarly record is now accurate; however, we recommend that readers take the additional context the corrected disclosures provide into account when reading the articles.

Correction

Article title: A review of the carcinogenic potential of glyphosate by four independent expert panels and comparison to the IARC assessment.

Authors: Williams, G. M., Aardema, M., Acquavella, J., Berry, C., Brusick, D., Burns, M. M., de Camargo, J. L. V., Garabrant, D., Greim, H. A., Kier, L. D., Kirkland, D. J., Marsh, G., Solomon, K. R., Sorahan, T., Roberts, A., & Weed, D. L.

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When this article was originally published on 28th September 2016, the contributions, contractual status and potential competing interests of all authors and non-author contributors were not fully disclosed to *Critical Reviews in Toxicology*. Specifically, the Acknowledgements and Declaration of Interest were not complete. After further clarification from the authors, these sections are corrected to reflect the full contributions, contractual status and, potential competing interests of all authors and non-author contributors and read as follows:

Acknowledgements

The authors gratefully acknowledge the extensive comments received from nine independent reviewers selected by the Editor and who were anonymous to the authors. These comments were very helpful in revising the manuscript. Ashley Roberts would like to thank his colleague at Intertek, Barry Lynch, for assistance in the preparation of the manuscript and William Heydens of Monsanto for providing a regulatory history overview for use by the authors in the preparation of this overview paper and his review of a preliminary draft of the overview manuscript and the final manuscript. The authors welcome the opportunity to correct the omission of the contributions of Barry Lynch, Intertek, and William Heydens, Monsanto in the original Acknowledgments. These individuals were not considered for authorship because they did not participate in the deliberations of the Panel and did not contribute to the conclusions drawn by the Panel. The conclusions were independently formulated by each of four Panel Sub-Groups as detailed in the individual papers.

Declaration of Interest

This overview paper (paper) is part of a supplement, the preparation of which was coordinated by Intertek Scientific & Regulatory Consultancy (Intertek) under the leadership of Ashley Roberts. It was prepared subsequent to completion of the four manuscripts as an overview and presented the opinions and conclusions of four groups of the expert panel.

The expert panels were organized and supported administratively by Intertek. Funding was provided to Intertek by Monsanto Company, which is a primary producer and marketer of glyphosate and related products. All the expert panelists other than John Acquavella and Larry D. Kier were compensated through a contract with Intertek. John Acquavella and Larry D. Kier were compensated through existing consulting contracts with Monsanto Company. The employment affiliations of the authors are as shown on the cover page. The authors participated in the review process and preparation of this overview paper as independent professionals and not as representatives of their employers.

Monsanto also supported presentation of the Panel's findings and conclusions by Gary Williams and Tom Sorahan as a poster entitled "Expert Panel Review of the Carcinogenic Potential of the Herbicide Glyphosate" at the Society for Risk Analysis Annual Meeting in Arlington, VA, December 6-10, 2015, prior to the publication of the manuscripts.

William Heydens of Monsanto reviewed a draft of this overview paper and suggested wording changes but did not comment on the opinions and conclusions of the expert panel. The opinions expressed, and final conclusions set out in this overview paper were those of the listed authors and no one else.

While Intertek (formerly Cantox) has not previously worked on glyphosate-related matters for the Monsanto Company, previous employees (Ian Munro and Douglass Bryant) of Cantox, have worked in this capacity. Ian Munro and Gary Williams, with the assistance of Douglass Bryant, prepared a safety and risk assessment of Roundup® herbicide (glyphosate), which was supported by Monsanto (Williams et al, 2000).

Gary Williams, Sir Colin Berry, David Brusick, Joao Lauro Viana de Camargo, Helmut A. Greim, David J. Kirkland, and Tom Sorahan have previously served as independent consultants for the Monsanto Company, some serving on the European Glyphosate Task Force. Keith R. Solomon previously served as an independent consultant for the Monsanto Company on the deregulation of RR alfalfa in the US (2012-2014). In collaboration with Cantox, Dr. Solomon contributed to an ecotoxicological risk assessment for Roundup® herbicide, which was published (Giesy et al, 2000). In addition, between 2014 and 2016, he served on a scientific advisory board to Dow AgroSciences, which markets pesticides, including glyphosate. John Acquavella and Larry D. Kier have also served as independent consultants and were previously employees of the Monsanto Company. John Acquavella was employed by Monsanto between the years 1989 and 2004. He is a consultant on a legal case unrelated to glyphosate that involved a former Monsanto industrial chemical plant. Larry Kier was employed as a consultant by Monsanto to provide support for the Glyphosate Expert Panel in the areas of genotoxicity and oxidative stress. Larry Kier did review the report as it was being written and provided his expertise when requested by the panel members. After the final draft of the report was written Larry was added as a co-author and genotoxicity Expert Panel member based on a unanimous decision of the original genotoxicity Expert Panel Members.

Helmut Greim has previously reviewed the available long-term studies in rodents and has published a paper (Greim et al., 2015) together with three coauthors. One of them, an employee of Monsanto, provided the original data from the studies conducted by Monsanto, the other two authors were independent consultants, one of them a member of the glyphosate task force.

David Garabrant served in 2014-16 on a scientific advisory board to Dow Agro Sciences, which markets pesticides including glyphosate. He was jointly retained by Bayer Corporation; Bayer CropScience LP; Bayer CropScience Holding, Inc.; Dow AgroSciences, L.L.C.; BASF Corporation; Syngenta Crop Protection, Inc., Deere & Company, Lesco, Inc.; and Monsanto in litigation matters concerning glyphosate and leukemia. He also provided consultation in February 2016 to an attorney representing Pharmacia (formerly Monsanto) in litigation that did not involve glyphosate. Tom Sorahan has consulted for Monsanto on litigation matters involving glyphosate. Tom Sorahan has received consultancy fees and travel grants from Monsanto Europe SA/NV as a member of the European Glyphosate Toxicology Advisory Panel and participated in the IARC Monograph Meeting for volume 112, as an Observer for the Monsanto Company. Douglas L. Weed has consulted on litigation matters for Monsanto that did not involve glyphosate.

Other than David Garabrant and Tom Sorahan, none of the authors had previously been involved in any litigation procedures involving Monsanto and glyphosate.

Marilyn Aardema, Michele M. Burns, Gary Marsh and Ashley Roberts had not been previously involved in any activity involving glyphosate and as such declare no potential conflicts of interest.

The authors apologize for any errors or omissions in the original disclosure.

Corrigendum

Solomon KR, (2016). Glyphosate in the general population and in applicators: a critical review of studies on exposures. *Crit Rev Toxicol*. 46(51), pp. 21–27.

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When this article was originally published on 28th September 2016, the contributions, contractual status and potential competing interests of all authors and non-author contributors were not fully disclosed. Specifically, the Declaration of Interest were not complete. These sections should read as follows:

Acknowledgment

The author gratefully acknowledges the extensive comments offered by five reviewers selected by the Editor and presented anonymously to the author. These comments were useful in revising the paper. I thank Monsanto Inc. for providing access to reports from exposure studies for glyphosate in applicators and Dr. Marian Bleeke (of Monsanto Inc.) for clarification of some of the methods used. I wish to thank the authors of the other papers in this series for their constructive suggestions and comments.

Declaration of interest

The employment affiliation of the author is shown on the cover page. However, it should be recognized that the author participated in the review process and preparation of this paper as an independent professional and not as a representative of his employer. Keith R. Solomon previously served as an independent consultant for the Monsanto Company on the deregulation of RR alfalfa in the US (2012–2014). In collaboration with Cantox, the predecessor company to Intertek Scientific and Regulatory Consultancy (Intertek) KRS contributed to an ecotoxicological risk assessment for Roundup® herbicide, which was published (Giesy et al., 2000). In addition, between 2014 and 2016, he served on a scientific advisory board to Dow AgroSciences, which markets pesticides including glyphosate. KRS has not been involved in any litigation procedures involving Monsanto Company and glyphosate. KRS's recruitment and evaluation of the data was organized and conducted by Intertek, acted as a consultant for Intertek. Intertek is a consultancy firm that provides scientific and regulatory advice, as well as safety and efficacy evaluations for the chemical, food and pharmaceutical industries. Intertek prepared the paper for submission to the journal, made some formatting and editorial changes prior to submission, and, after review provided the comments from the reviewers to KRS. KRS was not provided with comments from William Heydens of Monsanto Inc., either directly or via Intertek.

While Intertek Scientific & Regulatory Consultancy (Intertek) has not previously worked on glyphosate related matters for the Monsanto Company, previous employees of Cantox, the predecessor company to Intertek, had worked in this capacity. 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.

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.

The author apologizes for these errors.

Corrigendum

Acquavella J, Garabrant D, Marsh G, Sorahan T, Weed DL. (2016). Glyphosate epidemiology expert panel review: a weight of evidence systematic review of the relationship between glyphosate exposure and non-Hodgkin's lymphoma or multiple myeloma. *Crit Rev Toxicol.* 46(51), pp. 28–43.

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Acknowledgements

The authors gratefully acknowledge the very useful comments provided by seven reviewers who were selected by the Editor and anonymous to the authors. These comments helped improve the manuscript. William Heydens of Monsanto reviewed the initial draft of our manuscript and commented that the section on analytic selection bias was unclear to him and that we might define the term "grey literature." He also pointed out some typographical errors. Based on his feedback, the authors decided to clarify the section on analytic selection bias, define grey literature in a footnote, and correct the typos. All additions, deletions, and changes to the draft manuscript were made only by the authors, with unanimous agreement.

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. This expert panel evaluation was organized and conducted by Intertek Scientific & Regulatory Consultancy. Funding for this evaluation was provided by Monsanto Company, which is a primary producer of glyphosate and products containing this active ingredient. The authors had sole responsibility for the content of the paper, and the interpretations and opinions expressed in the paper are those of the authors.

JA worked for Monsanto from 1989 through 2004. He is currently a consultant on a legal case unrelated to glyphosate that involves a former Monsanto industrial chemical plant. DG serves on a scientific advisory board to Dow Agro Sciences, which markets pesticides including glyphosate. He was jointly retained by Bayer Corporation; Bayer CropScience LP; Bayer CropScience Holding, Inc.; Dow AgroSciences, L.L.C.; BASF Corporation, Syngenta Crop Protection, Inc., Deere & Company, Lesco, Inc.; and Monsanto in litigation matters concerning glyphosate and leukemia. He also provided consultation in February 2016 to an attorney representing Pharmacia (formerly Monsanto) in litigation that did not involve glyphosate. That consultation consisted of 0.3 hours of professional services, after which he did no further work on the litigation. GM has no additional declarations. TS has received consultancy fees and travel grants from Monsanto Europe SA/NV as a member of the European Glyphosate Toxicology Advisory Panel and participated in the IARC Monograph Meeting for volume 112 which reviewed the literature and provided a carcinogenic hazard assessment for glyphosate as an Observer for the Monsanto Company. In addition, TS has consulted for Monsanto on litigation matters involving glyphosate. DW has consulted on litigation matters concerning Monsanto that did not involve 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. JA was paid directly by Monsanto for his work on this expert panel through an existing consultant contract. The other authors (DG, GM, TS, DW) were paid by Intertek, which was funded by Monsanto.

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.

The authors apologize for these errors.

Corrigendum

Williams, G. M., Berry, C., Burns, M. M., de Camargo, J. L. V., & Greim, H. A. (2016). Glyphosate rodent carcinogenicity bioassay expert panel review. *Critical Reviews in Toxicology*, 46(51), pp. 44–55.

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Acknowledgements

The authors gratefully acknowledge the extensive comments received from nine independent reviewers selected by the Editor and who were anonymous to the authors. These comments were very helpful in revising the manuscript. Materials for consideration for use in the preparation of this paper were provided by Intertek. The authors thank Barry Lynch of Intertek for writing the Introduction to the paper. Dr. Williams thanks his colleague, Dr. Michael J. Iatropoulos for assistance in writing the section on mouse kidney tumors, and Ms. Sharon Brana for typing the manuscript.

Declaration of Interest

This paper is part of a series on glyphosate, which was sponsored and supported by Intertek Scientific & Regulatory Consultancy (Intertek) under the leadership of Ashley Roberts. Funding for preparation of this supplement was provided to Intertek by the Monsanto Company, which is a primary producer of glyphosate and products containing this active ingredient.

The employment affiliations of the authors of the carcinogenicity group of the expert panel are as shown on the cover page. 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 carcinogenicity group members recruitment and the evaluation of the data was organized and conducted by Intertek Scientific & Regulatory Consultancy (Intertek). The group panelists were engaged by Intertek, and acted as consultants to Intertek and were not directly contacted by the Monsanto Company. 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, Douglass W. Bryant, Barry Lynch) of Cantox, have worked in this capacity. Gary Williams coauthored a review of Roundup herbicide (glyphosate) (Williams et al, 2000), which was supported by Monsanto. Gary Williams, Sir Colin Berry, Jo~ao Lauro Viana de Camargo, and Helmut Greim have previously served as independent consultants for the Monsanto Company, some on the European Glyphosate Task Force. Helmut Greim has previously reviewed the available long-term studies in rodents and has published a paper (Greim et al., 2015) together with three coauthors. One of them, an employee of Monsanto, provided the original data of the Monsanto studies, the other two were independent consultants, one of them a member of the glyphosate task force. Michele Burns has not previously been involved in any activity involving glyphosate and as such declares no potential conflict of interest. None of the aforementioned authors have been involved in any litigation procedures concerning glyphosate.

Neither any Monsanto company employees nor any attorney provided any review of the Expert Panel's manuscript analysis and conclusions prior to submission to the journal.

The authors apologize for these errors.

Corrigendum

Brusick D, Aardema M, Kier LD, Kirkland DJ, Williams G. (2016). Genotoxicity Expert Panel review: weight of evidence evaluation of the genotoxicity of glyphosate, glyphosate-based formulations, and aminomethylphosphonic acid. *Crit Rev Toxicol.* 46(51), pp. 56–74.

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Acknowledgements

The authors gratefully acknowledge the extensive comments received from seven independent reviewers selected by the Editor and who were anonymous to the authors. These comments were very helpful in revising the original submitted manuscript. The authors also gratefully acknowledge the clerical assistance of Anna Bickel, a Monsanto employee, in formatting the final paper prior to submission to the journal.

Declaration of interest

The employment affiliation of the authors is as shown on the cover page. Each individual participated in the review process and preparation of this paper as an independent professional. No individuals other than the cited authors were involved in developing the analysis and conclusions of the manuscript prior to its submission to the journal.

The Expert Panel Member recruitment was organized and conducted by Intertek Scientific & Regulatory Consultancy (Intertek) and the initial Expert Panelists worked under individual consulting contracts with Intertek. 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 Scientific & Regulatory Consultancy has not previously worked on glyphosate related matters for the Monsanto Company, previous employees of Cantox had worked in this capacity.

Larry Kier did not have a consulting contract with Intertek; he was employed as a consultant by Monsanto to provide support for the Glyphosate Expert Panel in the areas of genotoxicity and oxidative stress. LK did review the report as it was being written and provided his expertise when requested by the panel members. After the final draft of the report was written Larry was added as a co-author and genotoxicity Expert Panel member based on a unanimous decision of the original genotoxicity Expert Panel Members.

Gary Williams, David Brusick, and David Kirkland have previously served as independent consultants for the Monsanto Company, some serving on the European Glyphosate Task Force. Larry Kier was previously an employee of the Monsanto Company (1974-2000) and has also served as an independent consultant for Monsanto Company. As consultants to the Glyphosate Task Force LK and DK prepared and published a review of the genotoxicity of glyphosate and glyphosate-based formulations (Kier and Kirkland, 2013) and as a consultant to Monsanto LK prepared and published a review of genotoxicity biomonitoring studies of glyphosate-based formulations (Kier, 2015). Marilyn Aardema has not previously been employed in the Monsanto Company or previously been involved in any activity involving glyphosate and as such declares no potential conflicts of interest. Ian Munro, Douglass W. Bryant, and Gary Williams prepared a safety and risk assessment paper of Roundup herbicide (glyphosate) (Williams G.M. et al., 2000).

Except for assistance with final formatting, neither any Monsanto company employees nor any attorney provided any review of the Expert Panel's manuscript analysis and conclusions prior to submission to the journal.

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.

The authors apologize for these errors.

- (6) All communications with Monsanto related to GBFs, AMPA, and/or surfactants for GBFs.

Response:

Roger O. McClellan has had no communications with Monsanto personnel related to GBFs, AMPA and/or surfactants for GBFs except as related to specific manuscripts submitted to Critical Reviews in Toxicology and disclosed below.

- (7) All communications with Intertek, Inc related to GBFs, AMPA, and/or surfactants for GBFs.

Response:

The only communications between Roger O. McClellan and Intertek, Inc. personnel related to GBFs, AMPA and/or surfactants for GBFs are those with Ashley Roberts in his role coordinating the preparation and publication of five papers included in the Special Supplement to Volume 46 (2016) of Critical Reviews in Toxicology as noted in Item 10 below.

- (8) All communications with Dr. Larry Kier related to GBFs, AMPA, and/or surfactants for GBFs.

Response:

The only communications Roger O. McClellan has had with Dr. Larry Kier related to GBFs, AMPA, and/or surfactants for GBFs are communications in McClellan's role as Editor-in-Chief of Critical Reviews in Toxicology and specifically relate to manuscripts authored or co-authored by Dr. Kier as identified below:

Larry D. Kier and David J. Kirkland (2013). Review of genotoxicity studies of glyphosate and glyphosate-based formulations. *Crit. Rev. in Toxicol.* 43(4):283-315.

Larry D. Kier (2015). Review of genotoxicity biomonitoring studies of glyphosate-based formulations. *Crit. Rev. in Toxicol.* 45(3):209-218.

Brusick, D., Aardema, M., Kier, L., Kirkland, D. and William, G. (2016). Genotoxicity expert panel review: Weight of evidence evaluation of the genotoxicity of glyphosate, glyphosate-based formulations, and aminomethylphosphonic acid. *Crit. Rev. in Toxicol.* 46 (Special Supplement): 56-74.

Copies of those published papers were provided in response to Item 5.

The third paper listed, authored by Brusick et al. (2016), which included Dr. Larry Kier as a co-author, was included in a special investigation addressed in Item 15.

Roger McClellan

From: Roger McClellan <[REDACTED]@att.net>
Sent: Monday, February 25, 2013 8:52 AM
To: Claire Summerfield
Cc: Bridget Sheppard; Lindsay Duncan; Mildred Morgan; Roger O. McClellan
Subject: Fw: Revised Proof Corrections/ Like to see it

Claire:

Welcome back> I was surprized I did not receive the revised galley's for review. Please send me a copy. I am curious as to how they turned out. I appreciate everyone's help with this manuscript.

Regards,
Roger

----- Forwarded Message -----

From: Larry Kier <[REDACTED]@q.com>
To: Roger O. McLellan <[REDACTED]@att.net>
Sent: Mon, February 25, 2013 8:16:34 AM
Subject: Revised Proof Corrections

Roger,

I received the revised proof on Friday and submitted corrections on Saturday morning. The corrections certainly weren't anything major but they were definitely worthwhile.

They were received and I believe they are being processed which shouldn't take much time at all.

Thanks for your help with this process.

Larry Kier

Roger McClellan

From: SALT MIRAS, DAVID A (AG/1000) <[REDACTED]@monsanto.com>
Sent: Thursday, January 9, 2014 2:35 PM
To: roger.o.mcclellan@[REDACTED]
Subject: Glyphosate carcinogenicity review manuscript

Roger,

I have been meaning to update you for some time on our progress on a glyphosate carcinogenicity review manuscript. We are making a few modifications since the Seralini paper was recently retracted by *Food & Chemical Toxicology*. We are also hard at work evaluating the tumor data tables on the thirteen industry studies (8 rat and 5 mouse). However, we just received the EU Rapporteur's Reevaluation Assessment Report (RAR) for glyphosate's EU Annex I Renewal, which will soon open up for a two month public comment period. The European Glyphosate Task Force (I chair the Toxicology Technical Working Group) will first complete our comments back to the German BvL. Then I will turn my attention to final tuning of our manuscript for submission to *Critical Reviews in Toxicology*.

Thanks for your patience.

Best wishes for 2014.

David Saltmiras, Ph.D., D.V.M.
Toxicology Manager
Regulatory, Toxicology and Nutrition Center
Monsanto
ph: [REDACTED] [REDACTED]

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Roger McClellan

From: SALTMIRAS, DAVID A [AG/1000] <[REDACTED]@monsanto.com>
Sent: Wednesday, October 1, 2014 10:00 AM
To: roger.o.mcclellan@[REDACTED]
Subject: Declaration of Interest

Roger,

I have framed the following declaration of interest similar to that of the Larry Kier & David Kirkland paper, but I am not sure this is as granular as you were requesting over the phone. Please let me know if this is acceptable or whether more details are necessary.

Declaration of Interest

Volker Mostert was a consultant involved in the preparation of the 2012 glyphosate Annex I Renewal dossier for the Glyphosate Task Force (GTF), a consortium of European glyphosate registrants (<http://www.glyphosatetaskforce.org/>). Volker Mostert and Helmut Greim have been reimbursed by the GTF for their work on this manuscript. The selection and interpretation of the data presented here were the sole responsibility of the four authors. David Saltmiras and Christian Strupp are employed by member companies of the GTF, Monsanto and Feinchemie Schwebda GmbH (Makhteshim Agan Industries Ltd.) respectively. David Saltmiras is also Chair of the Toxicology Technical Working Group of the Glyphosate Task Force. Monsanto Company was the original producer and marketer of glyphosate formulations. The authors had sole responsibility for the writing and content of the paper and the interpretations and opinions expressed in the paper are those of the authors and may not necessarily be those of the member companies of the Glyphosate Task Force.

Regards,

David Saltmiras, Ph.D., Ph.D., Ph.D.
Science Fellow
Novel Chemistry and Microbials Product Lead
Toxicology and Nutrition Center
Monsanto
ph: [REDACTED]

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Roger McClellan

From: SALT MIRAS, DAVID A [AG/1000] <[REDACTED]@monsanto.com>
Sent: Thursday, November 6, 2014 4:39 PM
To: roger.o.mcclellan@[REDACTED]
Subject: FW: Critical Reviews in Toxicology - Manuscript ID BTXC-2014-0081

Roger,

Finally submitted! Confirmation email below. Please let me know if you have any questions or require additional details, information, etc.

Regards,

David Saltmiras, Ph.D., D.A.B.T.
Science Fellow
Novel Chemistry and Microbials Product Lead Toxicology and Nutrition Center Monsanto ph [REDACTED]

-----Original Message-----

From: onbehalfof+mbmorgan@[REDACTED]@manuscriptcentral.com
[mailto:onbehalfof+mbmorgan+hargray.com@manuscriptcentral.com] On Behalf Of mbmorgan@[REDACTED]
Sent: Thursday, November 06, 2014 5:37 PM
To: SALT MIRAS, DAVID A [AG/1000]
Cc: mbmorgan@[REDACTED]
Subject: Critical Reviews in Toxicology - Manuscript ID BTXC-2014-0081

06-Nov-2014

Dear Dr Saltmiras:

Your manuscript entitled "Evaluation of Carcinogenic Potential of the Herbicide Glyphosate, Drawing on Tumor Incidence Data from Fourteen Chronic/Carcinogenicity Rodent Studies" has been successfully submitted online and is presently being given full consideration for publication in Critical Reviews in Toxicology.

Your manuscript ID is BTXC-2014-0081.

Please mention the above manuscript ID in all future correspondence or when calling the office for questions. If there are any changes in your street address or e-mail address, please log in to Manuscript Central at <https://mc.manuscriptcentral.com/btxc> and edit your user information as appropriate.

You can also view the status of your manuscript at any time by checking your Author Center after logging in to <https://mc.manuscriptcentral.com/btxc>.

Thank you for submitting your manuscript to Critical Reviews in Toxicology.

Sincerely,
Critical Reviews in Toxicology Editorial Office

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Roger McClellan

From: SALT MIRAS, DAVID A [AG/1000] <[REDACTED]@monsanto.com>
Sent: Friday, December 19, 2014 4:37 PM
To: roger.o.mcclellan@[REDACTED]
Attachments: Author Responses to Reviewer Comments.docx; Glyphosate Carcinogenic Potential - REVISED CRT Manuscript_12-19-2014.docx

Roger,

As discussed this afternoon, I have uploaded the responses to reviewer comments, the revised glyphosate carcinogenicity review manuscript, revised tables and a revised data supplement on manuscript central. I have also attached are my responses to reviewers comments and the revised manuscript in MS Word with tracked changes.

Regards,

David Saltmiras, Ph.D., D.L.S.T.
Science Fellow
Novel Chemistry and Microbials Product Lead
Toxicology and Nutrition Center
Monsanto
[REDACTED]

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Roger McClellan

From: Roger McClellan <roger.o.mcclellan+ [REDACTED]>
Sent: Tuesday, January 13, 2015 11:31 AM
To: Larry Kier
Cc: mbmorgan@ [REDACTED]; Roger McClellan
Subject: Re: Critical Reviews in Toxicology

Larry:

Your interpretation is correct. Please do not submit a revised manuscript until you receive the third reviewers comments or I give you a green light. Best regards, Roger

On Tuesday, January 13, 2015 11:25 AM, Larry Kier < [REDACTED]@q.com> wrote:

Roger and Mildred,

Thanks so much for sending the reviews and thanks to both you and the reviewers for their remarkably prompt responses.

I will get to work on these right away but assume I should wait for the third review to submit reviewer responses.

Thanks.

Larry Kier

-----Original Message-----

From: onbehalfof+roger.o.mcclellan+ [REDACTED]@manuscriptcentral.com
[mailto:onbehalfof+roger.o.mcclellan+ [REDACTED]@manuscriptcentral.com] On Behalf Of roger.o.mcclellan+ [REDACTED]
Sent: Tuesday, January 13, 2015 10:44 AM
To: ldkier@ [REDACTED]
Cc: mbmorgan@ [REDACTED]; roger.o.mcclellan+ [REDACTED]
Subject: Critical Reviews in Toxicology

13-Jan-2015

BTXC-2015-0001 - Review of Genotoxicity Biomonitoring Studies of Glyphosate-Based Formulations

Dear Dr Larry Kier:

I have have received two reviews of your paper and I am waiting for a third review. The two reviews received are quite positive. I am asking my assistant , Mildred Morgan, to send copies of the review to you so you can begin considering revisions to the text you submitted. In particular one reviewer suggests adding a table to clarify your findings. I concur with his recommendation. I will be sending you the third review as soon as it is received.

Best regards

Sincerely,

Roger

Dr Roger McClellan, Editor
Critical Reviews in Toxicology

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Claire.summerfield@informa.com
<http://www.tandfonline.com>

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From: Roger McClellan [mailto:roger.o.mcclellan@att.net]
Sent: 31 January 2015 17:10
To: Summerfield, Claire
Cc: Mildred; Roger McClellan
Subject: Fw: Submitted Corrections for Manuscript ID: BTXC 1010194/ Questions

Claire:

What is going on with the Production People on the Conflict of Interest / Declaration of Interest front? Queries like number 4 on the Kier manuscript are confusing to authors. I thought we had this issue resolved. Has CRT been shifted to another Production Company? If I am off base on this issue let me know.

Best regards,
Roger

On Saturday, January 31, 2015 10:01 AM, Roger McClellan <roger.o.mcclellan@att.net> wrote:

Larry:

Ignore the Query related to Conflict of Interest / Declaration of Interest. What you provided and I approved is just fine. I think the Production People are confused and are use to using "eye wash statements" like "the authors declare no conflict of interest".

Best regards,
Roger

On Saturday, January 31, 2015 9:54 AM, "Claire.summerfield@informa.com" <Claire.summerfield@informa.com> wrote:

This e-mail confirms that you have submitted your corrections to your proofs. Please review the journal and article/content titles below to make sure they are correct.

If any of this information is incorrect, please contact the Production Editor.

Review of Genotoxicity Biomonitoring Studies of Glyphosate-Based Formulations

By: Kier

Journal: BTXC Critical Reviews in Toxicology

Comments From: Roger McClellan

Date Returned: 31 Jan 2015

Correction#: 1

Query#: 4

Page#: 9

Line#: 39

This is exactly the same Declaration of Interest as provided by the author and approved by the Editor. I do NOT understand what the Production staff is doing inserting a Query like this that is pure NONSENSE. What is going on????

After your article has been published online, you will receive 15 eprints to share with colleagues. You will receive an email from us to let you know that it has been published. If you wish to order reprints, please place your order at the Rightslink website:

<http://cats.informa.com/PIS/go?t=rl&m=1010194>

Yours sincerely,

Claire Summerfield

Informa Business Information

Christchurch Court

10-15 Newgate Street

London

EC1A 7AZ

UNITED KINGDOM

Email: claire.summerfield@informa.com

Phone: +44

Roger McClellan

From: SALTMIRAS, DAVID A [AG/1000] <[REDACTED]@monsanto.com>
Sent: Thursday, February 19, 2015 10:57 AM
To: roger.o.mcclellan@att[REDACTED]
Subject: Recently Accepted Glyphosate Manuscripts

Hello Roger,

I trust the weather your way has been a little more amenable than what we have been experiencing!

I have a little inquiry of you. Monsanto's public affairs & scientific affairs folk asked whether *Critical Reviews in Toxicology* will be issuing a press release on the glyphosate papers recently accepted. If so, what does the press release entail?

Regards,

David Saltmiras, Ph.D., D.A.B.F.
Science Fellow
Novel Chemistry and Molecular Product Lead
Toxicology and Nutrition Center
Monsanto
or [REDACTED]

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Roger McClellan

From: SALTMIRAS, DAVID A [AG/1000] <[REDACTED]@monsanto.com>
Sent: Thursday, February 19, 2015 1:22 PM
To: roger.o.mcclellan@[REDACTED]
Subject: vol112-participants
Attachments: vol112-participants.pdf

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Roger McClellan

From: SALTMIRAS, DAVID A [AG/1000] <[REDACTED]@monsanto.com>
Sent: Thursday, February 19, 2015 8:36 PM
To: Roger McClellan
Cc: Larry Kier
Subject: Re: Greim et al. (2015) & Kier (2015) summaries, abstracts and sound bytes

Roger,

Thank you for looping me into the conversation. The two summaries were initially prepared by our Scientific Affairs personnel. I completely understand and empathize with Larry's concerns on his paper's "summary" as I had to prepare some significant rewording to ensure my paper's summary was an accurate reflection of the work. I was remiss in not first routing this by Larry and my sincere apologies go out to him.

Larry, I would like to discuss further if you are available tomorrow to see if we can come up with acceptable summaries for both of your recent publications, which you may be comfortable sharing with Roger.

Regards,

David

Sent from my iPhone

On Feb 19, 2015, at 6:21 PM, "Roger McClellan" <[REDACTED]@att.net> wrote:

Larry:

What I forwarded to T and F (Charles Whalley) is what I received from David Saltmiras. I assumed you were in the loop on what had been developed at Monsanto. I suggest you get in touch ASAP with David. In the mean time I will ask T and F to let me review whatever they develop prior to its release. IF T and F does something to publicize the two papers I suspect it will be very brief.

Thanks for your input.

Roger

On Thursday, February 19, 2015 5:12 PM, Larry Kier <[REDACTED]@a.com> wrote:

Dear Dr. McClellan (Roger):

I'm a little cautious about high levels of publicity for the biomonitoring review and have concerns about some of the suggested publicity material.

I don't know who wrote the "Summary" for my paper and certainly don't want to offend them but it is not the way I would have worded it and I would personally not want this used to characterize my paper. I have a revision below but I don't know whether these summaries are appropriate for publication authors:

Summary

A recent review examined several studies that measure damage to the DNA (genotoxicity) in cells collected from people exposed to pesticides including glyphosate-based herbicides. The author concluded that these studies do not indicate significant genotoxic risks to humans from glyphosate-based herbicides under normal exposure conditions. These findings are consistent with an earlier review of an extensive number of laboratory studies that indicated little likelihood of significant genotoxic risk or reaction with DNA under normal exposure conditions.

I also don't think the "Sound bytes for social media" are accurately worded. They are way too absolute for my taste and place undue emphasis on the strength of the biomonitoring study data. Unfortunately, I can't readily suggest alternatives that fit nicely into the "sound byte" format.

Frankly, the biomonitoring studies that are informative for GBF exposure were few in number (arguably 5) and the robustness of the results is pretty low (not unexpected for biomonitoring studies). My conclusion, as stated, was that the limited data from biomonitoring studies do not contradict the much more extensive and robust data from experimental studies that suggest no significant genotoxic risk or DNA-reactive mechanism, especially under expected much lower actual real-world exposures compared to experimental exposures. I would personally place much more emphasis on the experimental study data but the Summary and particularly the "Sound bytes for social media" don't do this and place undue emphasis on the strength of the biomonitoring data. This focus is understandable for publicity directed at the biomonitoring study but I still am not comfortable with this.

Please note that I believe this qualification applies particularly to the biomonitoring review and I support a stronger conclusion regarding low genotoxic risk from glyphosate and GBF's based on the experimental study review.

Thanks very much for the communication and please let me know if I can be of further assistance.

Larry Kier

From: Roger McClellan [mailto: [REDACTED]@att.net]
Sent: Thursday, February 19, 2015 3:43 PM
To: Whalley Charles
Cc: DAVID A (AG/1000) SALTMIRAS; Mildred; Claire; Roger McClellan; Larry Kier
Subject: Fw: Greim et al. (2015) & Kier (2015) summaries, abstracts and sound bytes

Publicity for Glyphosate Papers

Charles:

I spoke to David Saltmiras today concerning the two Glyphosate papers that will be the lead papers in the next issue of Critical Reviews in Toxicology with regard to F and F putting out any publicity on these two papers. The e-mail below includes complete citations for the papers, abstracts and some information developed by Monsanto Company on the papers.

As you may be aware, these papers have been forwarded to the International Agency for Research on Cancer (IARC) in Lyon, France. IARC at a meeting in early March will be considering the carcinogenic hazard classification of Glyphosate and some other phosphate containing agricultural chemicals. These papers will be a topic of discussion at that meeting. IARC will announce its carcinogenic hazard classification for all the chemical agents reviewed at the meeting, this will probably be done at a Press Conference on March 10. A brief paper describing the results of the meeting will also be published within a few weeks after the meeting concludes. A large Monograph documenting the reviews will be published in early 2016.

As a bottom line the two papers published on line in CRT are likely to attract some attention in the scientific and regulatory community and, possibly, by lay media. I am uncertain as to the policy of T and F on publicizing articles published in Journals such as CRT. If T and F is doing so, these two articles would be excellent candidates.

Please let me know your views on this matter and how you plan to proceed. Let me know if I can be assistance.

On a related matter, I am uncertain as to how T and F would like to handle access to these two papers. I suspect that Monsanto would be interested in purchasing "open access" if that is an option.

Best regards,

Roger

On Thursday, February 19, 2015 1:16 PM, "SALTMIRAS, DAVID A [AG/1000]"

<[REDACTED]@monsanto.com> wrote:

Roger – FYI on press releases.

Greim, H., D. Saltmiras, V. Mostert, and C. Strupp. 2015. Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies. *Crit. Rev. Toxicol.* In press

Summary: A new scientific publication examining 14 separate cancer studies in rats and mice conducted over the last several decades concludes that there is no evidence that glyphosate, the active ingredient in Roundup branded herbicides, causes cancer. The article, in *Critical Reviews in Toxicology*, evaluated the data from these long term studies to determine whether there were any patterns to suggest humans exposed to glyphosate would have any concern about developing cancer. Other scientifically relevant information such as expert regulator evaluations, human dietary exposures and epidemiological studies were also discussed. The clear and consistent view across over 30 years of relevant information continues to support the first expert opinions from the 1980's, that glyphosate does not cause cancer.

Abstract: Glyphosate, an herbicidal derivative of the amino acid glycine, was introduced to agriculture in the 1970s. Glyphosate targets and blocks a plant metabolic pathway not found in animals, the shikimate pathway, required for the synthesis of aromatic amino acids in plants. After almost forty years of commercial use, and multiple regulatory approvals including toxicology evaluations, literature reviews, and numerous human health risk assessments, the clear and consistent conclusions are that glyphosate is of low toxicological concern, and no concerns exist with respect to glyphosate use and cancer in humans. This manuscript discusses the basis for these conclusions. Most toxicological studies informing regulatory evaluations are of commercial interest and are proprietary in nature. Given the widespread attention to this molecule, the authors gained access to carcinogenicity data submitted to regulatory agencies and present overviews of each study, followed by a weight of evidence evaluation of tumor incidence data. Fourteen

carcinogenicity studies (nine rat and five mouse) are evaluated for their individual reliability, and select neoplasms are identified for further evaluation across the data base. The original tumor incidence data from study reports are presented in the online data supplement. 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.

Sound bytes for social media:

- New scientific review examines over 30 years of data, concludes glyphosate does not cause cancer in animals and poses no cancer risk to humans
- Over 30 years of data: no evidence that glyphosate causes cancer
- New glyphosate scientific review: over 30 years of data, demonstrates it does not cause cancer in animals and poses no cancer risk to humans

Kier, L. D. (2015). Review of Genotoxicity Biomonitoring Studies of Glyphosate-Based Formulations. Crit. Rev. Toxicol., in press

Summary: A recent review examined several studies that allege damage to the DNA in cells collected from people after self-reported exposures to glyphosate-based herbicides. The author concluded that there are no direct risks to human DNA under normal exposure conditions. These findings are consistent with an earlier review of an extensive number of laboratory studies that also demonstrated no direct effect on DNA. Taken together, these results confirm previous conclusions that glyphosate-based herbicides do not damage DNA in humans following real world exposures.

Abstract: Human and environmental genotoxicity biomonitoring studies involving exposure to glyphosate-based formulations (GBFs) were reviewed to complement an earlier review of experimental genotoxicity studies of glyphosate and GBF's (Kier and Kirkland, 2013). The environmental and many of the human biomonitoring studies were not informative because there was either a very low frequency of GBF exposure or exposure to a large number of pesticides. One human biomonitoring study indicated no statistically significant correlation between frequency of GBF exposure reported for the last spraying season and oxidative DNA damage. Negative results for the lymphocyte cytokinesis-block micronucleus (CBMN) endpoint were observed in a second human monitoring study with exposure to several pesticides including GBF. There were three studies of human populations exposed to GBF aerial spraying. One study found increases for the CBMN endpoint but these increases did not correlate with self-reported spray exposure or application rates. A second study found increases for the blood cell comet endpoint at high exposures causing toxicity. However, a follow-up to this study two years after spraying did not indicate chromosomal effects. The results of the biomonitoring studies do not contradict an earlier conclusion derived from experimental genotoxicity studies that typical GBF's do not appear to present significant genotoxic risk under normal conditions of human or environmental exposures.

Sound bytes for social media:

- New analysis of human data: glyphosate-based herbicides do not damage cellular DNA following realistic human exposures
- Human data: glyphosate-based herbicide following realistic human exposure not associated with DNA damage in human cells

David Saltmiras, Ph.D., D.A.B.T.
Science Fellow
Novel Chemistry and Microbials Product Lead
Toxicology and Nutrition Center
Monsanto
ph [REDACTED]

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Roger McClellan

From: Larry Kier <[REDACTED]@q.com>
Sent: Thursday, February 19, 2015 2:31 PM
To: Summerfield, Claire
Cc: Roger O. McClellan; Mildred B. Morgan
Subject: Revised Proof and Publication Process

Ref:

Journal: BTXC Critical Reviews in Toxicology
Manuscript ID: 1010194
Manuscript Title: Review of Genotoxicity Biomonitoring Studies of Glyphosate-Based Formulations

Dear Ms. Summerfield:

I was somewhat surprised to see that the above has appeared on the InformaHealthcare CRC website as an early online publication.

It was my understanding from an earlier email that I would see a revised proof on Monday. As far as I know this was not available and I sent an email inquiry yesterday but didn't receive a response.

When I now attempt to access the CATS system (<http://cats.informa.com/PTS/go?t=ri&m=1010194>) to see if the revised proof is there (it wasn't earlier this week) I somehow get redirected to the <https://s100.copyright.com/> site. My CATS user name and password doesn't work on this copyright.com page.

I would please like to see a copy of the proof or publication of my article. In my Wednesday (yesterday) email I asked for another one word change (the word "detectable" on page 8 line 94 of the original proof be replaced with "significant"). I would please like this considered for the publication.

While I certainly understand and appreciate the need to process manuscripts into publications efficiently and rapidly I think that there may have been a communication gap in this case.

I would also appreciate information on publication charges (e.g. page charges) when convenient.

Thanks for your help.

Larry Kier

Roger McClellan

From: Larry Kier <[REDACTED]@q.com>
Sent: Thursday, February 19, 2015 3:36 PM
To: Summerfield, Claire
Cc: Roger O. McClellan; Mildred B. Morgan
Subject: Publication Proof Revision

Ref:

Journal: BTXC Critical Reviews in Toxicology

Manuscript ID: 1010194

Manuscript Title: Review of Genotoxicity Biomonitoring Studies of Glyphosate-Based Formulations

Dear Ms. Summerfield:

I just checked my other email account (author correspondence account) and found that a notice of publication and an email token was sent on February 17.

I have checked the publication with my proof corrections and all corrections were successfully made with one minor exception too minor to change now. I suspect that changing "detectable" to "significant" [Page 8, right column, line 28] is not convenient now. Hopefully, this will not be a significant point.

Although I expected a revised proof on Monday I acknowledge the validity of all's well that ends well.

Thanks for your help and that of your team.

Larry Kier

Roger McClellan

From: Larry Kier <[REDACTED]@q.com>
Sent: Friday, February 20, 2015 8:02 AM
To: 'Summerfield, Claire'
Cc: 'Roger O. McClellan'; 'Mildred B. Morgan'
Subject: RE: Publication Proof Revision

Claire,

Thanks for the note and there is no problem here. You guys did a great job of addressing the proof corrections.

If it's not too much trouble I would really appreciate the word change from "detectable" to "significant" [Page 8, right column, line 28 of the publication pdf: These results provide limited evidence for this indirect genotoxic mechanism not operating at a significant level in humans using GBFs.]. This is admittedly fussy on my part but having accurate and precise wording is important to me.

I did notice that the Greim et al. (2015) is still an "in press" citation in the References section so maybe this could be updated when appropriate citation information is available but I would certainly defer to you on whether that is appropriate or necessary.

Thanks again.

Larry Kier

From: Summerfield, Claire [mailto:[REDACTED]@tandf.co.uk]
Sent: Friday, February 20, 2015 3:27 AM
To: Larry Kier
Cc: Roger O. McClellan; Mildred B. Morgan
Subject: RE: Publication Proof Revision
Importance: High

Dear Larry (if I may),

Bless you, many thanks for your understanding.

I experienced some major changes in my working status on Monday and have been given some additional resources this week to ensure everything is running smoothly by Monday next week. Unfortunately/fortunately your article was one of the items that was prioritised because of its imminent inclusion in this month's issue.

Despite the minor amendment not being included in the online file, I am happy to make this amendment in the printed file and online issue files, should you so wish.

I apologise once again for the confusion

Kindest regards,

Claire

Claire Summerfield
Production Editor, Journals
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From: Larry Kier [mailto:[REDACTED]@q.com]

Sent: 19 February 2015 22:36

To: Summerfield, Claire

Cc: Roger O. McLellan; Mildred B. Morgan

Subject: Publication Proof Revision

Ref:

Journal: BTXC Critical Reviews in Toxicology

Manuscript ID: 1010194

Manuscript Title: Review of Genotoxicity Biomonitoring Studies of Glyphosate-Based Formulations

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Although I expected a revised proof on Monday I acknowledge the validity of all's well that ends well.

Thanks for your help and that of your team.

Larry Kier

Roger McClellan

From: SALTMIRAS, DAVID A [AG/1000] <[REDACTED]@monsanto.com>
Sent: Saturday, February 21, 2015 8:58 AM
To: Summerfield, Claire
Cc: roger.o.mcclellan [REDACTED]
Subject: RE: BTXC 1003423 - Issue 3 Lead article

Claire,

I have been very pleased our interactions throughout the editorial process and commend you on your acumen and diligence. Thank you for ensuring the corrections will be included in the final version.

Regards,

David Saliminas, Ph.D., D.A.B.T.
Senior Fellow
Novel Chemistry and Microbials Product Lead
Toxicology and Nutrition Center
Monsanto
[REDACTED]

From: Summerfield, Claire [mailto:[REDACTED]@tandf.co.uk]
Sent: Friday, February 20, 2015 4:40 PM
To: SALTMIRAS, DAVID A [AG/1000]
Cc: roger.o.mcclellan [REDACTED]
Subject: RE: BTXC 1003423 - Issue 3 Lead article

The proof was the revised proof from those corrections you sent via CATS only. I trust these were all fine. The 3 additional ones will be included in the issue revises so as to be correct in the final issue. I will double check the 3 corrections are in before proceeding with finalising the issue.

Kind regards,
Claire

Claire Summerfield
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From: SALTMIRAS, DAVID A [AG/1000] [mailto: [REDACTED]@monsanto.com]
Sent: 19 February 2015 18:05
To: Summerfield, Claire
Cc: roger.o.mcclellan_@tandf.co.uk
Subject: RE: BTXC 1003423 - Issue 3 Lead article

Clare,

I left you a voice message – perhaps you sent me the wrong “final version”? None of the three items I mentioned in my last email on Saturday, below, were addressed.

-

Claire,

Sorry I couldn't reply on Friday as I was out of town and couldn't manage to review/respond on my phone. I have three small corrections.

1. Page 4, Table 1, line 16, column 2, change “197” to “300”
2. An essential rewording on page 17, lines 57-68. Please change from “unrelated to treatment” to “inconclusive but unrelated to treatment in the context of similar higher dosed studies”
3. Page 23, line 39. Please change the year (2013c) to (2015c).

Many Thanks,

David Saltmirus, Ph.D., D.A.B.T.
Science Fellow
Neuro-Cognitive and Molecular Psychiatry Lead
Technology and Network Center
Monsanto
of [REDACTED]

From: Summerfield, Claire [mailto: [REDACTED]@tandf.co.uk]
Sent: Friday, February 13, 2015 9:30 AM
To: SALTMIRAS, DAVID A [AG/1000]
Subject: BTXC: Issue 3 Lead article - final confirmation
Importance: High

Dear Author,

As you know your article is going to be the lead in the next issue of BTXC. I am about to send it off for issue revises but wanted to send you this last version in case there is anything minor to amend prior to final files. If you can e-mail me by REPLY email, I will double check my inbox prior to requesting final files.

Claire Summerfield
Production Editor, Journals
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David Saltmirus, Ph.D., D.Sc., F.R.S.
Science Fellow
Novel Chemistry and Microbials Product Lead
Toxicology and Nutrition Center
Monsanto
c/o [REDACTED]

From: Summerfield, Claire [mailto:[REDACTED]@tandf.co.uk]
Sent: Thursday, February 19, 2015 4:18 AM
To: SALTMIRAS, DAVID A [AG/1000]
Cc: Summerfield, Claire
Subject: RE: BTXC 1003423 - Issue 3 Lead article
Importance: High

Please find the final proof for final confirmation ☺

Claire Summerfield
Production Editor, Journals
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From: SALT MIRAS, DAVID A [AG/1000] [mailto: [REDACTED]@monsanto.com]
Sent: 18 February 2015 14:57
To: Summerfield, Claire
Subject: BTXC 1003423 - Issue 3 Lead article

Hi Claire,

I'm just following up to make sure you received my final three comments over the weekend. Do you have an ETA for incorporation of these small changes and online posting?

Thanks,

David Saltmiras, Ph.D., D.A.B.T.
Science Fellow
Novel Chemistry and Microbia's Product Lead
Toxicology and Nutrition Center
Monsanto
ph [REDACTED]

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Roger McClellan

From: Guengerich, Frederick P <[REDACTED]@Vanderbilt.Edu>
Sent: Sunday, February 22, 2015 1:18 PM
To: Roger McClellan
Cc: Larry Kier; Whalley Charles; Mildred; Herman Bolt; Russell, David Dorman; Gunnar Johanson; David Warheit; Shuji Tsuda
Subject: Re: Review Publication Concerns

Good points, Roger. Thanks for sharing. Fred

On Feb 22, 2015, at 1:07 PM, Roger McClellan <[REDACTED]@att.net> wrote:

Larry:

You make a number of important points in your letter. It is critical that all of us (authors, co-authors, editors, reviewers and publishers) who are involved with the publication of scientific papers adhere to several key principles to protect the confidential nature of the process.

First, it is critical that the peer review process be anonymous with all aspects treated with the highest degree of confidentiality. It is important that the names of reviewers and review comments not be released under any circumstances. In my opinion, a break down in confidentiality would do irreparable harm to the scientific process. In that vein, I have filed document attesting to my position in a court case where lawyers were attempting to gain access to peer review comments related to a publication in another scientific journal.

Second, it is important to recognize the responsibility of the Editor in selecting peer reviewers for any paper. As a matter of routine, I provide authors the opportunity to propose potential reviewers. For me, this is just the starting point. I read the paper and give particular attention to papers that are reviewed to identify potential reviewers. I also use my own knowledge of the subject matter to identify potential reviewers who will focus on the science being reviewed absent any particular ideological orientation or bias. At the end of the process I recognize my substantial responsibility as an Editor to select a final slate of reviewers. Moreover, when review comments are returned I use them to help guide my decision on accept, revise or reject AND, most importantly, convey the comments to authors in an anonymous manner anticipating that attention to the comments will help the authors revise and further improve the paper thereby enhancing its value to the scientific community and Society at large.

Again, thanks for your comments and for allowing me to elaborate on them. Because of the importance of this exchange I am forwarding a copy of your letter and my response with members of the CRT Editorial Advisory Board and Charles Whalley, Managing Editor, Medicine and Health Science Journals, Taylor and Francis Group, Oxford, England. I am confident that Mr Whalley and Taylor and Francis, as a Publisher, share my views as to the importance of maintaining the confidential nature of the peer review process and that T and F will resist any attempts to breach the process.

With best regards,
Roger

Roger O. McClellan, Editor
Critical Reviews in Toxicology

On Saturday, February 21, 2015 11:51 AM, Larry Kier <[REDACTED]@q.com> wrote:

Dear Editor McClellan:

Hopefully this communication won't be considered too presumptuous or a waste of your time. It certainly isn't intended as such.

A recent article in Science ("Agricultural researchers rattled by demands for documents". Science, 13 February 2015, p. 699.) indicates an aggressive campaign by a nonprofit organization to discredit academic scientists by demanding documentation of their interactions with industry.

Given the aggressive nature of this campaign I wonder if such organizations might consider a tactic of taking legal actions against authors, sponsors, editors and publishers of publications that represent industrial products as being of low risk where the authors) have industry connections.

While anonymous scientific peer review could represent a reasonable defense against accusations of improper bias I wonder if such legal actions could eventually include demands for legal discovery of the identities of the reviewers and the contents of their reviews. Of course, this is speculation and I am certainly not an attorney but I did want to bring this to your attention.

These concerns prompted me to think about and offer a specific example and generic suggestion. I could have suggested the three first authors (Bolognesi, Paz-y-Mino and Koureas) of the five informative papers on GBF biomonitoring results as potential reviewers of the GBF genotoxicity biomonitoring review manuscript. This simply didn't occur to me at the time and these particular individuals may not have agreed or been appropriately responsive but considering this as a generic approach may be useful.

The concept of considering significant primary publication authors as potential reviewers for a review publication seems to be a worthwhile suggestion. This could address bias issues for reviews, especially if authors of the primary review papers might have different affiliations, interpretations and conclusions than the authors of the review manuscript. The primary paper authors would have a chance to have their viewpoints considered by the review authors and editor as reviewer comments.

Thanks.

Larry Kier

F. Peter Guengerich, Ph. D.
Tadashi Inagami Professor of Biochemistry
Department of Biochemistry
Vanderbilt University School of Medicine
638 Robinson Research Bldg.
2200 Pierce Avenue
Nashville, TN 37232-0146
Telephone: [REDACTED]
FAX: [REDACTED]
E-mail: [REDACTED]@vanderbilt.edu

Roger McClellan

From: SALTMIRAS, DAVID A [AG/1000] <[REDACTED]@monsanto.com>
Sent: Wednesday, February 25, 2015 5:30 PM
To: Summerfield, Claire
Cc: roger.o.mcclellan@[REDACTED]
Subject: FW: BTXC 1003423 - Issue 3 Lead article

Hello Claire,

Do you know when we can expect the glyphosate carcinogenicity manuscript to be available online this week?

Cheers,

David Saltmirs, Ph.D., D.A.B.T.
Science Fellow
Novel Chemistry and Microbials Product Lead
Toxicology and Nutrition Center
Monsanto
ph [REDACTED]

From: SALTMIRAS, DAVID A [AG/1000]
Sent: Saturday, February 21, 2015 9:58 AM
To: 'Summerfield, Claire'
Cc: roger.o.mcclellan@[REDACTED]
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Claire,

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Regards,

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Novel Chemistry and Microbials Product Lead
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Kind regards,
Claire

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From: SALT MIRAS, DAVID A [AG/1000] [mailto:[REDACTED]@monsanto.com]

Sent: 19 February 2015 18:05

To: Summerfield, Claire

Cc: roger.o.mcclellan@[REDACTED]

Subject: RE: BTXC 1003423 - Issue 3 Lead article

Clare,

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3. Page 23, line 39. Please change the year (2013c) to (2015c).

Many Thanks,

David Saltmirus, Ph.D., D.A.B.F.

Science Fellow

Novel Chemistry and Microbials Product Lead

Toxicology and Nutrition Center

Monsanto

pl [REDACTED]

From: Summerfield, Claire [mailto: [REDACTED]@tandf.co.uk]
Sent: Friday, February 13, 2015 9:30 AM
To: SALTMIRAS, DAVID A [AG/1000]
Subject: BTXC: Issue 3 Lead article - final confirmation
Importance: High

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Production Editor, Journals
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David Saltmirus, Ph.D., D.V.M.T.
Science Fellow
Molecular Chemistry and Microbiology Product Lead
Technology and Nutrition Center
Molecular
ph [REDACTED]

From: Summerfield, Claire [mailto: [REDACTED]@tandf.co.uk]
Sent: Thursday, February 19, 2015 4:18 AM
To: SALTMIRAS, DAVID A [AG/1000]
Cc: Summerfield, Claire
Subject: RE: BTXC 1003423 - Issue 3 Lead article
Importance: High

Please find the final proof for final confirmation ☺

Claire Summerfield
Production Editor, Journals
Taylor & Francis



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From: SALTMIRAS, DAVID A [AG/1000] [[mailto:\[REDACTED\]@monsanto.com](mailto:[REDACTED]@monsanto.com)]
Sent: 18 February 2015 14:57
To: Summerfield, Claire
Subject: BTXC 1003423 - Issue 3 Lead article

Hi Claire,

I'm just following up to make sure you received my final three comments over the weekend. Do you have an ETA for incorporation of these small changes and online posting?

Thanks,

David Saltmiras, Ph.D., D.A.R.T.
Science Fellow
Novel Chemistry and Microbials Product Lead
Toxicology and Nutrition Center
Monsanto
[REDACTED]
pl

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Roger McClellan

From: Whalley, Charles <[REDACTED]@tandf.co.uk>
Sent: Tuesday, February 24, 2015 12:32 PM
To: Roger McClellan
Subject: RE: Greim et al. (2015) & Kier (2015) summaries, abstracts and sound bytes

Dear Roger,

Thank you for this. T&F's policy on publicising individual articles is, in short, that we're very much in favour! I'll discuss with my Marketing team. As for Open Access, we'll see if we can come up with a price for the authors. We're currently working on revising OA policy across all of the former Informa Healthcare journals, including your journal, so there's more to come on this point.

Best wishes,
Charles

From: Roger McClellan [mailto:[REDACTED]@att.net]
Sent: 19 February 2015 22:43
To: Whalley, Charles
Cc: DAVID A (AG/1000) SALTMIRAS; Mildred; Summerfield, Claire; Roger McClellan; Larry Kier
Subject: Fw: Greim et al. (2015) & Kier (2015) summaries, abstracts and sound bytes

Publicity for Glyphosate Papers

Charles:

I spoke to David Saltmiras today concerning the two Glyphosate papers that will be the lead papers in the next issue of Critical Reviews in Toxicology with regard to F and F putting out any publicity on these two papers. The e-mail below includes complete citations for the papers, abstracts and some information developed by Monsanto Company on the papers.

As you may be aware, these papers have been forwarded to the International Agency for Research on Cancer (IARC) in Lyon, France. IARC at a meeting in early March will be considering the carcinogenic hazard classification of Glyphosate and some other phosphate containing agricultural chemicals. These papers will be a topic of discussion at that meeting. IARC will announce its carcinogenic hazard classification for all the chemical agents reviewed at the meeting, this will probably be done at a Press Conference on March 10. A brief paper describing the results of the meeting will also be published within a few weeks after the meeting concludes. A large Monograph documenting the reviews will be published in early 2016.

As a bottom line the two papers published on line in CRT are likely to attract some attention in the scientific and regulatory community and, possibly, by lay media. I am uncertain as to the policy of T and F on publicizing articles published in Journals such as CRT. If T and F is doing so, these two articles would be excellent candidates.

Please let me know your views on this matter and how you plan to proceed. Let me know if I can be assistance.

On a related matter, I am uncertain as to how T and F would like to handle access to these two papers. I suspect that Monsanto would be interested in purchasing "open access" if that is an option.

Best regards,

Roger

On Thursday, February 19, 2015 1:16 PM. "SALTMIRAS, DAVID A [AG/1000]" <[REDACTED]@monsanto.com> wrote:

Roger – FYI on press releases.

Greim, H., D. Saltmiras, V. Mostert, and C. Strupp. 2015. Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies. *Crit. Rev. Toxicol.* In press

Summary: A new scientific publication examining 14 separate cancer studies in rats and mice conducted over the last several decades concludes that there is no evidence that glyphosate, the active ingredient in Roundup branded herbicides, causes cancer. The article, in *Critical Reviews in Toxicology*, evaluated the data from these long term studies to determine whether there were any patterns to suggest humans exposed to glyphosate would have any concern about developing cancer. Other scientifically relevant information such as expert regulator evaluations, human dietary exposures and epidemiological studies were also discussed. The clear and consistent view across over 30 years of relevant information continues to support the first expert opinions from the 1980's, that glyphosate does not cause cancer.

Abstract: Glyphosate, an herbicidal derivative of the amino acid glycine, was introduced to agriculture in the 1970s. Glyphosate targets and blocks a plant metabolic pathway not found in animals, the shikimate pathway, required for the synthesis of aromatic amino acids in plants. After almost forty years of commercial use, and multiple regulatory approvals including toxicology evaluations, literature reviews, and numerous human health risk assessments, the clear and consistent conclusions are that glyphosate is of low toxicological concern, and no concerns exist with respect to glyphosate use and cancer in humans. This manuscript discusses the basis for these conclusions. Most toxicological studies informing regulatory evaluations are of commercial interest and are proprietary in nature. Given the widespread attention to this molecule, the authors gained access to carcinogenicity data submitted to regulatory agencies and present overviews of each study, followed by a weight of evidence evaluation of tumor incidence data. Fourteen carcinogenicity studies (nine rat and five mouse) are evaluated for their individual reliability, and select neoplasms are identified for further evaluation across the data base. The original tumor incidence data from study reports are presented in the online data supplement. 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.

Sound bytes for social media:

- New scientific review examines over 30 years of data, concludes glyphosate does not cause cancer in animals and poses no cancer risk to humans
- Over 30 years of data: no evidence that glyphosate causes cancer
- New glyphosate scientific review: over 30 years of data, demonstrates it does not cause cancer in animals and poses no cancer risk to humans

Kier, L. D. (2015). Review of Genotoxicity Biomonitoring Studies of Glyphosate-Based Formulations. Crit. Rev. Toxicol., in press

Summary: A recent review examined several studies that allege damage to the DNA in cells collected from people after self-reported exposures to glyphosate-based herbicides. The author concluded that there are no direct risks to human DNA under normal exposure conditions. These findings are consistent with an earlier review of an extensive number of laboratory studies that also demonstrated no direct effect on DNA. Taken together, these results confirm previous conclusions that glyphosate-based herbicides do not damage DNA in humans following real world exposures.

Abstract: Human and environmental genotoxicity biomonitoring studies involving exposure to glyphosate-based formulations (GBFs) were reviewed to complement an earlier review of experimental genotoxicity studies of glyphosate and GBF's (Kier and Kirkland, 2013). The environmental and many of the human biomonitoring studies were not informative because there was either a very low frequency of GBF exposure or exposure to a large number of pesticides. One human biomonitoring study indicated no statistically significant correlation between frequency of GBF exposure reported for the last spraying season and oxidative DNA damage. Negative results for the lymphocyte cytokinesis-block micronucleus (CBMN) endpoint were observed in a second human monitoring study with exposure to several pesticides including GBF. There were three studies of human populations exposed to GBF aerial spraying. One study found increases for the CBMN endpoint but these increases did not correlate with self-reported spray exposure or application rates. A second study found increases for the blood cell comet endpoint at high exposures causing toxicity. However, a follow-up to this study two years after spraying did not indicate chromosomal effects. The results of the biomonitoring studies do not contradict an earlier conclusion derived from experimental genotoxicity studies that typical GBF's do not appear to present significant genotoxic risk under normal conditions of human or environmental exposures.

Sound bytes for social media:

- New analysis of human data: glyphosate-based herbicides do not damage cellular DNA following realistic human exposures
- Human data: glyphosate-based herbicide following realistic human exposure not associated with DNA damage in human cells

David Salzman, PhD, DABT
Scientist
Herbicide Safety and Worker Protection
University of Maryland Center
for Environmental
and Estuarine Science

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Roger McClellan

From: Roger McClellan <[REDACTED]@att.net>
Sent: Monday, July 27, 2015 2:28 PM
To: Mildred B. Morgan
Subject: Fw: Follow up questions on CRT manuscript "Evaluation of Carcinogenic Potential of the Herbicide Glyphosate, Drawing on Tumor Incidence Data from Fourteen Chronic/Carcinogenicity Rodent Studies?"

On Monday, July 27, 2015 3:50 PM, "SALTMIRAS, DAVID A [AG/1000]" <[REDACTED]@monsanto.com> wrote:

Hi Roger,

I hope this note finds you well in the absence of the humidity we face here in St Louis. I have a few follow up inquiries regarding the glyphosate *in vivo* cancer data review manuscript published several months ago in CRT, which I coauthored.

1. I have had a number of requests for this paper. Is there a way to pay to have this changed to "open access"? This wasn't a clear option when submitting, perhaps due to something with the change of publisher from Informa to Taylor & Francis, or more likely, ineptitude on my part. If open access is not an option, how may I order author copies for me to distribute? I can't seem to order these through Scholar One now.
2. In recently experiencing a few computer issues, I can no longer find the original supplementary materials I uploaded with the manuscript submission, which are posted online with the manuscript. Since I do not have a subscription to CRT and thus do not have a user name and password, I do not have access the online data supplement. Is there a way I can either access the online supplement or obtain a copy of the data supplement that I uploaded on Scholar One (it is now electronically archived by T&F)?
3. I am curious as to the volume and quality of correspondence you may have received, particularly in light of the IARC opinion that glyphosate is a "2a" probably human carcinogen.

Regards,

David Saltmiras, Ph.D., D.A.B.F.
Scientist, Senior
Novel Cell Counting and Microarray Protein and
Toxicology and Biomarkers Center
Monsanto
P [REDACTED]

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Roger McClellan

From: Whalley, Charles <[REDACTED]@tandf.co.uk>
Sent: Thursday, March 5, 2015 3:58 AM
To: Roger McClellan; Larry Kier
Cc: Mildred; Herman Bolt; Russell; David Dorman; F. Guengerich; Gunnar Johanson; David Warheit; Shuji Tsuda
Subject: RE: Review Publication Concerns

Dear all,

Thank you for the interesting discussion. To confirm Roger's points below, Taylor & Francis believes rigorous, anonymous peer review to be of the utmost importance, and do everything we can to support our editors and reviewers in maintaining the integrity of this process.

Best wishes,
Charles

Charles Whalley – Managing Editor, Medicine & Health Science Journals
Taylor & Francis Group
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK
Tel: [REDACTED]
Web: www.tandfonline.com
E-mail: [REDACTED]@tandf.co.uk

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From: Roger McClellan [mailto:[REDACTED]@att.net]
Sent: 22 February 2015 19:07
To: Larry Kier
Cc: Whalley, Charles; Roger McClellan; Mildred; Herman Bolt; Russell; David Dorman; F. Guengerich; Gunnar Johanson; David Warheit; Shuji Tsuda
Subject: Re: Review Publication Concerns

Larry:

You make a number of important points in your letter. It is critical that all of us (authors, co-authors, editors, reviewers and publishers) who are involved with the publication of scientific papers adhere to several key principles to protect the confidential nature of the process.

First, it is critical that the peer review process be anonymous with all aspects treated with the highest degree of confidentiality. It is important that the names of reviewers and review comments not be released under any circumstances. In my opinion, a break down in confidentiality would do irreparable harm to the scientific process. In that vein, I have filed document attesting to my position in a court case where lawyers were attempting to gain access to peer review comments related to a publication in another scientific journal.

Second, it is important to recognize the responsibility of the Editor in selecting peer reviewers for any paper. As a matter of routine, I provide authors the opportunity to propose potential reviewers. For me, this is just the starting point. I read the paper and give particular attention to papers that are reviewed to identify potential reviewers. I also use my own knowledge of the subject matter to identify potential reviewers who will focus on the science being reviewed absent any

particular ideological orientation or bias. At the end of the process I recognize my substantial responsibility as an Editor to select a final slate of reviewers. Moreover, when review comments are returned I use them to help guide my decision on accept, revise or reject AND, most importantly, convey the comments to authors in an anonymous manner anticipating that attention to the comments will help the authors revise and further improve the paper thereby enhancing its value to the scientific community and Society at large.

Again, thanks for your comments and for allowing me to elaborate on them. Because of the importance of this exchange I am forwarding a copy of your letter and my response with members of the CRT Editorial Advisory Board and Charles Whalley, Managing Editor, Medicine and Health Science Journals, Taylor and Francis Group, Oxford, England. I am confident that Mr Whalley and Taylor and Francis, as a Publisher, share my views as to the importance of maintaining the confidential nature of the peer review process and that T and F will resist any attempts to breach the process.

With best regards,
Roger

Roger O. McClellan, Editor
Critical Reviews in Toxicology

On Saturday, February 21, 2015 11:51 AM, Larry Kier <[REDACTED]@q.com> wrote:

Dear Editor McClellan:

Hopefully this communication won't be considered too presumptuous or a waste of your time. It certainly isn't intended as such.

A recent article in Science ("Agricultural researchers rattled by demands for documents", Science, 13 February 2015, p. 699.) indicates an aggressive campaign by a nonprofit organization to discredit academic scientists by demanding documentation of their interactions with industry.

Given the aggressive nature of this campaign I wonder if such organizations might consider a tactic of taking legal actions against authors, sponsors, editors and publishers of publications that represent industrial products as being of low risk where the authors have industry connections.

While anonymous scientific peer review could represent a reasonable defense against accusations of improper bias I wonder if such legal actions could eventually include demands for legal discovery of the identities of the reviewers and the contents of their reviews. Of course, this is speculation and I am certainly not an attorney but I did want to bring this to your attention.

These concerns prompted me to think about and offer a specific example and generic suggestion. I could have suggested the three first authors (Bolognesi, Paz-y-Mino and Koureas) of the five informative papers on GBF biomonitoring results as potential reviewers of the GBF genotoxicity biomonitoring review manuscript. This simply didn't occur to me at the time and these particular individuals may not have agreed or been appropriately responsive but considering this as a generic approach may be useful.

The concept of considering significant primary publication authors as potential reviewers for a review publication seems to be a worthwhile suggestion. This could address bias issues for reviews, especially if authors of the primary review papers might have different affiliations, interpretations and conclusions than the authors of the review manuscript. The primary paper authors would have a chance to have their viewpoints considered by the review authors and editor as reviewer comments. Thanks.

Larry Kier

Roger McClellan

From: Ashley Roberts Intertek <[REDACTED]@intertek.com>
Sent: Wednesday, July 11, 2018 11:35 AM
To: Roger McClellan
Subject: RE: An Independent Review of the Carcinogenic Potential of Glyphosate

Roger,

Sorry I missed your call but I was in the UK on business (addressing questions in the houses of parliament but not related to glyphosate).

I must admit I do not remember making any recommendation to Charles that the title of the journal should have included the term "independent".

Regarding the other matters, maybe we can discuss when we are both in town. Unfortunately, I leave on business again on Saturday for a while and will not be back in the office until July 25th.

Hope to speak to you then.

Best Wishes

Ashley

Ashley Roberts, Ph.D.
Senior Vice President – Food & Nutrition Health, Environmental & Regulatory Services (HERS)

Direct [REDACTED]
Office [REDACTED]
Skype [REDACTED]
www.intertek.com

Intertek, 2233 Argentia Rd., Suite 201, Mississauga, ON L5N 2X7

-----Original Message-----

From: Roger McClellan <roger.o.mcclellan@[REDACTED]>
Sent: October-16-16 2:28 AM
To: [REDACTED]@tandf.co.uk
Cc: Ashley Roberts Intertek <[REDACTED]@intertek.com>
Subject: Fw: An Independent Review of the Carcinogenic Potential of Glyphosate

Charles:

You will find this of interest. Can you tell me how many times the Supplement has been accessed and the number of downloads on each article? Best regards, Roger

Roger McClellan

From: roger.o.mcclellan <roger.o.mcclellan@[REDACTED]>
Sent: Wednesday, July 29, 2015 2:12 AM
To: Charles Whalley
Cc: mbmorgan@hargray[REDACTED] roger.o.mcclellan@[REDACTED]
Subject: Fwd: Follow up questions on CRT manuscript "Evaluation of Carcinogenic Potential of the Herbicide Glyphosate, Drawing on Tumor Incidence Data from Fourteen Chronic/Carcinogenicity Rodent Studies"?

Charles Please help Dr Saltmiras out with the access issue. I would also like your views on giving additional publicity to the several papers on glyphosate published in CRT.

The controversial decision by IARC makes these papers even more important. Roger

Sent via the Samsung Galaxy S P 6, an AT&T 4G LTE smartphone

----- Original message -----

From: "SALTMIRAS, DAVID A [AG/1000]" <[REDACTED]@monsanto.com>

Date: 07/27/2015 9:49 PM (GMT+01:00)

To: roger.o.mcclellan@[REDACTED]

Subject: Follow up questions on CRT manuscript "Evaluation of Carcinogenic Potential of the Herbicide Glyphosate, Drawing on Tumor Incidence Data from Fourteen Chronic/Carcinogenicity Rodent Studies"?

Hi Roger,

I hope this note finds you well in the absence of the humidity we face here in St Louis. I have a few follow up inquiries regarding the glyphosate *in vivo* cancer data review manuscript published several months ago in CRT, which I coauthored.

1. I have had a number of requests for this paper. Is there a way to pay to have this changed to "open access"? This wasn't a clear option when submitting, perhaps due to something with the change of publisher from Informa to Taylor & Francis, or more likely, ineptitude on my part. If open access is not an option, how may I order author copies for me to distribute? I can't seem to order these through Scholar One now.
2. In recently experiencing a few computer issues, I can no longer find the original supplementary materials I uploaded with the manuscript submission, which are posted online with the manuscript. Since I do not have a subscription to CRT and thus do not have a user name and password, I do not have access the online data supplement. Is there a way I can either access the online supplement or obtain a copy of the data supplement that I uploaded on Scholar One (it is now electronically archived by T&F)?
3. I am curious as to the volume and quality of correspondence you may have received, particularly in light of the IARC opinion that glyphosate is a "2a" probably human carcinogen.

Regards,

David Saffman, Ph.D., D.V.P.E.
Science Fellow

Novel Chemistry and Molecular Biology
Toxicology and Nutrition Center
Monsanto
at [REDACTED]

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Roger McClellan

From: Roger McClellan <[REDACTED]@att.net>
Sent: Wednesday, October 21, 2015 11:13 AM
To: SALTMIRAS, DAVID A [AG/1000]; Elaine Roberts; Charles Whalley
Cc: Mildred B. Morgan; Roger McClellan
Subject: Re: Glyphosate Papers

David:

I am confident Charles Whalley, the Managing Editor for CRT will be able to work out "open access" for the Greim article on Glyphosate. I will notify him of your interest by copy of this e-mail since the fee for "open access" is a business matter and outside of my purview as the Scientific Editor for CRT. As an aside, did you purchase "open access" for the earlier articles?

If you are interested in Taylor and Francis providing some publicity for these papers I suggest you compile a set of key points for each article and send them to Elaine Roberts at Tand F with a copy to me and Charles Whalley. I would encourage Monsanto to note the availability of the important review papers published in CRT. Alternatively, I am sure Tand F (Elaine Roberts) would be pleased to work with you on a press release coming from T and F. Since, this issue is clearly of international interest I am sure they can make certain the press release receives international distribution.

Best regards,
Roger

On Wednesday, October 21, 2015 9:41 AM, "SALTMIRAS, DAVID A [AG/1000]" <david.a.saltmiras@monsanto.com> wrote:

Roger,

Thank you for opening this discussion.

I would like to procure open access for the Greim et al. (2015) publication. This was my original intent upon submission of the manuscript. However, in the transition from Informa to Taylor and Francis, I was not able to navigate this request online. Please let me know if and how I can pay for open access to help facilitate broader reader distribution.

Regards,

David Saltmiras, Ph.D., D.A.B.T.
Science Fellow
Novel Chemistry and Microbials Product Lead
Toxicology and Nutrition Center
Monsanto
ph [REDACTED]

From: Roger McClellan [mailto:[REDACTED]@att.net]
Sent: Wednesday, October 21, 2015 10:28 AM
To: Elaine Roberts; Charles Whalley
Cc: SALTMIRAS, DAVID A [AG/1000]; Mildred B. Morgan; Roger McClellan
Subject: Glyphosate Papers

Elaine and Charles:

During the last several years several review papers on the very important chemical, Glyphosate, the key ingredient in the herbicide, Roundup, were published in Critical Reviews in Toxicology. These papers were considered by the International Agency for Cancer Research review in early 2015 of the carcinogenic hazard of the chemical. Much to the surprise of many scientists IARC classified Glyphosate as a "probable human carcinogen". This decision is still being discussed around the world. For example, the decision will be the focus of a US Senate Hearing this week.

This causes me to raise the question of whether Taylor and Francis might give the Glyphosate papers some publicity. The decision by IARC and the underlying science is going to be a topic of debate for some time.

My principal contact on the Glyphosate papers has been Dr David Saltmiras at Monsanto. If T and F were interested in publicizing the papers I am sure David could provide some key talking points as to the key conclusions in the papers. I have copied him on this memo.

You should be aware that Monsanto has asked an independent organization based in Canada to review the Glyphosate science relevant to evaluating its carcinogenic hazard including the IARC decision. A paper describing the review panel's work is in preparation. I have advised David that I will be pleased to consider that paper for publication in CRT.

Please let me know your views on this matter including if you want some key summary points from the papers.

Best regards,

Roger

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Roger McClellan

From: Whalley, Charles <[REDACTED]@tandf.co.uk>
Sent: Thursday, October 22, 2015 4:54 AM
To: Roger McClellan
Cc: Mildred B. Morgan; Roberts, Elaine
Subject: RE: Glyphosate Papers

Dear Roger,

I've emailed Dr Saltmiras about Open Access for the Greim et al. article

Can you please confirm that the relevant articles in *CRT*, besides the recent Greim et al., are the following?

Kimmel et al in 43(4)
Kier et al in 43(4)
Kier in 45(3)

Of these only the later Kier article is not currently Open Access.

Best wishes,
Charles

From: Roger McClellan [mailto:[REDACTED]@att.net]
Sent: 21 October 2015 16:28
To: Roberts, Elaine; Whalley, Charles
Cc: DAVID A (AG/1000) SALTMIRAS; Mildred B. Morgan; Roger McClellan
Subject: Glyphosate Papers

Elaine and Charles:

During the last several years several review papers on the very important chemical, Glyphosate, the key ingredient in the herbicide, Roundup, were published in *Critical Reviews in Toxicology*. These papers were considered by the International Agency for Cancer Research review in early 2015 of the carcinogenic hazard of the chemical. Much to the surprise of many scientists IARC classified Glyphosate as a "probable human carcinogen". This decision is still being discussed around the world. For example, the decision will be the focus of a US Senate Hearing this week.

This causes me to raise the question of whether Taylor and Francis might give the Glyphosate papers some publicity. The decision by IARC and the underlying science is going to be a topic of debate for some time.

My principal contact on the Glyphosate papers has been Dr David Saltmiras at Monsanto. If T and F were interested in publicizing the papers I am sure David could provide some key talking points as to the key conclusions in the papers. I have copied him on this memo.

You should be aware that Monsanto has asked an independent organization based in Canada to review the Glyphosate science relevant to evaluating its carcinogenic hazard including the IARC decision. A paper describing the review panel's work is in preparation. I have advised David that I will be pleased to consider that paper for publication in *CRT*.

Please let me know your views on this matter including if you want some key summary points from the papers.

Best regards,
Roger

Roger McClellan

From: Roger McClellan <[REDACTED]@att.net>
Sent: Thursday, October 22, 2015 11:08 AM
To: Whalley, Charles
Cc: Mildred B. Morgan; Roberts, Elaine; DAVID A (AG/1000) SALTMIRAS; Roger McClellan
Subject: Re: Glyphosate Papers

Charles

I believe these are the only recent articles in CRT on Glyphosates that are of interest. I am including David Saltmiras on this e=mail so he can weigh in if I have missed any articles. As an aside, the Kimmel etal paper is in Volume 43, issue 2. Thanks for your help on this matter. Roger

On Thursday, October 22, 2015 3:54 AM, "Whalley, Charles" <Charles.Whalley@landf[REDACTED]> wrote:

Dear Roger,

I've emailed Dr Saltmiras about Open Access for the Greim et al. article.

Can you please confirm that the relevant articles in *CRT*, besides the recent Greim et al., are the following?

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Kier in 45(3)

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Charles

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Sent: 21 October 2015 16:28
To: Roberts, Elaine; Whalley, Charles
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Please let me know your views on this matter including if you want some key summary points from the papers.

Best regards,
Roger

Roger McClellan

From: SALTMIRAS, DAVID A [AG/1000] <[REDACTED]@monsanto.com>
Sent: Tuesday, December 1, 2015 7:17 PM
To: Roger McClellan
Subject: Correction SRA (not ACT) Glyphosate Expert Panel Poster

Roger,

Correction, poster at SRA, not ACT.

David

Sent from my iPhone

Begin forwarded message:

From: "SALTMIRAS, DAVID A [AG/1000]" <[REDACTED]@monsanto.com>
Date: December 1, 2015 at 6:47:27 PM CST
To: Roger McClellan <[REDACTED]att.net>
Subject: Glyphosate Expert Panel Poster

Roger,

FYI, attached is the poster that an Expert Panel is presenting at ACT on Monday. Four different subcommittee sections reviewing the corresponding glyphosate IARC review panels are exposure, animal bioassays, epidemiology and genetic toxicology/oxidative stress (mechanisms). This poster summarizes the Expert Panel subcommittee and overall conclusions. Details of the Expert Panel subcommittee reviews are in the process of being consolidated into a multipart manuscript or manuscripts.

Regards,

David Saltmiras, Ph.D., D. V.B.T.
Science Fellow
Novel Chemistry and Molecular Biology
Toxicology and Nutrition
Monsanto
[REDACTED]

<Expert Panel Poster proof.pdf>

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- (9) All communications with Wallace Hayes related to GBFs, AMPA and/or surfactants for GBFs.

Response:

I do not recall any communications with Wallace Hayes related to GBFs, AMPA and/or surfactants for GBFs.

- (10) All communications with Ashley Roberts related to GBFs, AMPA, and/or surfactants for GBFs.

Response:

The communications I have had with Ashley Roberts related to GBFs, AMPA, and/or surfactants for GBFs relate to the five papers published in the Special Supplement to Volume 46 (2016).

- (11) All medical literature, studies, journal articles, tests and/or scientific analyses authored and/or conducted by You related to the potential adverse human health effects of GBFs, AMPA, and/or surfactants for GBFs. This request includes drafts.

Response:

I have not conducted independent research on the potential adverse health effects of GBFs, AMPA, and/or surfactants for GBFs and, thus, have not published on these topics. I did prepare a "Foreword" to the Special Supplement to Volume 46 of Critical Reviews in Toxicology in my role as Editor-in-Chief of the Journal. The Foreword, noted in the response to Item 5, was intended to provide an editorial context to the five papers published in the Supplement.

(12) All communications with Monsanto related to the documents in Request No. 9.

Response:

I had no communications with Wallace Hayes as I noted in my response to Request No. 9. I did have a communication from David Saltmiras of Monsanto (January 9, 2014) related to preparation of a "glyphosate carcinogenicity review manuscript" for submission to Critical Reviews in Toxicology. This manuscript, authored by Greim, Saltmiras, Mostert and Strupp (2015) was ultimately submitted to Critical Reviews in Toxicology and was noted in my response to Item 5. A second manuscript, authored by Larry Kier (2015), is also noted in the communications with David Saltmiras.

- (13) All documents and communications related to Williams, et al., *A Review of the Carcinogenic Potential of Glyphosate by Four Independent Expert Panels and Comparison to the IARC Assessment* 46 Crit. Rev. Toxicol. 3-20 (2016), including all documents and communications related to the four contemporaneously published companion papers by the expert panel organized by Intertek, Inc ("Intertek Expert Panel"). This request includes drafts.

Response:

The five papers referred to in Item 13 were previously noted in Item 5 and are listed below:

Williams, Gary, Marilyn Aardena, John Acquavella, Sir Colin Berry, David Brusick and Michele M. Burns (2016). *A Review of the Carcinogenic Potential of Glyphosate by Four Independent Expert Panels & Comparison to IARC Assessment*. Crit. Rev. Toxicol. 46(S1): 3-20.

Solomon, Keith R. (2016). *Glyphosate in the General Population and in Applications: A Critical Review of Studies on Exposures*. Crit. Rev. Toxicol. 46(S1): 21-27.

Acquavella, John, David Garabrant, Gary Marsh, Tom Sorahan and Douglas L. Weed. (2016). *Glyphosate Epidemiology Expert Panel Review: A Weight of Evidence Systematic Review of the Relationship Between Glyphosate Exposure and Non-Hodgkin's Lymphoma or Multiple Myeloma*. Crit. Rev. Toxicol. 46(S1): 28-43.

Williams, Gary, Colin Berry, Michele Burns, Joao LauroViana de Camargo and Helmut Greim. (2016). *Glyphosate Rodent Carcinogenicity Bioassay Expert Panel Review*. Crit. Rev. Toxicol. 46(S1): 44-55.

Brusick, David, Marilyn Aardema, Larry Kier, David Kirkland and Gary Williams. (2016). *Genotoxicity Expert Panel Review: Weight of Evidence Evaluation of the Genotoxicity of Glyphosate, Glyphosate-Based Formulations, and Aminomethylphosphonic Acid*. Crit. Rev. Toxicol. 46(S1): 56-74.

As noted earlier, these papers were all submitted to Critical Reviews in Toxicology through the Manuscript Central/Scholar One portal. Each of the manuscripts was reviewed by from 5 to 9 reviewers with the review comments provided to the authors to assist in revising the manuscripts. In total, the five manuscripts were reviewed by 27 different reviewers who provided 36 sets of review comments.

The reviewers were all selected and contacted by the Editor-in-Chief via the Manuscript Central/Scholar One System. The identity of the reviewers was not made known to the authors, a "single blind" review system. The review comments are considered to be confidential communications among the authors, the Editor and reviewers as discussed in response to Item 5.

The Editor does not retain an independent file of reviewer comments on individual papers. The author does not retain a file of original manuscripts nor revised manuscripts.

Roger McClellan

From: Whalley, Charles <[REDACTED]@tandf.co.uk>
Sent: Tuesday, March 8, 2016 7:23 AM
To: Roger McClellan
Cc: Mildred
Subject: RE: Glyphosate Manuscripts --Potential Supplement

Dear Roger,

Thank you for this. and my apologies for being slow to respond.

First off, the download figures for the glyphosate papers (unless I've missed some) are as follows:

Kimmel et al in 43(2)	847
Kier & Kirkland in 43(4)	2,688
Kier in 45(3)	272
Greim et al in 45(3)	732

These download figures understate their impact, as all have been discussed on news sites and blogs, etc. It is, as you say, a controversial topic of some public interest.

With that in mind, I'm grateful for your usual diligence in pursuing a thorough Declaration of Interest.

As for your plans on how to publish this series of papers should they be accepted, I agree that combining the introduction and summary makes sense, with the others split out into separate papers. As ever, I'm grateful to be kept informed and happy to be guided by your judgement! As for the question of a supplement, I can take this up with Dr Roberts as appropriate.

I'll try giving you a ring later today, as I want to catch up about SoT. If you see this email before I get hold of you, do give me a tinkle, as we say over here.

All best wishes,
Charles

From: Roger McClellan [mailto:[REDACTED]@att.net]
Sent: 26 February 2016 22:05
To: Whalley, Charles
Cc: Mildred; Roger McClellan
Subject: Fw: Glyphosate Manuscripts --Potential Supplement

Charles:

I have been in discussions with multiple parties over the past year on publishing one or a series of review papers on the evaluation of the human carcinogenic potential of "glyphosate". Several excellent reviews on the toxicity of this compound have been published previously in CRT. Can you tell me how many times those papers have been accessed?

As you know this compound is a leading agro-chemical. Moreover, the IARC has recently evaluated the compound and made a determination as to its carcinogenicity that is very controversial. That led to the work covered in these six papers. As an aside, much of my discussions have related to whether this might be published as one or multiple papers.

At this stage, I am leaning to recommending that for the initial review what has been billed as an introduction and a second paper billed as a summary should be rolled together as a single paper. That single paper and the

other six papers would be sent for external review with the reviewers of each paper being given access to all the papers.

I have already alerted the coordinating author, Ashley Roberts, to the need for more robust Declarations of Interest. The topic is controversial and the papers when published are likely to be controversial.

At his stage I would envision the papers being published as a single issue Supplement. At the appropriate juncture it will be useful for you to make contact with Dr Roberts to negotiate terms and conditions for publication of the Supplement, assuming it moves through the rigorous review process.

The purpose of this e-mail is to alert you to this large project and ask if you have any special advice to offer at this time.

Best regards,

Roger

--- On Fri, 2/26/16, Ashley Roberts Intertek <[REDACTED]@intertek.com> wrote:

> From: Ashley Roberts Intertek <[REDACTED]@intertek.com>
> Subject: Glyphosate Manuscripts
> To: "Roger.o.mcclellan@[REDACTED]" <Roger.o.mcclellan@[REDACTED]>
> Date: Friday, February 26, 2016, 11:41 AM

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> Dear Dr. McClellan,

>

> In follow-up to our
> discussions this morning, please find attached the
> individual manuscripts covering the Expert panels responses
> to the IARC Monograph. I have not included all of the
> figures and supplemental information at this stage
> for risk of clogging up your email.

>

> If you have any
> comments/questions, please do not hesitate to contact
> me.

>

> Looking forward to hearing
> from you

>

> Many Best Wishes

>

> Ashley

>

> Ashley Roberts,
> Ph.D.

>

> Senior Vice President

>

> Food & Nutrition Group
>
> Intertek Scientific
> & Regulatory Consultancy
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> Tel: +1
> [REDACTED]
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> Fax: +1 [REDACTED]
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> E-mail: [REDACTED]@intertek.com
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Roger McClellan

From: Ashley Roberts Intertek [REDACTED]@intertek.com>
Sent: Friday, March 11, 2016 10:36 AM
To: Roger.o.mcclellan@[REDACTED]
Subject: RE: Glyphosate Manuscripts

Dear Roger,

Nice to talk to you the other day about our current very interesting scientific climate!!! I have put together a declaration of interest preamble below (in red,) which would cover all of the authors of the introductory manuscript. This would obviously be revised for the individual groups publications. Please could you let me know if this is in line with your thinking and the Journals requirements?

The authors of the manuscript is as shown on the cover page. The authors had sole responsibility for the writing and the content of the article, and the interpretations and opinions expressed in the paper are those of the authors.

Gary Williams, Sir Colin Berry, David Brusick, João Lauro Viana de Camargo, Helmut Greim, David Kirkland, Keith Solomon and Tom Sorahan have previously served as independent consultants for the Monsanto Company or the European Glyphosate Task Force. John Acquavella and Larry Kier were previously employees of the Monsanto Company, while Marilyn Aardema, Michele Burns, David Garabrant, Gary Marsh, Ashley Roberts and Douglas Weed declare no potential conflicts of interest.

The Expert Panel Members recruitment and evaluation of the data was organized and conducted by Intertek Scientific & Regulatory Consultancy (Intertek). The Expert Panelists acted as consultants for Intertek. 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 Scientific & Regulatory Consultancy has not previously worked on glyphosate related matters for the Monsanto company, previous employees of Cantox had worked in this capacity.

Funding for this evaluation was provided by the Monsanto Company which is a primary producer of glyphosate and products containing this active ingredient. Neither Monsanto nor any attorney reviewed any of the Expert Panel's manuscripts prior to submission to the journal.

If you think some revisions/amendments are required, I would be most happy to receive your suggestions.

I will be sending you the introductory chapter on Monday as I have just been told that one of the authors is going to work on this over the weekend. I gave him over a week to do this and gave him a deadline of today but what can you do!!!

All the Best

Ashley

Ashley Roberts, Ph.D.
Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Tel: +1 [REDACTED]
Fax: +1 [REDACTED]
E-mail: [REDACTED]@intertek.com

2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

Roger McClellan

From: Ashley Roberts Intertek <[REDACTED]@intertek.com>
Sent: Monday, March 14, 2016 10:26 AM
To: Roger.o.mcclellan@[REDACTED]
Subject: FW: Glyphosate Manuscripts
Attachments: Summary March 10 FINAL.docx

Dear Roger,

In follow-up to our chat on Friday, please find attached the final introductory manuscript to go alongside the 4 main papers sent previously.

Also I amended the declaration of interest slightly as per your recommendations. Please see below. I hope this is more along the lines you were looking for?

Gary Williams, Sir Colin Berry, David Brusick, João Lauro Viana de Camargo, Helmut Greim, David Kirkland, Keith Solomon and Tom Sorahan have previously served as independent consultants for the Monsanto Company or the European Glyphosate Task Force. John Acquavella and Larry Kier were previously employees of the Monsanto Company. Marilyn Aardema, Michele Burns, David Garabrant, Gary Marsh, Ashley Roberts and Douglas Weed have not previously been employed the Monsanto Company or previously been involved in any activity involving glyphosate and as such declare no potential conflicts of interest. Furthermore, none of the afore mentioned authors have been involved in any litigation procedures involving glyphosate.

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Funding for this evaluation was provided by the Monsanto Company which is a primary producer of glyphosate and products containing this active ingredient. Neither any Monsanto company employees nor any attorney reviewed any of the Expert Panel's manuscripts prior to submission to the journal.

I am out of the office today but would be happy to call you if you think necessary. Just send me a quick email and I will respond.

Best Wishes

Ashley

Ashley Roberts, Ph.D.
Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Tel: +1 [REDACTED]
Fax: +1 [REDACTED]
E-mail: [REDACTED]@intertek.com

2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

From: Ashley Roberts Intertek
Sent: March-11-16 12:36 PM
To: 'Roger.o.mcclellan@[REDACTED]'
Subject: RE: Glyphosate Manuscripts

Dear Roger,

Nice to talk to you the other day about our current very interesting scientific climate!!! I have put together a declaration of interest preamble below (in red,) which would cover all of the authors of the introductory manuscript. This would obviously be revised for the individual groups publications. Please could you let me know if this is in line with your thinking and the Journals requirements?

The authors of the manuscript is as shown on the cover page. The authors had sole responsibility for the writing and the content of the article, and the interpretations and opinions expressed in the paper are those of the authors.

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All the Best

Ashley

Ashley Roberts, Ph.D.
Senior Vice President
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Tel: +1 [REDACTED]
Fax: +1 [REDACTED]
E-mail: [REDACTED]@intertek.com

2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

From: Ashley Roberts Intertek
Sent: February-26-16 5:19 PM
To: 'Roger.o.mcclellan@[REDACTED]'
Subject: RE: Glyphosate Manuscripts

Dear Dr. McClellan,

I received your voice mail message. Thank you.

Unfortunately, I will not be attending the SOT this year. I have young staff members hungry to learn and grow within the industry, so I feel that it much more worthwhile for them to attend than myself. We have 9 people going from our group and some will be presenting posters etc.

Best Wishes

Ashley

Ashley Roberts, Ph.D.
Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Tel: +1 [REDACTED]
Fax: +1 [REDACTED]
E-mail: [REDACTED]@intertek.com

2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

From: Ashley Roberts Intertek
Sent: February-26-16 1:41 PM
To: 'Roger.o.mcclellan@[REDACTED]'
Subject: Glyphosate Manuscripts

Dear Dr. McClellan,

In follow-up to our discussions this morning, please find attached the individual manuscripts covering the Expert panels responses to the IARC Monograph. I have not included all of the figures and supplemental information at this stage for risk of clogging up your email.

If you have any comments/questions, please do not hesitate to contact me.

Looking forward to hearing from you

Many Best Wishes

Ashley

Ashley Roberts, Ph.D.
Senior Vice President
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Fax: +1 [REDACTED]
E-mail: [REDACTED]@intertek.com

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Roger McClellan

From: Roger McClellan <[REDACTED]@att.net>
Sent: Friday, March 20, 2015 2:17 PM
To: Mildred Morgan; Susan Felter
Cc: Roger McClellan
Subject: Re: Roger O. McClellan's Note on CRT Journal

Susan:

Thanks for your quick response. The exact position of Taylor and Francis with regard to the 'Open Access' policy is still evolving. I will be meeting with the Taylor and Francis Managing Editor, Charles Whalley, who I report to at the SOT meeting and discussing the details of the "open access" policy with him. After that meeting on Saturday evening I will be able to give you an up date on the "open access" policy for CRT. If you should stop by the Taylor and Francis / CRC Press booth at SOT and see Mr Whaley please convey to him your expectations on "open access". I hope to see you in San Diego

Best regards,
Roger

On Friday, March 20, 2015 10:39 AM, Mildred Morgan <[REDACTED]@hargray.com> wrote:

Susan would like for you to respond to her.

From: Felter, Susan [mailto:[REDACTED]@pg.com]
Sent: Friday, March 20, 2015 11:55 AM
To: Mildred Morgan
Subject: RE: Roger O. McClellan's Note on CRT Journal

Hi Mildred,

Thanks for the email below. I am interested in the details of the open access policies for Taylor and Francis. I just hit "reply" to this email and then realized it was going to you and not Roger. Please let me know if I should contact him directly, or if you can send this. Thanks!

Best regards,
Susan

From: Mildred Morgan [mailto:[REDACTED]@hargray.com]
Sent: Friday, March 20, 2015 11:12 AM
To: ken.unice@cardno[REDACTED]; jmsweeney@[REDACTED] Antonis Christou; 'James Bus'; 'Robertson, Larry'; FGrimm@cvm.tamu[REDACTED] Felter, Susan; edonovan@cardno[REDACTED] Annahita.ghassemi@churchdwright[REDACTED] Lewis, R Jeffrey; sherilyn.gross@cardno[REDACTED] C.R.Tyler@exeter.ac[REDACTED] 'Brooke Tvermoes'; brent.finley@cardno[REDACTED] JL Mauderly
Subject: Roger O. McClellan's Note on CRT Journal

Critical Reviews in Toxicology

I am writing to you as a recent author of a paper published in Critical Reviews in Toxicology (CRT) and/or a reviewer of a paper published in CRT. I anticipate seeing many of you next week at the Society of Toxicology (SOT) meeting in San Diego. Please seek me out if you wish to discuss any potential review manuscript submissions with me.

In preparation for a meeting of the Editorial Advisory Board for CRT at next week's SOT Meeting, I have reviewed the most recent Publisher's Report. The Report confirms that CRT continues to be ranked in the top 10% of Journals published in the Toxicology category. In addition, the Report confirms our tradition of prompt and rigorous review of manuscripts, received from around the world, on contemporary topics in toxicology and risk/safety assessment.

It was a special pleasure to note the download statistics for recently published papers on a diverse range of agents such as chrysotile asbestos, atrazine, glyphosate, bisphenol A, phthalates, aflatoxins and nanomaterials. Other papers focused on new methods for evaluating the risk/safety of chemicals and other agents and improved human risk assessment approaches. Other papers that were frequently downloaded were concerned with over-arching issues such as exposure(dose)-response extrapolations and weight of evidence approaches to evaluating diverse data sets. These papers are already being widely cited in the global peer-reviewed literature ensuring that the Citation Impact Factor for CRT will remain high in the future.

Most importantly, Critical Reviews in Toxicology is now being managed as one of the Journals within Taylor and Francis' portfolio of more than 2,200 Journals. The move of CRT to this portfolio will result in some changes to the Journal's open access policy. I am confident that these new open access policies will be well received by authors and their funders. Please let me know if you are interested in the details of these open access policies.

Best regards to all and best wishes for safe travel if you are heading to San Diego.

Roger

Roger O. McClellan
Editor, Critical Review in Toxicology

[REDACTED]
Albuquerque, NM 87111

Tel: [REDACTED]

E-mail: [roger.o.mcclellan@\[REDACTED\]](mailto:roger.o.mcclellan@[REDACTED])

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[REDACTED]>
Sent: Friday, March 20, 2015 11:08 AM
To: Samuel M. Cohen; Russell Cattley; David Dorman; Gunnar Johanson; F. Guengerich; David Warheit; Herman Bolt; Shuji Tsuda; Mildred B. Morgan
Cc: Roger McClellan; Charles Whalley; Claire Summerfield, mbmorgan@hargray[REDACTED]
Subject: Publisher's Report - March 2015

To all:

Attached is a copy of the Publisher's Report (March 2015) that I just received from Charles Whalley, Managing Editor, Taylor and Francis Group. Charles is now my primary Editorial contact at T and F. On a very regular basis basis, I have continuing contact with our superb Production Editor, Claire Summerfield. I am looking forward to meeting Charles, face to face, over dinner in San Diego on Saturday evening. I am personally very excited about Critical Reviews in Toxicology moving under the main Taylor and Francis umbrella effective January 1, 2015 to the Taylor and Francis portfolio of some 2,200 journals. They are very experienced in the world of scientific publishing.

I urge you to treat this as a confidential report and not share it with others. We will discuss the contents at our breakfast meeting on Tuesday morning at the Marriott Hotel in San Diego. I believe you will agree with me that the report is very comprehensive and professional in tone. It contains some very positive information about Critical Reviews in Toxicology.. I have conveyed that view in a message sent out this morning to over 300 individuals (authors who have previously published in the Journal and past reviewers).

One of the topics I will be discussing with Charles is the Journals "open Access" policy. As you know , I was concerned that a change in the journals "open access" policy imposed by the former Informa Health Care management would have potential negative impact on the Journal's manuscript flow. Indeed that has happened. One of the primary topics I will be discussing with Charles is the "open access" policy under T and F management. A glimpse in to this policy is apparent on page 7 of the Publisher's Report. I am optimistic that the "open policy" under T and F management will be more favorably received by authors and sponsors than the previous policy. I will likely be sending a memo to authors and reviewers on this new policy after I meet with Charles. My e-mail earlier this morning has already stimulated queries back to me on the new "open access" policy.

The importance of "open access" is apparent when one notes that three of the articles in Issue 44, Supplement 3 have been down loaded more than 1,000 time. As an aside, Sam is a co-author on those articles and was very helpful in facilitating their publication in CRT. Thanks, Sam!

I am flying from Albuquerque to San Diego on Saturday morning. I will be staying at the Marriott, the SOT headquarters hotel. As soon as I can identify a location for our Tuesday morning breakfast meeting I will let you know.

Thanks again for all your help with Critical Reviews in Toxicology.
Best regards,
Roger

Roger McClellan

From: Mildred Morgan <mbmorgan@[REDACTED]>
Sent: Tuesday, August 30, 2016 3:40 PM
To: bolt@ifado[REDACTED] rcc0022@auburn[REDACTED] scohen@unmc[REDACTED] Vicki Dellarco;
david_dorman@ncsu[REDACTED] f.guengerich@vanderbilt[REDACTED] "Gunnar Johanson"; Shuji Tsuda;
David Warheit
Cc: Roger McClellan
Subject: Editorial Draft for Glyphosates Papers
Attachments: Special Supplemental Issue on Glyphosates Document for CRT.docx

Dear Board Members:

Attached is a draft editorial for the Special Supplemental Issue on "An Independent Review of the Carcinogenic Potential of Glyphosates." Dr. McClellan would appreciate your reviewing this draft and provide him any comments, additions, changes, etc.

Thanks.

Mildred B. Morgan
Assistant to Dr. Roger O. McClellan
Tel: [REDACTED]
Fax: [REDACTED]

Roger McClellan

From: Whalley, Charles <[REDACTED]@tandf.co.uk>
Sent: Tuesday, April 5, 2016 8:53 AM
To: Roger McClellan ([REDACTED]@att.net)
Subject: Glyphosate papers

Dear Roger,

I hope this finds you very well.

I spoke to Ashley Roberts at Intertek today about the options for publishing a supplement in *CRT*. It was my understanding that we were waiting for some changes to the Declaration of Interest statements on the glyphosate manuscripts before they were submitted to ScholarOne, but it seems things have progressed beyond that. Dr Roberts thought he was waiting for contact from me.

We can negotiate a supplement whilst the manuscripts are in review, on the assumption (as I made clear to Dr Roberts) that any discussion is conditional on acceptance. With this in mind, is there anything else waiting for Dr Roberts to address, or should we advise him to submit his group's manuscripts into ScholarOne?

Best wishes as ever,
Charles

Charles Whalley - Managing Editor, Medicine & Health Science Journals

Taylor & Francis Group

4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK

Direct line: +[REDACTED]

Switchboard: +[REDACTED]

[REDACTED]@tandf.co.uk

www.tandfonline.com

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registered in England under no. 1072954

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[REDACTED]>
Sent: Tuesday, April 5, 2016 2:36 PM
To: Ashley Roberts Intertek
Cc: Charles Whalley@[REDACTED]; roger.o.mcclellan@[REDACTED]; Mildred
Subject: Re: FW: Glyphosate Manuscripts

Ashley:

I understand that you and Charles Whalley have initiated discussions with regard to publishing the glyphosate manuscripts as a Supplement to Critical Reviews in Toxicology conditioned on the papers all being accepted for publication in CRT after external scientific review. Both Charles and I agree that we should proceed with the scientific review of the papers in parallel with you and Charles working out the details including costs associated with publication of the Supplement.

Hence, I urge you to enter the papers in the Scholar One system. For each paper please enter the names of 10 potential reviewers. In addition, please send me an e-mail listing the suggested reviewers for each paper including their name, affiliation, e-mail address, area of expertise and whether or not their work is cited in the particular review paper. It is OK to recommend a specific reviewer to review more than one paper. As always, I retain the right as Editor to select the reviewers for any particular paper.

In addition to submitting the papers via Scholar One please send me an e-mail with each of the papers as an attachment.

Each paper should include a comprehensive Declaration of Interest as we have discussed.

I am looking forward to receiving the papers via Scholar One and as attachments to your e-mail to me.

Best regards,

Roger

On Mon, 3/14/16, Ashley Roberts Intertek <[REDACTED]@intertek.com> wrote:

Subject: FW: Glyphosate Manuscripts
To: "Roger.o.mcclellan@[REDACTED]" <Roger.o.mcclellan@[REDACTED]>
Date: Monday, March 14, 2016, 9:25 AM

Dear Roger,

In follow-up to our chat on Friday, please find attached the final introductory manuscript to go alongside the 4 main papers sent previously.

Also I amended the declaration of interest slightly as per your recommendations. Please see below. I hope this is more along the lines you were looking for?

Gary Williams, Sir Colin Berry, David

Brusick, João Lauro Viana de Camargo, Helmut Greim, David Kirkland, Keith Solomon and Tom Sorahan have previously served as independent consultants for the Monsanto Company or

the European Glyphosate Task Force. John Acquavella and Larry Kier were previously employees of the Monsanto Company. Marilyn Aardema, Michele Burns, David Garabrant, Gary Marsh, Ashley Roberts and Douglas Weed have not previously been employed the Monsanto

Company or previously been involved in any activity involving glyphosate and as such declare no potential conflicts of interest. Furthermore, none of the afore mentioned authors have been involved in any litigation procedures involving glyphosate.

The Expert Panel Members recruitment and evaluation of the data was organized and conducted by Intertek Scientific & Regulatory Consultancy (Intertek).

The Expert Panelists acted as consultants for Intertek. 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 Scientific & Regulatory Consultancy has not previously

worked on glyphosate related matters for the Monsanto company, previous employees of Cantox had worked in this capacity.

Funding for this evaluation was provided by the Monsanto Company which is a primary producer of glyphosate and products containing this active ingredient.

Neither any Monsanto company employees nor any attorney reviewed any of the Expert Panel's manuscripts prior to submission to the journal.

I am out of the office today but

would be happy to call you if you think necessary. Just send me a quick email and I will respond.

Best Wishes

Ashley

Ashley Roberts,
Ph.D.

Senior Vice President

Food & Nutrition Group

Intertek Scientific
& Regulatory Consultancy

Tel: +1

[REDACTED]

Fax: +1

[REDACTED]

E-mail: [REDACTED]@intertek.com

2233 Argentia Road,
Suite 201

Mississauga, Ontario Canada L5N 2X7

From: Ashley
Roberts Intertek

Sent: March-11-16 12:36 PM

To: 'Roger.o.mcclellan@[REDACTED]'

Subject: RE: Glyphosate Manuscripts

Dear Roger,

Nice to talk to you the other day about our current very interesting scientific climate!!! I have put together a declaration of interest preamble below (in red,) which would cover all of the authors of the introductory manuscript. This would obviously be revised for the individual groups publications. Please could you let me know if this is in line with your thinking and the Journals requirements?

The authors of the manuscript is as shown on the cover page. The authors had sole responsibility for the writing and the content of the article, and the interpretations and opinions expressed in the paper are those of the authors.

Gary Williams, Sir Colin Berry, David Brusick, João Lauro Viana de Camargo, Helmut Greim, David Kirkland, Keith Solomon and Tom Sorahan have previously served as independent consultants for the Monsanto Company or the European Glyphosate Task Force. John Acquavella and Larry Kier were previously employees of the Monsanto Company, while Marilyn Aardema, Michele Burns, David Garabrant, Gary Marsh, Ashley Roberts and Douglas Weed declare no potential conflicts of interest.

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Funding for this evaluation was provided by the Monsanto Company which is a primary producer of glyphosate and products containing this active ingredient.

Neither Monsanto nor any attorney reviewed any of the Expert Panel's manuscripts prior to submission to the journal.

If you think some revisions/amendments are required, I would be most happy to receive your suggestions.

I will be sending

you the introductory chapter on Monday as I have just been told that one of the authors is going to work on this over the weekend. I gave him over a week to do this and gave him a deadline of today but what can you do!!!

All the

Best

Ashley

Ashley Roberts,
Ph.D.

Senior Vice President

Food & Nutrition Group

Intertek Scientific
& Regulatory Consultancy

Tel: +1

[REDACTED]

Fax: +1

[REDACTED]

E-mail: [REDACTED]@intertek.com

2233 Argentia Road,
Suite 201

Mississauga, Ontario Canada L5N 2X7

From: Ashley
Roberts Intertek

Sent: February-26-16 5:19 PM

To: 'Roger.o.mcclellan@[REDACTED]'

Subject: RE: Glyphosate Manuscripts

Dear Dr. McClellan,

I received your voice mail message. Thank you.

Unfortunately, I will not be attending the SOT this year. I have young staff members hungry to learn and grow within the industry, so I feel that it much more worthwhile for them to attend than myself. We have 9 people going from our group and some will be presenting posters etc.

Best Wishes

Ashley

Ashley Roberts,
Ph.D.

Senior Vice President

Food & Nutrition Group

Intertek Scientific
& Regulatory Consultancy

Tel: +1
[REDACTED]

Fax: +1 [REDACTED]

E-mail: [REDACTED]@intertek.com

2233 Argentia Road,
Suite 201

Mississauga, Ontario Canada L5N 2X7

From: Ashley
Roberts Intertek

Sent: February-26-16 1:41 PM

To: 'Roger.o.mcclellan@[REDACTED]'

Subject: Glyphosate Manuscripts

Dear Dr. McClellan,

In follow-up to our discussions this morning, please find attached the individual manuscripts covering the Expert panels responses to the IARC Monograph. I have not included all of the figures and supplemental information at this stage for risk of clogging up your email.

If you have any comments/questions, please do not hesitate to contact me.

Looking forward to hearing from you

Many Best Wishes

Ashley

Ashley Roberts,
Ph.D.

Senior Vice President

Food & Nutrition Group

Intertek Scientific
& Regulatory Consultancy

Tel: +1
[REDACTED]

Fax: +1 [REDACTED]

E-mail: [REDACTED]@intertek.com

2233 Argentia Road,
Suite 201

Mississauga, Ontario Canada L5N 2X7

Valued Quality. Delivered.

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this email in error then you should not copy this for any purpose nor disclose its contents to any other person.
<http://www.intertek.com>

Roger McClellan

From: Whalley, Charles <[REDACTED]@tandf.co.uk>
Sent: Friday, April 15, 2016 5:25 AM
To: Roger McClellan
Cc: mbmorgan@[REDACTED]
Subject: RE: Any legal requests to T and F or related companies

Dear Roger,

Further to the below, I can confirm that our current understanding is that Taylor & Francis has not disclosed any reviewer comments on this article. We're still investigating with the various parties who could've had access to the reviewer comments. I'll update you on our findings.

As for your broader question, for now I can only refer you to mine and Didi's previous emails to you on T&F's policy on this issue. I'll get back to you on this soon. I'm still seeking further legal guidance.

In return, could you let me know the nature of the litigation in which these reviewer comments have been raised, and your understanding of how this relates to the journal? I'd be grateful for whatever background you can give here.

Best wishes,
Charles

-----Original Message-----

From: Whalley, Charles
Sent: 15 April 2016 08:14
To: 'Roger McClellan'
Cc: mbmorgan@[REDACTED]
Subject: RE: Any legal requests to T and F or related companies

Dear Roger,

Thanks for passing this on. I'm going to need to consult internally on this, I'm afraid. I'll get back to you as soon as I can.

I'm working from home today, so won't be reachable via telephone, but I'm back at my desk next week.

All best wishes as ever,
Charles

-----Original Message-----

From: Roger McClellan [mailto:roger.o.mcclellan@[REDACTED]]
Sent: 14 April 2016 22:48
To: Whalley, Charles
Cc: roger.o.mcclellan@[REDACTED]; mbmorgan@[REDACTED]
Subject: Any legal requests to T and F or related companies

Charles:

I was very disturbed to recently learn that reference was made in US Federal Court to "confidential review comments" for a paper Paustenbach et al, A review of the health hazards of cobalt, CRT, 43; 316-362 (2013). Does T and F have a record of releasing "confidential review comments" for this or any other paper published by Dr Dennis Paustenbach

and/or his associates in CRT? It is possible that the lawyers might have attempted to use a subpoena or merely made contact by telephone or e-mail. It is possible the lawyers used some means other than contacting T and F to obtain the "confidential review comments", possibly contacting a reviewer. This case is remarkable since the lawyers apparently had copies of multiple review comments on the paper.

I am hoping that this does not occur again in the future. Can you provide me assurance that in the event T and F receives a legal or any inquiry for release of "confidential review comments" that T and F will immediately contact me before taking any action with regard to release of the "confidential review comments"?

As you know, I have strongly held views that all transactions between authors, reviewers and the Editor concerning a paper are confidential and private. Moreover, if this curtain of confidentiality is removed it can cause irreparable harm to the review process and, in doing so, to the author(s), Editor, reviewers and publisher. Hence, I will personally strongly object to release of any "confidential review comments" even if served a legal subpoena. I would hope T and F and its affiliates would hold similar views and support me and my position as an Editor under contract to T and F.

I welcome your response to my specific question on release of comments on this specific paper. Moreover, I welcome your comments on the larger issue.

Best regards,
Roger

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[REDACTED]>
Sent: Friday, April 15, 2016 12:39 PM
To: Charles.Whalley@tandf@[REDACTED]
Cc: roger.o.mcclellan@[REDACTED]; mbmorgan@hargray@[REDACTED]; Didi.Peng@informa@[REDACTED]
Subject: Fw: RE: Any legal requests to T and F or related companies
Attachments: jj trial scan 2.pdf

Charles:

Thanks for the quick response on this matter. I left a telephone message for you before I read your e-mail indicating you were working from your home today. Your message is re-assuring.

The official title of the legal case is shown on the top of the transcript which I have attached. You can obtain additional details by googling on key words such as hip implants, Depuy, Johnson and Johnson, etc. It is my understanding that more than 6000 cases have been filed alleging failure of the implant and/or harm to health from these particular "metal on metal" implants which have now been removed from the market.

In this specific case the court consolidated several cases. It is my understanding the Jury awarded the plaintiffs represented by Attorney Mark Lanier about \$500 million. Other cases are in the "pipeline. It is my understanding that Johnson and Johnson has set aside about \$2.5 billion in US dollars to cover potential losses related to these cases.

What I know about the case is derived from the transcript I have attached. The paper by Paustenbach et al (2013) was apparently introduced as evidence by the Defendants in the case just tried. The paper concludes that systemic toxicity from Cobalt reaching the blood occurs only when very high blood levels of Cobalt are encountered. As I understand it, the Plaintiff's counsel apparently tried to trash the Defendants expert, Dr Boyer, by indicating he had not considered the negative review comments (reviewer 3) on the paper thereby under-mining the credibility of Dr Boyer and the paper. Dr Boyer was obviously surprised because he had never seen the reviewers comments. The key question is how did the plaintiffs lawyer, Mark Lanier, gain access to the review comments?

As an aside, I have reviewed the process and specifics of how the paper was submitted, reviewed and accepted. I feel confident that the paper was rigorously reviewed and the authors appropriately responded to review comments which helped improve the paper resulting in its acceptance. Indeed, one could argue the Journal comes out OK in the exchange.

My concern relative to the Journal is whether a breach occurred in the review / production process that allowed release of "confidential review comments". This could cause authors and reviewers to lose confidence in the Editor, the journal and publisher.

I appreciate what you have done to date. Moreover, I will appreciate further efforts by you, Didi and Taylor and Francis to identify any potential breaches in the confidentiality of the review and production system.

Best regards,
Roger

> From: Whalley, Charles <Charles.Whalley@tandf@[REDACTED]>
> Subject: RE: Any legal requests to T and F or related companies
> To: "Roger McClellan" <roger.o.mcclellan@[REDACTED]>
> Cc: "mbmorgan@hargray@[REDACTED]" <mbmorgan@hargray@[REDACTED]>
> Date: Friday, April 15, 2016, 4:24 AM
> Dear Roger,
>
> Further to the below, I can
> confirm that our current understanding is that Taylor & Francis has
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> To: 'Roger
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> Sent: 14 April 2016 22:48
> To: Whalley, Charles
> Cc: roger.o.mcclellan@[REDACTED];
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> I will personally strongly object to release of any "confidential
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> Cc: roger.o.mcclellan@[redacted].t;
> mbmorgan@hargray [redacted]
> Subject: Any legal requests to T and F or related companies
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> Roger
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Roger McClellan

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Sent: Friday, April 15, 2016 1:31 PM
To: Charles.Whalley@tandf@[REDACTED]
Cc: roger.o.mcclellan@[REDACTED]; mbmorgan@[REDACTED]; Didi.Peng@informa@[REDACTED]
Subject: Re: Fw: RE: Any legal requests to T and F/ FOLLOWUP - MAJOR GOOF

Charles and Didi:

Mildred Morgan and I have gone back to the Critical Reviews in Toxicology web site and reviewed the Paustenbach et al (2013) paper available on line. Much to our dismay, under Supplemental Material, the review comments on the paper are available.

It appears that the authors attached the Review Comments as Supplemental material when the revised paper was submitted. This error was not caught by either Mildred or me. Most importantly, this error was not caught later during the production process by the Production Editor, the Production staff, me, Mildred or the authors. It is my opinion, the key final check points should be the checking of the galleys by authors and, for the Journal, the Production Editor.

With regard to this specific paper, please have the Supplemental Material removed ASAP from the CRT web site.

With regard to the Production process, Mildred will more carefully check as materials are handed off to the Production Editor to see the files are appropriate. I am also asking T and F to work with Scholar One to see that the process is as simple and straight forward as possible, I ask that because I am concerned the process has become more complex over time And see changes introduced that I have never approved. I assume the changes have been made in response to requests from others. I also strongly recommend that a specific step be added to the Production Process in which the Production Editor reviews ALL files BEFORE the material is sent to the Production staff. It is my understanding that step is not taken now. This major problem on the Paustenbach paper illustrates that past practices have not been adequate.

Please keep me posted as to actions taken by you and others. Also, let me know if you have any special insights on these matters.

Best regards,
Roger

On Fri, 4/15/16, Roger McClellan <roger.o.mcclellan@[REDACTED]> wrote:

Subject: Fw: RE: Any legal requests to T and F or related companies
To: Charles.Whalley@tandf@[REDACTED]
Cc: roger.o.mcclellan@[REDACTED]; mbmorgan@hargray@[REDACTED]; Didi.Peng@informa@[REDACTED]
Date: Friday, April 15, 2016, 11:39 AM

Charles:

Thanks for the quick response on this matter. I left a telephone message for you before I read your e-mail indicating you were working from your home today. Your message is re-assuring.

The official tile of the legal case is shown on the top of the transcript which I have attached. You can obtain additional details by goggling on key words such as hip implants, Depuy, Johnson and Johnson, etc. It is my understanding that more than 6000 cases have been filed alleging failure of the implant and/or harm to health from these particular "metal on metal" implants which have now been removed from the market.

In this specific case the court consolidated several cases. It is my understanding the Jury awarded the plaintiffs represented by Attorney Mark Lanier about \$500 million. Other cases are in the "pipeline."

It is my understanding that Johnson and Johnson has set aside about \$2.5 billion in US dollars to cover potential losses related to these cases.

What I know about the case

is derived from the transcript I have attached. The paper by Paustenbach et al (2013) was apparently introduced as evidence by the Defendants in the case just tried. The paper concludes that systemic toxicity from Cobalt reaching the blood occurs only when very high blood levels of Cobalt are encountered. As I understand it, the Plaintiff's counsel apparently tried to trash the Defendants expert, Dr Boyer, by indicating he had not considered the negative review comments (reviewer 3) on the paper thereby under-mining the credibility of Dr Boyer and the paper. Dr Boyer was obviously surprised because he had never seen the reviewers comments.

The key question is how did the plaintiffs lawyer, Mark Lanier, gain access to the review comments?

As an aside, I have reviewed

the process and specifics of how the paper was submitted, reviewed and accepted. I feel confident that the paper was rigorously reviewed and the authors appropriately responded to review comments which helped improve the paper resulting in its acceptance. Indeed, one could argue the Journal comes out OK in the exchange. .

My concern relative to the

Journal is whether a breach occurred in the review / production process that allowed release of "confidential review comments". This could cause authors and reviewers to lose confidence in the Editor, the journal and publisher.

I appreciate what you

have done to date. Moreover, I will appreciate further efforts by you, Didi and Taylor and Francis to identify any potential breaches in the confidentiality of the review and production system.

Best regards,

Roger

> From: Whalley, Charles <Charles.Whalley@tand[REDACTED]> > Subject: RE: Any legal requests to T and F or related companies > To: "Roger McClellan" <roger.o.mcclellan@[REDACTED]> > Cc: "mbmorgan@hargray [REDACTED]" <mbmorgan@hargray [REDACTED]>

> Date: Friday, April 15, 2016, 4:24 AM > Dear Roger, > > Further to the below, I can > confirm that our current understanding is that Taylor & > Francis has not disclosed any reviewer comments on this > article. We're still investigating with the various > parties who could've had access to the reviewer > comments. I'll update you on our findings.

>

> As for your broader question,

> for now I can only refer you to mine and Didi's previous > emails to you on T&F's policy on this issue.

> I'll get back to you on this soon. I'm still seeking > further legal guidance.

>

> In

> return, could you let me know the nature of the litigation > in which these reviewer comments have been raised, and your > understanding of how this relates to the journal? I'd be > grateful for whatever background you can give here.

>

> Best wishes,

> Charles

>

> -----Original Message-----

> From: Whalley, Charles

> Sent:

> 15 April 2016 08:14

> To: 'Roger

> McClellan'

> Cc: mbmorgan@hargray [REDACTED]

> Subject: RE: Any legal requests to T and F or > related companies > > Dear > Roger, > > Thanks for passing > this on. I'm going to need to consult internally on > this, I'm afraid. I'll get back to you as soon as I > can.

>

> I'm working from
> home today, so won't be reachable via telephone, but > I'm back at my desk next week.
>
> All best wishes as ever,
> Charles
>
> -----Original Message-----
> From: Roger McClellan [mailto:roger.o.mcclellan@██████████]
>
> Sent: 14 April 2016 22:48
> To: Whalley, Charles
> Cc: roger.o.mcclellan@██████████
> mbmorgan@██████████
> Subject: Any legal requests to T and F or > related companies > > Charles:
> I was
> very disturbed to recently learn that reference was made in > US Federal Court to "confidential review comments"
> for a paper Paustenbach et al, A review of the health hazards > of cobalt, CRT, 43; 316-362 (2013). Does T and F have
> a > record of releasing "confidential review comments"
> for this or any other paper published by Dr Dennis > Paustenbach and/or his associates in CRT? It is possible > that
> the lawyers might have attempted to use a subpoena or > merely made contact by telephone or e-mail. It is possible >
> the lawyers used some means other than contacting T and F to > obtain the "confidential review comments", >
> possibly contacting a reviewer. This case is remarkable > since the lawyers apparently had copies of multiple review >
> comments on the paper.
> I am hoping
> that this does not occur again in the future. Can you > provide me assurance that in the event T and F receives a >
> legal or any inquiry for release of "confidential > review comments" that T and F will immediately contact >
> me before taking any action with regard to release of the > "confidential review comments"?
>
> As you know, I have strongly held views that > all transactions between authors, reviewers and the Editor >
> concerning a paper are confidential and private.
> Moreover,
> if this curtain of confidentiality is removed it can cause > irreparable harm to the review process and , in doing so, >
> to the author(s), Editor, reviewers and publisher.
> Hence, I
> will personally strongly object to release of any > "confidential review comments" even if served a > legal subpoena. I
> would hope T and F and its affiliates > would hold similar views and support me and my position as > an Editor under
> contract to T and F.
> I welcome your response to my
> specific question on release of comments on this specific > paper. Moreover, I welcome your comments on the larger
> issue.
> Best regards,
> Roger
>

Roger McClellan

From: Whalley, Charles <Charles.Whalley@tand[REDACTED]>
Sent: Monday, April 18, 2016 10:18 AM
To: Roger McClellan (roger.o.mcclellan@[REDACTED])
Cc: Mildred; Peng, Didi; Whittle, Jenna
Subject: CONFIDENTIAL -- CRT Paustenbach et al 43(4) and supplemental material

Dear Roger,

It was a pleasure to chat this afternoon, as ever, albeit unfortunately only on things that have gone wrong. Once again, please accept my apologies for the inadvertent publishing of the comments to reviewers as supplemental material for the Paustenbach article. As we've discussed before, T&F considers review comments in CRT to be confidential, so I do regret that this error occurred.

Based on our investigations, it would seem that this error explains how the review comments came to be cited in federal court in Texas earlier this year. To confirm, we've no record of consciously releasing any information relating to this manuscript on any request. Additionally, any 3rd party with access to review comments is bound to inform us of any request, and we've had no such notification. Whilst this is all a little academic now that we've found the problem, I hope this reassures you as to our general practice.

As I mentioned on the phone, I would stress that the Production processes in place now are much changed from those on the journal in 2012 and 2013, and that I wouldn't take this error as indicative of any serious procedural problems. However, I do think we could do with looking at how we work with supplemental material, both in ScholarOne Manuscripts and through CATS, and will discuss this with Jenna and with you and Mildred in due course.

I'll discuss some of the steps with Jenna tomorrow, as well as how supplemental material is presented in the typeset articles. I know you've some concerns here, in particular in regards to proofs for the Maronpot manuscript. Jenna and I will get to work on addressing them for you.

Finally, as agreed, I'd be grateful if you can either forward the attachments from Dr Tvermoes to me or ask the authors to send them to me directly, so that I can pursue some remaining mysteries around the Paustenbach article if possible.

All best wishes,
Charles

Charles Whalley - Managing Editor, Medicine & Health Science Journals
Taylor & Francis Group
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK
Direct line: +[REDACTED]
Switchboard: +[REDACTED]
[REDACTED]@tandf.co.uk
www.tandfonline.com

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Roger McClellan

From: Ashley Roberts Intertek [REDACTED]@intertek.com>
Sent: Tuesday, May 3, 2016 2:13 PM
To: roger.o.mcclellan@[REDACTED]
Cc: mbmorgan@hargray [REDACTED]
Subject: RE: Critical Reviews in Toxicology

Dear Roger,

Hope all is going well? I was just wondering if you could give me a quick update as to where we currently stand on the review of the glyphosate manuscripts.

Thanking you in anticipation

Ashley

Ashley Roberts, Ph.D.
Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Tel: +1 [REDACTED]
Fax: +1 [REDACTED]
E-mail: [REDACTED]@intertek.com
2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

-----Original Message-----

From: onbehalfof+roger.o.mcclellan@[REDACTED]@manuscriptcentral.com
[mailto:onbehalfof+roger.o.mcclellan@[REDACTED]@manuscriptcentral.com] On Behalf Of roger.o.mcclellan@[REDACTED]
Sent: April-23-16 7:14 PM
To: Ashley Roberts Intertek; Judy Vowles Intertek
Cc: roger.o.mcclellan@[REDACTED] mbmorgan@hargray [REDACTED]
Subject: Critical Reviews in Toxicology

23-Apr-2016

BTXC-2016-0027 - Carcinogenicity bioassay Expert Panel review

Dear Dr Ashley Roberts:

The review comments on the five papers are starting to come in and are generally quite positive.

One issue that has been raised is access to ALL the bioassay results including material submitted for registration. Apparently, some of these results were not considered by IARC. If there is any question about such information you could include the basic data for any previously unpublished paper as Supplemental Information to one of the submitted papers. Supplemental Material is not included in the hard copy version of the papers that have been type set, rather the Supplemental Material is available electronically just as submitted.

At least one of the reviewers from Europe has made reference to a review meeting starting about May 8th. You are probably aware of the meeting. Do you intend to submit these papers to that meeting. I am not certain the reviews will be completed by then, I am certain any required revision of the papers will not be completed by then. I would be willing to have the papers submitted to such a meeting for distribution only to participants with the understanding the papers have been submitted to CRT and are still undergoing review.

Sincerely,
Dr Roger McClellan
Critical Reviews in Toxicology

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<http://www.intertek.com>

Roger McClellan

From: onbehalfof+roger.o.mcclellan@[REDACTED]@manuscriptcentral.com on behalf of roger.o.mcclellan(
Sent: Sunday, May 8, 2016 5:57 PM
To: ashley.roberts@intertek@[REDACTED]; judy.vowles@intertek@[REDACTED]
Cc: roger.o.mcclellan@[REDACTED]; mbmorgan@hargray@[REDACTED]
Subject: Critical Reviews in Toxicology

08-May-2016

BTXC-2016-0025 - Glyphosate: Carcinogenic potential – A Critical review using four Expert Panels

Dear Dr Ashley Roberts:

I have spent the afternoon re-reading the glyphosate papers and reading the comments received to date from external reviewers. I have reached several over-riding conclusions on the papers as a group that I wish to convey to you now.

First, I suggest that you start now to develop revised Declarations of Interest. These need to be as complete and transparent as possible. When reference is made to past employment by or consulting for Monsanto it will be important to note the specific years. I think you will need to critically review how authors show their affiliation. This is important since the individuals, the review process, the writing of the papers and the journal review process are likely to be intensively scrutinized. For example, many show an academic appointment. Is this appropriate as a first affiliation if they were compensated via their private consulting firm?

Second, these papers are a critique of the IARC review process and conclusions. Thus, it is critical to be very specific about the IARC review process and specific conclusions. Then it will be necessary to clearly compare and contrast the IARC conclusions and those of your Panels. This can be done most readily in some cases using direct quotes from IARC and a compare and contrast approach. The authors should not try to hide behind the argument they were conducting a scientific review and not really critiquing IARC. That will not fly with many readers.

Third, the present reviews suffer from a lack of time lines other than revealed by references. Much of this review has a historical time line. I suggest that this should be revealed in tables and or graphs. This is critically important for the carcinogenicity assays, the exposure studies and epidemiology studies. As an aside, having read the papers I am still uncertain as to when it first went on the market in the USA and other countries. Likewise, the reference to multiple past reviews was interesting but rambling. It is not clear when many were conducted. I kept looking for "the table" I would use to present this to an interested audience. Unfortunately, it was not there.

Fourth, access to unpublished data is of paramount importance. Please make certain all unpublished data that is of key importance is available in the papers, electronic supplements or key linkages are available. For example, how does one access the various exposure reports prepared for Monsanto.

Fifth, it is time to be thinking about a more appropriate set of titles for the linked papers.

I hope these comments are useful to you now since I think it will be important that they are covered as the papers are revised. It is important that to recognize that the majority of readers do not have the same background knowledge on IARC and glyphosate as you and the Panel members. Another small group of readers know the material inside and out and will be ready to attack the panel and conclusions on every slipup.

Sincerely,
Dr Roger McClellan
Critical Reviews in Toxicology

Visit www.informapharmascience.com and sign up for free eTOC alerts to all Informa Pharmaceutical Science journals

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[REDACTED]>
Sent: Wednesday, May 11, 2016 10:08 AM
To: Ashley Roberts
Cc: Mildred; Roger McClellan
Subject: Papers to Ashley Roberts

Ashley:

By copy of this e-mail I am asking Mildred Morgan to send you the 8 reviews we have in hand on BTXC-2016-0025 (Summary) and the 3 reviews we have in hand on BTXC-2016-0026 (Exposure). I am waiting for 2 additional sets of review comments on both papers before sending you an official decision letter. You will find these comments helpful in jump starting your revision of both papers.

As I have noted it is going to be very important to clearly state the approach used by IARC and their conclusions and the approach used by the InterTek review team and their conclusions and then compare and contrast the two processes and results. In referencing IARC it will be important to be very precise in use of language. For example, the summary paper concludes with a statement that the InterTek Panel concluded " glyphosate is not carcinogenic". In contrast, IARC for category 4 uses the descriptor "probably not carcinogenic to humans". As I recall, IARC has only placed one chemical, caprolactam, in this category.

Best regards,
Roger

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@██████████>
Sent: Wednesday, May 11, 2016 12:07 PM
To: Ashley Roberts
Cc: Roger McClellan; Mildred
Subject: Re: Reviews of Summary and Exposure Papers/ Followup

Ashley:

I urge you at some point in the process to share these comments on the Summary paper with the lead authors on all the papers (indeed, perhaps all authors) so they will appreciate the range of comments offered on the Summary. To a large extent, these comments are also highly relevant to the other papers in this constellation.

Best regards, Roger

On Wed, 5/11/16, Mildred Morgan <mbmorgan@hargray.██████████> wrote:

Subject: Reviews of Summary and Exposure Papers
To: ashley.roberts@intertek.██████████
Cc: "Roger McClellan" <roger.o.mcclellan@██████████>
Date: Wednesday, May 11, 2016, 10:56 AM

Dear Dr. Roberts:

Dr. McClellan asked me to send you the attached 8 reviews in hand on the Summary Paper and the 3 reviews on the Exposure paper.

Mildred Morgan

Roger McClellan

From: Gunnar Johanson <[REDACTED]@ki.se>
Sent: Thursday, May 12, 2016 8:50 AM
To: Whalley, Charles; Roger McClellan
Cc: s.tsuda@iwate-u[REDACTED]; dellarcov@[REDACTED]; david.warheit@[REDACTED]; david.dorman@nscu[REDACTED]; mbmorgan@hargray[REDACTED]; rcc0022@auburn[REDACTED]; f.guengerich@vanderbilt[REDACTED]; Samuel Cohen
Subject: SV: SV: 5 Glyphosate Papers/ Comments from Gunnar

Thank you Charles for your prompt answer. What you say is all well, except that it is not satisfying with the secret agreement monetary agreement between T&F and the authors/sponsors. In my view, this should not be a business secret but similar as for regular open access articles where T&F openly declares the fees. The secrecy around the supplements opens up for suspicions of economic incentives for Taylor & Francis which in turns spills over to the journal since, even if there are no extra incentives for the supplements, I assume that the Chief Editor receives a salary or honorarium for his work (as he rightly should considering the importance of the task and all the effort he puts into it). Does anyone else have thoughts on this?

Best regards,
Gunnar

Gunnar Johanson | Ph.D | Professor

Head, Unit of Work Environment Toxicology
Institute of Environmental Medicine

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Nobels väg 13, | P.O. Box 210 | SE-171 77 Stockholm, Sweden
[REDACTED] Mobile [REDACTED]
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<http://ki.se/en/unit-of-work-environment-toxicology>
<http://www.nordicexpertgroup.org>

Från: Whalley, Charles [mailto:[REDACTED]@tandf.co.uk]
Skickat: den 10 maj 2016 18:05
Till: Gunnar Johanson; Roger McClellan
Kopia: s.tsuda@iwate-u.ac[REDACTED]; dellarcov@gmail[REDACTED]; david.warheit@gmail[REDACTED]; david.dorman@nscu[REDACTED]; mbmorgan@hargray[REDACTED]; rcc0022@auburn[REDACTED]; f.guengerich@vanderbilt[REDACTED]; Samuel Cohen
Ämne: RE: SV: 5 Glyphosate Papers/ Comments from Gunnar

Dear all,

Many thanks for including me on your discussions here, as I'm grateful to hear your thoughts on this crucial issue for the journal.

As Gunnar has noted, *CRT* commonly publishes supplements funded by industry sponsorship. These allow the authors to publish as a stand-alone issue separate from the normal schedule of issues, meaning that they can

publish as soon as the articles are accepted. These supplements are commonly made free-to-view, and are promoted by Taylor & Francis. Unsurprisingly, industry groups often find this publication option attractive.

The sponsorship in no way guarantees acceptance. To reiterate Roger's comments, the commercial and editorial elements of the journal are entirely separate. Editorial policy is Roger's responsibility. We do not overrule or interfere in his decisions for commercial reasons. Similarly, these articles are subject to all the same peer review and scrutiny of their declarations of interest as any other manuscript. Additionally, to be clear, there is no financial incentive for anyone involved in the editorial process relating to sponsored supplements.

I can't comment on how much sponsors pay for these supplements, as this is commercially sensitive.

Regarding publishing a commentary alongside this proposed issue, I'd be happy to make room for such an editorial, if that's Roger's decision following this suggestion. I would suggest that the focus of such a commentary should be on the significance of these articles, as Vicki has suggested, with an additional opportunity to remind our readership of editorial policy around sponsored supplements and how it applies in this case. I will, however, leave this up to Roger.

I hope this helps clarify matters from the publisher's perspective. Please do let me know if you have any further questions or comments on this. I'm very eager to hear them!

All best wishes,
Charles

Charles Whalley - Managing Editor, Medicine & Health Science Journals

Taylor & Francis Group
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From: Gunnar Johanson [mailto:[REDACTED]@ki.se]

Sent: 09 May 2016 14:44

To: Roger McClellan

Cc: s.tsuda@iwate-u[REDACTED]dellarcov@[REDACTED] david.warheit@[REDACTED] david.dorman@nscu[REDACTED]
mbmorgan@hargray[REDACTED] rcc0022@auburn[REDACTED] Whalley, Charles; f.guengerich@vanderbilt[REDACTED] Samuel Cohen

Subject: SV: SV: 5 Glyphosate Papers/ Comments from Gunnar

Thank you Roger for clarifying. It is good with the rigorous review and detailed COIs of CRT, I have no problem with those items or, for that matter, that industry (or other vested interests) funds research and expert groups and seek to publish their results.

My remaining concern is that it may be seen as industry is paying their way into the journal ("*The authors/ sponsors of these Supplemental Issues pay a special fee negotiated between the Authors / Sponsors and Taylor and Francis. As the CRT Editor, I have nothing to do with this business transaction. My role is to assure that all papers published in any Special Supplement receive the same, high quality rigorous review as papers published in regular issues.*"). I checked the last 15 supplemental papers in CRT, all stem from industry. It is reasonable that the authors/sponsors pay for the publication costs but not a lot more, as this might bias the review and publishing processes.

So, I would appreciate a clarification how much is paid by the authors/sponsors to the publisher and how editors and reviewers are reimbursed (if at all). Maybe Charles Whalley can respond to this?

Best regards,
Gunnar

PS. I agree with Vicky about an accompanying commentary.

-----Ursprungligt meddelande-----

Från: Roger McClellan [mailto:roger.o.mcclellan@]

Skickat: den 8 maj 2016 21:42

Till: Gunnar Johanson

Kopia: s.tsuda@iwate-u.ac.jp; dellarcov@ ; david.warheit@ ; david.dorman@nscu

mbmorgan@hargray; roger.o.mcclellan@ ; rcc0022@auburn; Charles.Whalley@tandf

f.guengerich@vanderbilt; Samuel Cohen

Ämne: Re: SV: 5 Glyphosate Papers/ Comments from Gunnar

Gunnar and other members of the CRT Editorial Advisory Board

Gunnar, thank you for your e-mail concerning the publication of a Supplemental Issue including 5 papers on Glyphosate. Your e-mail was a follow up to our discussion of this matter at our Editorial Advisory Board in New Orleans and my distribution of copies of the papers.

By way of background, CRT in recent years has included 920 pages each year which have been published on line electronically and last year published at year end as a single printed copy. The authors of some papers have purchased on line access.

In addition to the regular issues, CRT has a long standing practice of publishing Special Supplements. The authors/ sponsors of these Supplemental Issues pay a special fee negotiated between the Authors / Sponsors and Taylor and Francis. As the CRT Editor, I have nothing to do with this business transaction. My role is to assure that all papers published in any Special Supplement receive the same, high quality rigorous review as papers published in regular issues. Indeed, the agreement between T and F and the Authors/ Sponsors specifically note that publication of the Special Issue is contingent upon scientific review and acceptance of the papers. It does not guarantee acceptance. . The primary reason for publishing a Special Issue of CRT is to minimize the impact on our limited page budget. Papers included in the Special Supplements do not count against the current annual 920 page limit.

As I recall, CRT has published 3 papers in the recent past on Glyphosate. All three papers were downloaded many times and have been widely cited, including by IARC. One paper by Griem etal contained extensive supplemental material (This is different than a Special Issue Supplement). It is not clear how well IARC reviewed this paper and , especially, the electronic supplement. However, I can assure you that the electronic supplement is clearly marked in the text.

After the IARC review of glyphosate I was contacted by personnel from Monsanto and InterTek, a private consulting firm, as to my interest in considering one or multiple papers on glyphosate that would be a critique of the IARC review. I responded that I would be enthusiastic about considering one or multiple papers. I indicated my preference would be to have one large paper or a collection of papers to be published in a single issue. I indicated that since it was anticipated that these papers would be comprehensive and long I thought it unlikely these papers could be published in a regular issue. I noted that I would expect the papers to have comprehensive and transparent Declarations Of Interest , as is routine for CRT. As an aside, I know of no other scientific journal that has as rigorous a Declaration of Interest policy as CRT with publication of each DOI.

Gunnar has raised the issue of the employment affiliation of the authors and the past association of some of the authors with Monsanto. I expect that to be made clear in the DOIs. As a matter of policy, I do not think where an individual author is employed (academe, government, consulting firm, private consultant, etc) should be a determinant of whether a paper should be considered for publication. I do expect all relevant material relating to potential conflicts of interest to be disclosed in the DOI. Quite frankly, I am concerned by many journals allowing self proclamations from authors --"We have no conflicts of interest to declare." That is "eye wash". Conflicts of Interest are in the eyes of the beholder not the Declarer.

I think my job as an Editor is to see that the submitted paper receive a rigorous review by outstanding experts from around the globe. In the case of the submitted glyphosate papers I think I have selected some outstanding reviewers, in some case up to 7 per paper. As an aside, how many of you have received 7 sets of external review comments on any paper, original research or review paper, you have authored? Many of you agreed to review one or more of the five papers. For that special effort I extend my thanks. I will be pleased to have you review any or all of the revised papers. I use the review comments to help guide my decision to accept, request revision or reject a paper. Most importantly, I expect the authors to use the review comments to further improve their revised paper.

The five glyphosate papers are still under review. In general, the review comments are very positive and constructive. Many reviewers noted they were pleased to have these papers published in CRT.

Gunnar has raised the issue of my publishing a commentary on the five papers as part of the Special Supplement . I have never published such a commentary for either a regular issue or Special Issue. MY basic view is that all papers published in CRT "speak for them selves". However, I am willing to consider such a commentary for this Special Issue if you think it useful. If I were to prepare one it would include many of the points made here. Of course, I would also need to refer to the IARC process and the IARC decision on glyphosate. It is my view that the five papers published in CRT will represent the most comprehensive review of the world's literature on the potential carcinogenicity of glyphosate and be widely cited by others.

I welcome you views on this important matter.

Best regards,
Roger

On Mon, 5/2/16, Gunnar Johanson <[REDACTED]@ki.se> wrote:

Subject: SV: 5 Glyphosate Papers

To: "Roger McClellan" <roger.o.mcclellan@[REDACTED]>, "David Warheit" <david.warheit@[REDACTED]>, "David Dorman" <david.dorman@ncsu@[REDACTED]>

Cc: "s.tsuda@iwate-u.ac.jp" <s.tsuda@iwate-u.ac.jp>, "Mildred" <mbmorgan@hargray@[REDACTED]>

Date: Monday, May 2, 2016, 4:27 AM

Dear Roger,

How will this will be introduced in the journal, i.e. how will it be explained that the 5 papers appear in a separate volume (assuming they will be accepted for publication) ?

Nearly early all

authors are more or less connected to Monsanto. My concern is that this may be viewed as an industry input and, more important, that the integrity and independence of CRT may be questioned by the scientific community.

All the best

Gunnar

-----Ursprungligt meddelande-----

Från: Roger McClellan [mailto:roger.o.mcclellan@[REDACTED]]

Skickat: den 14 april 2016 20:55

Till: david.warheit@[REDACTED]

david.dorman@ncsu@[REDACTED]

Gunnar Johanson

Kopia: s.tsuda@iwate-u@[REDACTED];

roger.o.mcclellan@[REDACTED]

Mildred

Ämne: Fw: 5 Glyphosate Papers

--- On Thu, 4/14/16, Roger McClellan <roger.o.mcclellan@[REDACTED]> wrote:

> From: Roger McClellan <roger.o.mcclellan@[REDACTED]>
> Subject: Fw: 5 Glyphosate Papers
> To: bolt@ifado@[REDACTED] rcc0020@auburn.edu [REDACTED] guengerich@vanderbilt.edu [REDACTED]

> "Samuel Cohen" <scohen@unmc@[REDACTED]>
> Cc: "Roger McClellan" <roger.o.mcclellan@[REDACTED]> "Mildred" <mbmorgan@hargray@[REDACTED]>

> Date: Thursday, April 14, 2016, 11:51 AM To all:
> Attached are five papers

critiquing the IARC review of glyphosate.

> Assuming the papers are accepted after rigorous review, they will be published in a single Special Supplement to CRT. I would be pleased if you would agree to review the general paper and one or more of the four detailed papers. If you are willing to review one or more paper please inform my assistant, Mildred Morgan, [mbmorgan@hargray@\[REDACTED\]](mailto:mbmorgan@hargray@[REDACTED]) and you will be formally invited.

Thanks in advance for your help. Best

> regards, Roger

>

>

--- On Thu, 4/14/16, Mildred Morgan <mbmorgan@hargray@[REDACTED]> wrote:

>

>> From: Mildred Morgan <mbmorgan@hargray@[REDACTED]> >> Subject: 5 Glyphosate Papers >> To: "Roger McClellan" <roger.o.mcclellan@[REDACTED]>

>> Date: Thursday, April 14, 2016, 9:38 AM The 5 glyphosate papers >> attached.

>>

>

>

>>

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[REDACTED]>
Sent: Thursday, May 12, 2016 10:16 AM
To: David Dorman
Subject: Fw: Re: SV: SV: 5 Glyphosate Papers/ Comments from Gunnar

--- On Thu, 5/12/16, Roger McClellan <roger.o.mcclellan@[REDACTED]> wrote:

> From: Roger McClellan <roger.o.mcclellan@[REDACTED]>
> Subject: Re: SV: SV: 5 Glyphosate Papers/ Comments from Gunnar
> To: "CharlesWhalley" <[REDACTED]@tandf.co.uk>, "Roger McClellan"
> <roger.o.mcclellan@[REDACTED]>, "Gunnar Johanson" <[REDACTED]@ki.se>
> Cc: mbmorgan@hargray [REDACTED], "s.tsuda@iwate-u.ac.jp" <[REDACTED]>
> <s.tsuda@iwate-u.ac.jp>, "dellarcov@[REDACTED]" <dellarcov@[REDACTED]>, "david.warheit@[REDACTED]" <david.warheit@[REDACTED]>, "david.dorman@nscu" <david.dorman@nscu.edu>, "rcc0022@auburn.edu" <rcc0022@auburn.edu>, "f.guengerich@vanderbilt.edu" <f.guengerich@vanderbilt.edu>, "Samuel Cohen" <scohen@unmc.edu>
> Date: Thursday, May 12, 2016, 9:10 AM
> Gunnar:
> Thanks for your follow up note on the Special Glyphosate Supplement. I will off some clarification on some of the issues you raise.
> First, let me address my role as the Editor of Critical Reviews in Toxicology. I do have a contract with Informa / Taylor and Francis for my services as Editor of CRT. That contract provides me a flat fee to cover all of my time and expenses for serving as Editor, the most important aspects of which are the maintenance of manuscript flow and the delivery of high quality, peer-reviewed manuscript to T and F. To assist me, I engage Mildred Morgan, who has worked effectively and efficiently with me for decades. The fee I receive is the same irrespective of the number of manuscripts moving through the system and whether CRT includes any Special Supplements.
> Hence, there is no financial incentive for me to promote the publication of Special Supplements. Indeed, every Special Supplement requires more effort from me and Mildred for which I receive NO additional reimbursement.
> It follows logically to ask why I should consider recommending publication of any Special Supplements. I do so as part of my professional responsibility as Editor. I want to see the 920 pages allotted each year for regular issues of CRT used to publish high quality, high impact papers in a timely manner. That is a difficult balancing act involving (a) high scientific impact, (b) high scientific quality and (c) timeliness.
> Impact and quality are not the same. By impact I am referring to scientific information that is relevant to contemporary Societal issues. Scientific quality is independent of whether the content is

> relevant to Societal issues. Timeliness is obviously of concern for
 > all authors, they would like to have their paper published as soon as
 > possible. T and F addresses that issue in part by promptly processing
 > all accepted manuscripts and posting them on line at the earliest
 > possible date. However, no one would like to have their paper in limbo
 > as to formal publication for months and months. Hence, the dilemma of
 > every Editor and ,especially Review Journal Editor. I want to have a
 > modest back log but not an excessive back log. I can assure you I have
 > had more then a few sleepless nights thinking about whether I have the
 > right balance.
 > This brings me to the five
 > Glyphosate papers. This is one of the world's highest impact
 > chemicals. IARC operates one of the world's most widely recognized
 > cancer hazard classification schemes. CRT previously published at
 > least three widely cited review papers on Glyphosates that were
 > considered in the IARC review. The IARC cancer hazard classification
 > of Glyphosate is one of the most controversial cancer hazard
 > classifications rendered in recent years. Although let me quickly note
 > that the cancer hazard classifications rendered for "outdoor air" and
 > "airborne particulate material" follow close behind. When I learned
 > that Monsanto was going to sponsor a critical review of the cancer
 > hazard of glyphosate, including a critique of the IARC review, managed
 > by InterTek , I decided it would be highly desirable to publish that
 > critical review in CRT. I thought then and now that CRT was the ideal
 > publication venue for this review because of the rigor of CRT's review
 > process, our transparent "Declaration of Interest" process and our
 > desire to provide access to all underlying data through use of
 > electronic supplements and electronic linkages.
 > In anticipation of the number of pages involved I quickly
 > decided that it would be best to publish the new review as a Special
 > Supplement. At that point I handed off to Charles Whalley, the
 > Managing Editor of CRT, and the business office of T and F the
 > negotiation of the details , including fees, for publishing the
 > Special Supplement. As the recipients of this memo know I have 60
 > years of experience as a scientist, scientific manager and science
 > advisor. What may not be as well known is I have over 50 years of
 > business experience running large scale research enterprises,
 > including responsibility for the bottom line. That means making tough
 > decisions as to when you hire and fire your scientific colleagues. To
 > provide me better tools for working as a scientific business manager I
 > enrolled and completed a Master of Management Science degree at the
 > University of New Mexico, the equivalent of an MBA. I understand
 > business - it is rough and tumble!!!
 > I fully understand the T and F
 > business decision to not release details, including publication fees,
 > of the agreement between T and F and InterTek for publishing the
 > Special Supplement containing the glyphosate papers. Indeed, I suspect
 > the agreement at this stage has not yet been published because the
 > number of pages to be published is not yet known.
 > Wearing my "business hat" I can assure you that T and F has very
 > straight forward business procedures for deciding what is a reasonable
 > fee for publishing a Special Supplement containing 125, 150, 175 or

> 200 pages. It is not some arbitrary process guided by a "lets charge
> as much as possible" approach. Indeed, I suspect an examination of the
> fees typically charged by T and F for "open access" will provide clues
> as to the cost to the sponsor of publishing the Special Supplement. As
> I hope everyone knows the "scientific publishing business" is a tough
> business today with rapidly changing practices. [As an aside, how many
> paper solicitations from fly by night journals have you received this
> month?] Bottom line, I count on T and F to run their publishing
> business in an ethical and business like manner. I am counting on that
> because I want them to be in business and publishing CRT
> indefinitely. I certainly do not want them to go out of business. The
> counter point is that I will continue to deliver them high scientific
> quality, high impact , rigorously peer reviewed manuscripts to fill
> the 920 pages of regular issues they have contractually agreed to
> provide to their subscribers and occasional provide papers for a
> Special Supplement.
> As an update, the five glyphosate papers are moving through an
> extraordinarily rigorous review process. The review comments meet the
> high standards of CRT and will help the authors further improve the
> final accepted version of the papers. I do anticipate preparing a
> "prelude" that will introduce the Special Supplement".
> I hope the foregoing material is helpful to all of you I welcome
> any further inquiries by e-mail or phone. (redacted).
> Again, thank you for your assistance with CRT and , especially,
> with the glyphosate Special Supplement.
> With best regards,
> Roger
> PS This is a "business sensitive communication". I would appreciate
> your not sharing it or communicating the contents with any individuals
> other than the recipients.

> -----
> On Thu, 5/12/16, Gunnar Johanson <(redacted)@ki.se>
> wrote:

>
> Subject: SV: SV: 5 Glyphosate Papers/ Comments from Gunnar
> To: "Whalley, Charles" <(redacted)@tandf.co.uk>, "Roger
> McClellan" <roger.o.mcclellan@att(redacted)>
> Cc: "s.tsuda@iwate-u.a(redacted)"
> <s.tsuda@iwate-u.ac.jp>,
> "dellarcov@(redacted)"
> <dellarcov@(redacted)>,
> "david.warheit@(redacted)"
> <david.warheit@(redacted)>,
> "david.dorman@nscu(redacted)"
> <david.dorman@nscu(redacted)>,
> "mbmorgan@hargray(redacted)"
> <mbmorgan@hargray(redacted)>
> "rcc0022@auburn(redacted)"
> <rcc0022@auburn(redacted)>
> "f.guengerich@vanderbilt(redacted)"
> <f.guengerich@vanderbilt(redacted)>
> "Samuel Cohen" <scohen@unmc(redacted)>

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> Date: Thursday, May 12, 2016, 7:49 AM
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> Thank you Charles for your prompt
> answer. What you say is all well, except that it is not satisfying
> with the secret agreement monetary agreement
> between T&F and the authors/sponsors. In my view, this should not
> be a business secret but similar as for regular open access articles
> where T&F openly declares the fees.
> The secrecy around the supplements opens up for suspicions of
> economic incentives for
> Taylor & Francis which in turns spills over to the journal since,
> even if there are no extra incentives for the supplements, I assume
> that the Chief Editor receives a salary or honorarium for his work
> (as he rightly should considering the importance of the
> task and all the effort he puts into it).
> Does anyone else have thoughts on
> this?

> Best regards,
> Gunnar

>
>
> Gunnar Johanson
> | Ph.D. |
> Professor

>
>
> Head, Unit of Work
> Environment Toxicology
>
> Institute of Environmental Medicine

>
>
> Karolinska Institutet

>
> Nobels väg 13 | P.O. Box 210 | SE-171 77 Stockholm, Sweden

> + [REDACTED] Mobile +4 [REDACTED]

> [REDACTED]@ki.se

>
>
> <http://ki.se/en/imm/unit-of-work-environment-toxicology>

>
>
> <http://www.nordicexpertgroup.org>

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>
> Karolinska Institutet is one of the
> world's leading medical universities.
> Its mission is to contribute to the
> improvement of human health through research and education.

> Karolinska Institutet accounts for
> over 40 per cent of the medical academic research conducted in
> Sweden and offers the country's broadest range of education in
> medicine and health sciences.
> Since 1901 the Nobel Assembly at
> Karolinska Institutet has selected the
>
> Nobel laureates in Physiology or
> Medicine.
>
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>
> Från: Whalley, Charles
> [mailto: [REDACTED]@tandf.co.uk]
>
>
> Skickat: den 10 maj 2016 18:05
>
> Till: Gunnar Johanson; Roger McClellan
>
> Kopia: s.tsuda@iwate-u.ac [REDACTED]
> dellarcov@[REDACTED]
> david.warheit@[REDACTED]
> david.dorman@nscu [REDACTED]
> mbmorgan@hargray [REDACTED]
> rcc0022@auburn [REDACTED]
> f.guengerich@vanderbilt [REDACTED]
> Samuel Cohen
>
> Ämne: RE: SV: 5 Glyphosate Papers/ Comments from Gunnar
>
>
>
> Dear all,
>
> Many thanks for including me on
> your discussions here, as I'm grateful to hear your thoughts on this
> crucial issue for the journal.
>
> As Gunnar has noted,
> CRT commonly publishes supplements funded by industry sponsorship.
> These allow the authors to publish as a stand-alone issue separate
> from the normal schedule of issues, meaning that they can publish as
> soon as the articles are accepted. These supplements
> are commonly made free-to-view, and are promoted by Taylor &
> Francis. Unsurprisingly, industry groups often find this publication
> option attractive.
>
> The sponsorship in no way
> guarantees acceptance. To reiterate Roger's comments, the commercial

> and editorial elements of the journal are entirely
> separate. Editorial policy is Roger's responsibility. We do not
> overrule or interfere in his decisions for commercial reasons.
> Similarly, these articles are subject to all the same peer review and
> scrutiny of their declarations of interest as any other manuscript.
> Additionally, to be clear, there is no financial incentive for
> anyone involved in the editorial process relating to sponsored
> supplements.
>
> I can't comment on how much
> sponsors pay for these supplements, as this is commercially
> sensitive.
>
> Regarding publishing a commentary
> alongside this proposed issue, I'd be happy to make room for such an
> editorial, if that's Roger's decision following
> this suggestion. I would suggest that the focus of such a
> commentary should be on the significance of these articles, as Vicki
> has suggested, with an additional opportunity to remind our
> readership of editorial policy around sponsored supplements and how
> it
> applies in this case. I will, however, leave this up to Roger.
>
> I hope this helps clarify
> matters from the publisher's perspective. Please do let me know if
> you have any further questions or comments on this.
> I'm very eager to hear them!
>
> All best wishes,
> Charles
>
> Charles Whalley
> -
> Managing Editor, Medicine & Health Science Journals Taylor &
> Francis Group
> 4 Park Square, Milton Park,
> Abingdon, Oxon, OX14 4RN, UK
> Direct line: + [REDACTED]
> [REDACTED]
> Switchboard: + [REDACTED]
> [REDACTED]
> [REDACTED]@tandf.co.uk
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> www.tandfonline.com
>
>
> Taylor & Francis is a trading
> name of Informa UK Limited,
> registered in England under no.
> 1072954
>
>

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>
> From: Gunnar Johanson [mailto:██████████@ki.se]
>
>
> Sent: 09 May 2016 14:44
>
> To: Roger McClellan
>
> Cc: s.tsuda@iwate-u.ac.██████████
>
> dellarcov@██████████;
> david.warheit@██████████;
> david.dorman@nscu██████████
>
> mbmorgan@hargray██████████
> rcc0022@auburn██████████
> Whalley, Charles;
> f.guengerich@vanderbilt██████████
> Samuel Cohen
>
> Subject: SV: SV: 5 Glyphosate Papers/ Comments from Gunnar
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>
> Thank you Roger for clarifying. It
> is good with the rigorous review and detailed COIs of CRT, I have no
> problem with those items or, for that matter, that
> industry (or other vested interests) funds research and expert
> groups and seek to publish their results.
>
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>
> My remaining concern is that it
> may be seen as industry is paying their way into the journal ("The
> authors/ sponsors of these Supplemental Issues pay a special
> fee negotiated between the Authors / Sponsors and Taylor and
> Francis. As the CRT Editor, I have nothing to do with this business
> transaction. My role is to assure that all papers published in any
> Special Supplement receive the same, high quality rigorous
> review as papers published in regular issues."). I checked the last
> 15 supplemental papers in CRT, all stem from industry. It is
> reasonable that the authors/sponsors pay for the publication costs
> but not a lot more, as this might bias the review and publishing
> processes.
>
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>
> So, I would appreciate a
> clarification how much is paid by the authors/sponsors to the
> publisher and how editors and reviewers are reimbursed (if at all).
> Maybe
> Charles Whalley can respond to this?
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> Best regards,
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>
> Gunnar
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> PS. I agree with Vicky about an
> accompanying commentary.
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> -----Ursprungligt
> meddelande-----
>
> Från: Roger McClellan (mailto:roger.o.mcclellan@att[REDACTED])
>
>
> Skickat: den 8 maj 2016 21:42
>
> Till: Gunnar Johanson
>
> Kopia: s.tsuda@iwate-u.ac[REDACTED]
>
> dellarcov@gmail[REDACTED];
> david.warheit@gmail[REDACTED];
> david.dorman@nsc[REDACTED]
>
> mbmorgan@hargray[REDACTED];
> roger.o.mcclellan@att[REDACTED]
> rcc0022@auburn[REDACTED]

>
> Charles.Whalley@tandf[REDACTED];
> f.guengerich@vanderbilt[REDACTED]
> Samuel Cohen
>
> Ämne: Re: SV: 5 Glyphosate Papers/ Comments from Gunnar
>
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>
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>
> Gunnar and other members of the
> CRT Editorial Advisory Board
>
>
> Gunnar, thank you
> for your e-mail concerning the publication of a Supplemental Issue
> including 5 papers on Glyphosate. Your e-mail was a follow up to
> our discussion of this matter at our Editorial Advisory Board in
> New Orleans and my distribution of copies of the papers.
>
>
> By way of background,
> CRT in recent years has included 920 pages each year which have been
> published on line electronically and last year published at
> year end as a single printed copy. The authors of some papers have
> purchased on line access.
>
>
> In addition to the
> regular issues, CRT has a long standing practice of publishing
> Special Supplements. The authors/ sponsors of these Supplemental
> Issues
> pay a special fee negotiated between the Authors / Sponsors and
> Taylor and Francis. As the CRT Editor, I have nothing to do with
> this business transaction. My role is to assure that all papers
> published in any Special Supplement receive the same, high quality
> rigorous review as papers published in regular issues.
> Indeed, the agreement between T and F and the Authors/ Sponsors
> specifically note that publication of the Special Issue is contingent
> upon scientific review and acceptance of the papers. It does not
> guarantee
> acceptance. . The primary reason for publishing a Special Issue of
> CRT is to minimize the impact on our limited page budget. Papers
> included in the Special Supplements do not count against the current
> annual 920 page limit.
>
>
> As I recall, CRT has
> published 3 papers in the recent past on Glyphosate. All three
> papers were downloaded many times and have been widely cited,
> including

> by IARC. One paper by Griem et al contained extensive supplemental
 > material (This is different than a Special Issue Supplement). It is
 > not clear how well IARC reviewed this paper and, especially, the
 > electronic supplement.
 > However, I can assure you that the
 > electronic supplement is clearly marked in the text.
 >
 >
 >
 > After the IARC review
 > of glyphosate I was contacted by personnel from Monsanto and
 > InterTek, a private consulting firm, as to my interest in considering
 > one or multiple papers on glyphosate that would be a critique of
 > the IARC review. I responded that I would be enthusiastic about
 > considering one or multiple papers. I indicated my preference would
 > be to have one large paper or a collection of papers to be
 > published in a single issue. I indicated that since it was
 > anticipated that these papers would be comprehensive and long I
 > thought it unlikely these papers could be published in a regular
 > issue. I noted that I would expect the papers to have comprehensive
 > and transparent Declarations Of Interest, as is routine for CRT.
 > As an aside, I know of no other scientific journal that has as
 > rigorous a Declaration of Interest policy as CRT with publication of
 > each DOI.
 >
 >
 > Gunnar has raised the
 > issue of the employment affiliation of the authors and the past
 > association of some of the authors with Monsanto. I expect that to
 > be made clear in the DOIs. As a matter of policy, I do not think
 > where an individual author is employed (academe, government,
 > consulting firm, private consultant, etc) should be a determinant of
 > whether a paper should be considered for publication. I do expect
 > all relevant material relating to potential conflicts of interest
 > to be disclosed in the DOI. Quite frankly, I am concerned by many
 > journals allowing self proclamations from authors -- "We have no
 > conflicts of interest to declare." That is "eye wash". Conflicts
 > of Interest are in the eyes of the beholder not the Declarer.
 >
 >
 > I think my job as an
 > Editor is to see that the submitted paper receive a rigorous review
 > by outstanding experts from around the globe. In the case of the
 > submitted glyphosate papers I think I have selected some
 > outstanding reviewers, in some case up to 7 per paper. As an aside,
 > how many of you have received 7 sets of external review comments on
 > any paper, original research or review paper, you have authored?
 > Many of you agreed to review one or more of the five papers. For
 > that special effort I extend my thanks. I will be pleased to have
 > you review any or all of the revised papers. I use the review
 > comments to help guide my decision to accept, request revision
 > or reject a paper. Most importantly, I expect the authors to use

>
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>
> Subject: SV: 5 Glyphosate
> Papers
>
>
> To: "Roger McClellan"
> <roger.o.mcclellan@att[REDACTED]>,
> "david.warheit@[REDACTED]"
> <david.warheit@[REDACTED]>,
> "david_dorman@ncsu[REDACTED]"
> <david_dorman@ncsu[REDACTED]>
>
>
>
> Cc: "s.tsuda@iwate-u.ac[REDACTED]"
> <s.tsuda@iwate-u.ac[REDACTED]>
> "Mildred" <mbmorgan@hargray[REDACTED]>
>
>
>
> Date: Monday, May 2, 2016, 4:27
> AM
>
>
>
>
>
> Dear Roger,
>
>
> How will this will be introduced
> in the journal, i.e. how will it be explained that the 5 papers
> appear in a separate volume (assuming they will be accepted
> for publication) ?
>
>
> Nearly early all
>
>
> authors are more or less connected
> to Monsanto. My concern is that this may be viewed as
> an
> industry input and, more important, that the integrity
> and independence
> of CRT may be questioned by the scientific
> community.
>
>
> All the best

> McClellan" <roger.o.mcclellan@██████████>
> "Mildred"
>
>
>
> > <mbmorgan@hargray██████████>
>
>
>
> > Date: Thursday, April 14,
> 2016, 11:51 AM To all:
>
>
> > Attached are five
> papers
>
>
> critiquing the IARC review of
> glyphosate.
>
>
>
> > Assuming the papers are
> accepted after rigorous review , they will be >
> published in a single Special Supplement to CRT. I would
> be pleased if > you would
> agree to review the general paper and one or more
> of
> the > four detailed papers. If you are willing to
> review one or more paper > please linform my
> assistant, Mildred Morgan,
> mbmorgan@hargray██████████
> and > you will be formally invited.
>
>
> Thanks in advance for your help.
> Best
>
>
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>
> regards, Roger
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>
> --- On Thu, 4/14/16, Mildred

> Morgan <mbmorgan@hargray [REDACTED]>
> > wrote:
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>
> >
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>
> > > From: Mildred Morgan
> <mbmorgan@hargray [REDACTED]>
> > > Subject: 5 Glyphosate Papers > > To:
> "Roger McClellan"
>
>
> <roger.o.mcclellan@[REDACTED].t>
>
>
>
> > > Date: Thursday, April
> 14, 2016, 9:38 AM The 5 glyphosate papers > >
> attached.
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Roger McClellan

From: Whalley, Charles <[REDACTED]@tandf.co.uk>
Sent: Wednesday, June 1, 2016 3:37 AM
To: Gunnar Johanson; Roger McClellan
Cc: mbmorgan@hargray[REDACTED]; s.tsuda@iwate-u.ac[REDACTED]; dellarcov@gmail[REDACTED]; david.warheit@[REDACTED]; david.dorman@nscu[REDACTED]; rcc0022@auburn[REDACTED]; f.guengerich@vanderbilt[REDACTED]; Samuel Cohen
Subject: RE: SV: SV: 5 Glyphosate Papers/ Comments from Gunnar

Dear Gunnar,

I understand your point about the extent of sponsorship, but I'm afraid this will have to remain confidential. I'm glad, otherwise, that the change I suggest below makes sense. I intend to implement this with the next published supplement, likely to be that of the glyphosate papers discussed below.

Once again, I'm grateful for this discussion, as it is a particularly pertinent issue for the journal. Any other thoughts, perspectives or suggestions on this from the board are very welcome, as ever.

All best wishes,
Charles

From: Gunnar Johanson [mailto:[REDACTED]@ki.se]
Sent: 24 May 2016 14:01
To: Whalley, Charles; Roger McClellan
Cc: mbmorgan@hargray[REDACTED]; s.tsuda@iwate-u.a[REDACTED]; dellarcov@[REDACTED]; david.warheit@[REDACTED]; david.dorman@nscu[REDACTED]; rcc0022@auburn[REDACTED]; f.guengerich@vanderbilt[REDACTED]; Samuel Cohen
Subject: SV: SV: SV: 5 Glyphosate Papers/ Comments from Gunnar

Dear Charles,
Sounds good, with that I am satisfied for now (although I would be happier if the extent of sponsorship was also indicated somehow).
All the best,
Gunnar

Dear Gunnar,

A change that I am planning for any sponsored supplements published in the 2016 volume and thereafter is to include a statement appended to each article, stating the name of the sponsor. In previous years this information was included with issue preliminary information, although as most sponsored supplements are now online-only this has become redundant. I also think that it's important for those reading an individual article to see the information without having to seek it out.

Do you think this would be a helpful change?

Best wishes,
Charles

From: Gunnar Johanson [mailto: [REDACTED]@ki.se]
Sent: 13 May 2016 14:29
To: Whalley, Charles; Roger McClellan
Cc: mbmorgan@hargray [REDACTED]; s.tsuda@iwate-u.ac [REDACTED]; dellarcov@ [REDACTED]; david.warheit@ [REDACTED]; david.dorman@nscu [REDACTED]; rcc0022@auburn [REDACTED]; f.quengerich@vanderbilt [REDACTED]; Samuel Cohen
Subject: SV: SV: SV: 5 Glyphosate Papers/ Comments from Gunnar

Dear Charles,

Thank you for the info. As far as can see, the T&F Annual Report is not helpful as it contains no information specific for CRT. I am happy to note that you are "... working to ensure ... making readers aware of which issues of the journal have been sponsored..." Can you give some more details how this will be done? By downloading and reading a random paper (Vol 45 S2 1-55), I find no information telling that T&F has been sponsored by the authors to publish the paper. If the sponsorship is not openly declared, it looks very much like "native advertising" or "embedded marketing". The elaborate peer-review and extensive DOI at the end of each paper are good but not sufficient, as the don't cover the relation between the authors and T&F.

Best regards,
Gunnar

PS. Roger, I see these mails as an internal discussion within the Editorial Board.

Från: Whalley, Charles [mailto: [REDACTED]@tandf.co.uk]
Skickat: den 13 maj 2016 11:27
Till: Roger McClellan; Gunnar Johanson
Kopia: mbmorgan@hargray [REDACTED]; s.tsuda@iwate-u.ac [REDACTED]; dellarcov@ [REDACTED]; david.warheit@ [REDACTED]; david.dorman@nscu [REDACTED]; rcc0022@auburn [REDACTED]; f.quengerich@vanderbilt [REDACTED]; Samuel Cohen
Ämne: RE: SV: SV: 5 Glyphosate Papers/ Comments from Gunnar

Dear Gunnar,

Thanks for your thoughts. I wanted to add to Roger's points below.

You're right to say that we publish the cost of publishing Open Access in CRT, which is \$2,950 and a flat fee across the journal and indeed across the majority of the journals we publish. However, as I mentioned, the cost of sponsoring a supplement in the journal (which varies) is confidential, as a commercial matter between us and the sponsor. The owner of CRT and my employer, Informa, is a public company and so publishes its annual report (<http://informa.com/investors/annual-reports/>), but I'm afraid that's as much information about the business operations of the journal and of Taylor & Francis that I can give you.

What we are doing is working to ensure that we are making readers aware of which issues of the journal have been sponsored, on top of the extensive Declarations of Interest that Roger insists upon. This information I think has more bearing than the actual monetary amount of any sponsorship. We would hope that readers can make their own judgement.

Even so, this is a particularly pertinent issue for CRT, due to the area it works in, and so your thoughts here, and the thoughts of the board, are very welcome. I'd be grateful for any other comments or suggestions as to how we can ensure that the journal continues to be seen as making an impartial and critical contribution to the literature. Short of areas of commercial sensitivity, I'm open to any other areas where we can increase transparency or demonstrate fairness. I also wonder if there's anything we can do to build bridges with all sides of these debates, although I'm speculating a little here.

As ever, I'd invite you all to feel free to contact me separately at my details below if you'd like to discuss personally.

Best wishes,
Charles

Charles Whalley - Managing Editor, Medicine & Health Science Journals

Taylor & Francis Group

4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK

Direct line: [REDACTED]

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registered in England under no. 1072954

From: Roger McClellan [[mailto:roger.o.mcclellan@\[REDACTED\]](mailto:roger.o.mcclellan@[REDACTED])]

Sent: 12 May 2016 17:11

To: Whalley, Charles; Roger McClellan; Gunnar Johanson

Cc: [mbmorgan@hargray\[REDACTED\]](mailto:mbmorgan@hargray[REDACTED]); [s.tsuda@iwate-u.ac.jp\[REDACTED\]](mailto:s.tsuda@iwate-u.ac.jp[REDACTED]); [dellarcov@gmail.com\[REDACTED\]](mailto:dellarcov@gmail.com[REDACTED]); [david.warheit@\[REDACTED\]](mailto:david.warheit@[REDACTED]); [david.dorman@nscu\[REDACTED\]](mailto:david.dorman@nscu[REDACTED]); [rcc0022@auburn\[REDACTED\]](mailto:rcc0022@auburn[REDACTED]); [f.quengerich@vanderbilt\[REDACTED\]](mailto:f.quengerich@vanderbilt[REDACTED]); Samuel Cohen

Subject: Re: SV: SV: 5 Glyphosate Papers/ Comments from Gunnar

Gunnar:

Thanks for your follow up note on the Special Glyphosate Supplement. I will off some clarification on some of the issues you raise.

First, let me address my role as the Editor of Critical Reviews in Toxicology. I do have a contract with Informa / Taylor and Francis for my services as Editor of CRT. That contract provides me a flat fee to cover all of my time and expenses for serving as Editor, the most important aspects of which are the maintenance of manuscript flow and the delivery of high quality, peer-reviewed manuscript to T and F. To assist me, I engage Mildred Morgan, who has worked effectively and efficiently with me for decades. The fee I receive is the same irrespective of the number of manuscripts moving through the system and whether CRT includes any Special Supplements. Hence, there is no financial incentive for me to promote the publication of Special Supplements. Indeed, every Special Supplement requires more effort from me and Mildred for which I receive NO additional reimbursement.

It follows logically to ask why I should consider recommending publication of any Special Supplements. I do so as part of my professional responsibility as Editor. I want to see the 920 pages allotted each year for regular issues of CRT used to publish high quality, high impact papers in a timely manner. That is a difficult balancing act involving (a) high scientific impact, (b) high scientific quality and (c) timeliness. Impact and quality are not the same. By impact I am referring to scientific information that is relevant to contemporary Societal issues. Scientific quality is independent of whether the content is relevant to Societal issues. Timeliness is obviously of concern for all authors, they would like to have their paper published as soon as possible. T and F addresses that issue in part by promptly processing all accepted manuscripts and posting them on line at the earliest possible date. However, no one would like to have their paper in limbo as to formal publication for months and months. Hence, the dilemma of every Editor and, especially Review Journal Editor. I want to have a modest back log but not an excessive back log. I can assure you I have had more than a few sleepless nights thinking about whether I have the right balance.

This brings me to the five Glyphosate papers. This is one of the world's highest impact chemicals. IARC operates one of the world's most widely recognized cancer hazard classification schemes. CRT previously published at least three widely cited review papers on Glyphosates that were considered in the IARC review. The IARC cancer hazard classification of Glyphosate is one of the most controversial cancer hazard classifications rendered in recent years. Although let me quickly note that the cancer hazard classifications rendered for "outdoor air" and "airborne particulate material" follow close behind. When I learned that Monsanto was going to sponsor a critical review of the cancer hazard of glyphosate, including a critique of the IARC review, managed by InterTek, I decided it would be highly desirable to publish that critical review in CRT. I thought then and now that CRT was the ideal publication venue for this review because of the rigor of CRT's review process, our transparent "Declaration of Interest" process and our desire to provide access to all underlying data through use of electronic supplements and electronic linkages.

In anticipation of the number of pages involved I quickly decided that it would be best to publish the new review as a Special Supplement. At that point I handed off to Charles Whalley, the Managing Editor of CRT, and the business office of T and F the negotiation of the details, including fees, for publishing the Special Supplement. As the recipients of this

memo know I have 60 years of experience as a scientist, scientific manager and science advisor. What may not be as well known is I have over 50 years of business experience running large scale research enterprises, including responsibility for the bottom line. That means making tough decisions as to when you hire and fire your scientific colleagues. To provide me better tools for working as a scientific business manager I enrolled and completed a Master of Management Science degree at the University of New Mexico, the equivalent of an MBA. I understand business - it is rough and tumble!!! I fully understand the T and F business decision to not release details, including publication fees, of the agreement between T and F and InterTek for publishing the Special Supplement containing the glyphosate papers. Indeed, I suspect the agreement at this stage has not yet been published because the number of pages to be published is not yet known. Wearing my "business hat" I can assure you that T and F has very straight forward business procedures for deciding what is a reasonable fee for publishing a Special Supplement containing 125, 150, 175 or 200 pages. It is not some arbitrary process guided by a "lets charge as much as possible" approach. Indeed, I suspect an examination of the fees typically charged by T and F for 'open access" will provide clues as to the cost to the sponsor of publishing the Special Supplement. As I hope everyone knows the "scientific publishing business" is a tough business today with rapidly changing practices. [As an aside, how many paper solicitations from fly by night journals have you received this month?] Bottom line, I count on T and F to run their publishing business in an ethical and business like manner. I am counting on that because I want them to be in business and publishing CRT indefinitely. I certainly do not want them to go out of business. The counter point is that I will continue to deliver them high scientific quality, high impact , rigorously peer reviewed manuscripts to fill the 920 pages of regular issues they have contractually agreed to provide to their subscribers and occasional provide papers for a Special Supplement. As an update, the five glyphosate papers are moving through an extraordinarily rigorous review process. The review comments meet the high standards of CRT and will help the authors further improve the final accepted version of the papers. I do anticipate preparing a "prelude" that will introduce the Special Supplement". I hope the foregoing material is helpful to all of you I welcome any further inquiries by e-mail or phone. (505-296-7083). Again, thank you for your assistance with CRT and , especially, with the glyphosate Special Supplement. With best regards,

Roger

PS This is a "business sensitive communication". I would appreciate your not sharing it or communicating the contents with any individuals other than the recipients.

On Thu, 5/12/16, Gunnar Johanson <[REDACTED]@ki.se> wrote:

Subject: SV: SV: 5 Glyphosate Papers/ Comments from Gunnar

To: "Whalley, Charles" <[REDACTED]@tandf.co.uk>, "Roger McClellan" <[REDACTED]@att.net>

Cc: "s.tsuda@iwate-u.ac.jp" <s.tsuda@iwate-u.ac.jp>, "dellarcov" <dellarcov@[REDACTED]>

"david.warheit" <david.warheit@[REDACTED]>, "david.dorman" <david.dorman@[REDACTED]>

"mbmorgan" <mbmorgan@[REDACTED]>, "rcc0022@auburn" <rcc0022@auburn>

"f.guengerich@vanderbilt.edu" <f.guengerich@vanderbilt.edu>, "Samuel Cohen" <scohen@unmc>

Date: Thursday, May 12, 2016, 7:49 AM

#yiv4818449056

#yiv4818449056 --

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5 2 2 2 4 3 2 4;}

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6 4 3 5 4 4 2 4;}

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div.yiv4818449056MsoNormal

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#yiv4818449056 .yiv4818449056MsoChpDefault
{font-size:10.0pt;}
_filtered #yiv4818449056 {margin:72.0pt 72.0pt 72.0pt
72.0pt;}
#yiv4818449056 div.yiv4818449056WordSection1
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#yiv4818449056

Thank you Charles for your prompt answer. What you say is all well, except that it is not satisfying with the secret agreement monetary agreement between T&F and the authors/sponsors. In my view, this should not be a business secret but similar as for regular open access articles where T&F openly declares the fees. The secrecy around the supplements opens up for suspicions of economic incentives for Taylor & Francis which in turns spills over to the journal since, even if there are no extra incentives for the supplements, I assume that the Chief Editor receives a salary or honorarium for his work (as he rightly should considering the importance of the task and all the effort he puts into it). Does anyone else have thoughts on this?
Best regards,
Gunnar

Gunnar Johanson
| Ph.D. |
Professor

Head, Unit of Work
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Nobels väg 13 | P.O. Box 210 | SE-171 77 Stockholm,
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<http://www.nordicexpertgroup.org>

Karolinska Institutet is one of the world's leading medical universities. Its mission is to contribute to the improvement of human health through research and education. Karolinska Institutet accounts for over 40 per cent of the medical academic research conducted in Sweden and offers the country's broadest range of education in medicine and health sciences. Since 1901 the Nobel Assembly at Karolinska Institutet has selected the

Nobel laureates in Physiology or Medicine.

Från: Whalley, Charles
[mailto:Charles.Whalley@tandf.co.uk]

Skickat: den 10 maj 2016 18:05

Till: Gunnar Johanson; Roger McClellan

Kopia: s.tsuda@iwate-u.ac.jp; dellarcov@gmail.com;
david.warheit@gmail.com; david.dorman@nscu.edu;
mbmorgan@hargray.com; rcc0022@auburn.edu;
f.guengerich@vanderbilt.edu; Samuel Cohen

Ämne: RE: SV: 5 Glyphosate Papers/ Comments from Gunnar

Dear all,

Many thanks for including me on your discussions here, as I'm grateful to hear your thoughts on this crucial issue for the journal.

As Gunnar has noted, CRT commonly publishes supplements funded by industry sponsorship. These allow the authors to publish as a stand-alone issue separate from the normal schedule of issues, meaning that they can publish as soon as the articles are accepted. These supplements are commonly made free-to-view, and are promoted by Taylor & Francis. Unsurprisingly, industry groups often find this publication option attractive.

The sponsorship in no way guarantees acceptance. To reiterate Roger's comments, the commercial and editorial elements of the journal are entirely separate. Editorial policy is Roger's responsibility. We do not overrule or interfere in his decisions for commercial reasons. Similarly, these articles are subject to all the same peer review and scrutiny of their declarations of interest as any other manuscript. Additionally, to be clear, there is no financial incentive for anyone involved in the editorial process relating to sponsored supplements.

I can't comment on how much sponsors pay for these supplements, as this is commercially sensitive.

Regarding publishing a commentary alongside this proposed issue, I'd be happy to make room for such an editorial, if that's Roger's decision

following
this suggestion. I would suggest that the focus of such a
commentary should be on the significance of these articles,
as Vicki has suggested, with an additional opportunity to
remind our readership of editorial policy around sponsored
supplements and how it
applies in this case. I will, however, leave this up to
Roger.

I hope this helps clarify
matters from the publisher's perspective. Please do let me
know if you have any further questions or comments on this.
I'm very eager to hear them!

All best wishes,
Charles

Charles Whalley

-
Managing Editor, Medicine & Health Science
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registered in England under no.
1072954

From: Gunnar Johanson [mailto:[REDACTED]@ki.se]

Sent: 09 May 2016 14:44

To: Roger McClellan

Cc: s.tsuda@iwate-u.ac.jp [REDACTED]

dellarcov@██████████ david.warheit@██████████
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mbmorgan@hargrav██████████; rcc0022@auburn██████████
Whalley, Charles;
f.guengerich@vanderbilt██████████
Samuel Cohen

Subject: SV: SV: 5 Glyphosate Papers/ Comments from
Gunnar

Thank you Roger for clarifying. It is good with the rigorous review and detailed COIs of CRT, I have no problem with those items or, for that matter, that industry (or other vested interests) funds research and expert groups and seek to publish their results.

My remaining concern is that it may be seen as industry is paying their way into the journal ("The authors/ sponsors of these Supplemental Issues pay a special fee negotiated between the Authors / Sponsors and Taylor and Francis. As the CRT Editor, I have nothing to do with this business transaction. My role is to assure that all papers published in any Special Supplement receive the same, high quality rigorous review as papers published in regular issues."). I checked the last 15 supplemental papers in CRT, all stem from industry. It is reasonable that the authors/sponsors pay for the publication costs but not a lot more, as this might bias the review and publishing processes.

So, I would appreciate a clarification how much is paid by the authors/sponsors to the publisher and how editors and reviewers are reimbursed (if at all). Maybe Charles Whalley can respond to this?

Best regards,

Gunnar

PS. I agree with Vicky about an accompanying commentary.

-----Ursprungligt meddelande-----

Från: Roger McClellan [mailto:roger.o.mcclellan@]

Skickat: den 8 maj 2016 21:42

Till: Gunnar Johanson

Kopia: s.tsuda@iwate-u.ac

dellarcov@ david.warheit@
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mbmorgan@hargrav roger.o.mcclellan@
rcc0022@auburn

Charles.Whalley@tan f.euengerich@vanderbilt
Samuel Cohen

Ämne: Re: SV: 5 Glyphosate Papers/ Comments from Gunnar

Gunnar and other members of the
CRT Editorial Advisory Board

Gunnar, thank you
for your e-mail concerning the publication of a Supplemental
Issue including 5 papers on Glyphosate. Your e-mail was a
follow up to
our discussion of this matter at our Editorial Advisory
Board in New Orleans and my distribution of copies of the
papers.

By way of background,
CRT in recent years has included 920 pages each year which
have been published on line electronically and last year
published at
year end as a single printed copy. The authors of some
papers have purchased on line access.

In addition to the
regular issues, CRT has a long standing practice of
publishing Special Supplements. The authors/ sponsors of
these Supplemental Issues
pay a special fee negotiated between the Authors / Sponsors
and Taylor and Francis. As the CRT Editor, I have
nothing to do with this business transaction. My role is to
assure that all papers published in any Special Supplement
receive the same, high quality
rigorous review as papers published in regular issues.
Indeed, the agreement between T and F and the Authors/
Sponsors specifically note that publication of the Special
Issue is contingent upon scientific review and acceptance of
the papers. It does not guarantee
acceptance. . The primary reason for publishing a Special
Issue of CRT is to minimize the impact on our limited page
budget. Papers included in the Special Supplements do not
count against the current annual 920 page
limit.

As I recall, CRT has
published 3 papers in the recent past on Glyphosate. All
three papers were downloaded many times and have been widely
cited, including
by IARC. One paper by Griem et al contained extensive
supplemental material (This is different than a Special
Issue Supplement). It is not clear how well IARC reviewed
this paper and , especially, the electronic supplement.
However, I can assure you that the
electronic supplement is clearly marked in the text.

After the IARC review of glyphosate I was contacted by personnel from Monsanto and InterTek, a private consulting firm, as to my interest in considering one or multiple papers on glyphosate that would be a critique of the IARC review. I responded that I would be enthusiastic about considering one or multiple papers. I indicated my preference would be to have one large paper or a collection of papers to be published in a single issue. I indicated that since it was anticipated that these papers would be comprehensive and long I thought it unlikely these papers could be published in a regular issue. I noted that I would expect the papers to have comprehensive and transparent Declarations Of Interest , as is routine for CRT. As an aside, I know of no other scientific journal that has as rigorous a Declaration of Interest policy as CRT with publication of each DOI.

Gunnar has raised the issue of the employment affiliation of the authors and the past association of some of the authors with Monsanto. I expect that to be made clear in the DOIs. As a matter of policy, I do not think where an individual author is employed (academe, government, consulting firm, private consultant, etc) should be a determinant of whether a paper should be considered for publication. I do expect all relevant material relating to potential conflicts of interest to be disclosed in the DOI. Quite frankly, I am concerned by many journals allowing self proclamations from authors --"We have no conflicts of interest to declare." That is "eye wash". Conflicts of Interest are in the eyes of the beholder not the Declarer.

I think my job as an Editor is to see that the submitted paper receive a rigorous review by outstanding experts from around the globe. In the case of the submitted glyphosate papers I think I have selected some outstanding reviewers, in some case up to 7 per paper. As an aside, how many of you have received 7 sets of external review comments on any paper, original research or review paper, you have authored? Many of you agreed to review one or more of the five papers. For that special effort I extend my thanks. I will

be pleased to have you review any or all of the revised papers. I use the review comments to help guide my decision to accept, request revision or reject a paper. Most importantly, I expect the authors to use the review comments to further improve their revised paper.

The five glyphosate papers are still under review. In general, the review comments are very positive and constructive. Many reviewers noted they were pleased to have these papers published in CRT.

Gunnar has raised the issue of my publishing a commentary on the five papers as part of the Special Supplement . I have never published such a commentary for either a regular issue or Special Issue. MY basic view is that all papers published in CRT "speak for themselves". However, I am willing to consider such a commentary for this Special Issue if you think it useful. If I were to prepare one it would include many of the points made here. Of course, I would also need to refer to the IARC process and the IARC decision on glyphosate. It is my view that the five papers published in CRT will represent the most comprehensive review of the world's literature on the potential carcinogenicity of glyphosate and be widely cited by others.

I welcome you views on this important matter.

Best regards,

Roger

On Mon, 5/2/16, Gunnar Johanson

<[REDACTED]@kj.se>

wrote:

Subject: SV: 5 Glyphosate
Papers

To: "Roger McClellan"

<roger.o.mcclellan@[REDACTED]>

"david.warheit@[REDACTED]"

<david.warheit@[REDACTED]>

"david.dorman@ncsu"

<david.dorman@ncsu@[REDACTED]>

Cc: "s.tsuda@iwate-u.ac.jp"

<s.tsuda@iwate-u.ac.jp>

"Mildred" <mbmorgan@hargray.com>

Date: Monday, May 2, 2016, 4:27
AM

Dear Roger,

How will this will be introduced
in the journal, i.e. how will it be explained that the 5
papers appear in a separate volume (assuming they will be
accepted
for publication) ?

Nearly early all

authors are more or less connected
to Monsanto. My concern is that this may be viewed as an
industry input and, more important, that the integrity

and independence
of CRT may be questioned by the scientific
community.

All the best

Gunnar

-----Ursprungligt
meddelande-----

Från: Roger McClellan [mailto:[roger.o.mcclellan@\[REDACTED\]](mailto:roger.o.mcclellan@[REDACTED])]

Skickat: den 14 april 2016
20:55

Till:
[david.warheit@\[REDACTED\]](mailto:david.warheit@[REDACTED])

[david_dorman@\[REDACTED\]](mailto:david_dorman@[REDACTED])

Gunnar Johanson

Kopia:
s.tsuda@iwate-u.ac.jp

[roger.o.mcclellan@\[REDACTED\]](mailto:roger.o.mcclellan@[REDACTED]);

Mildred

Ämne: Fw: 5 Glyphosate
Papers

--- On Thu, 4/14/16, Roger
McClellan <[roger.o.mcclellan@\[REDACTED\]](mailto:roger.o.mcclellan@[REDACTED])>

wrote:

> From: Roger

McClellan <[roger.o.mcclellan@\[REDACTED\]](mailto:roger.o.mcclellan@[REDACTED])>

> Subject: Fw: 5 Glyphosate
Papers

> To:
bolt@ifado [REDACTED]
rcc0020@auburn [REDACTED] f.guengerich@vanderbilt [REDACTED]

> "Samuel Cohen"

<scohen@unmc>

> Cc: "Roger
McClellan" <roger.o.mcclellan@>,
"Mildred"

> <mbmorgan@hargray>

> Date: Thursday, April 14,
2016, 11:51 AM To all:

> Attached are five
papers

critiquing the IARC review of
glyphosate.

> Assuming the papers are
accepted after rigorous review , they will be >
published in a single Special Supplement to CRT. I would
be pleased if > you would
agree to review the general paper and one or more of
the > four detailed papers. If you are willing to
review one or more paper > please inform my
assistant, Mildred Morgan,
mbmorgan@hargray
and > you will be formally invited.

Thanks in advance for your help.
Best

>

regards, Roger

>

>

--- On Thu, 4/14/16, Mildred
Morgan <[mbmorgan@hargrav\[REDACTED\]](mailto:mbmorgan@hargrav[REDACTED])>
> wrote:

>

>> From: Mildred Morgan
<[mbmorgan@hargrav\[REDACTED\]](mailto:mbmorgan@hargrav[REDACTED])>
>> Subject: 5 Glyphosate Papers >> To:
"Roger McClellan"

<[roger.o.mcclellan@att\[REDACTED\]](mailto:roger.o.mcclellan@att[REDACTED])>

>> Date: Thursday, April
14, 2016, 9:38 AM The 5 glyphosate papers >>
attached.

>>

>

>

>>

Roger McClellan

From: onbehalfof+mbmorgan+hargray.com@manuscriptcentral.com on behalf of
mbmorgan@hargray.com
Sent: Friday, May 13, 2016 4:58 AM
To: roger.o.mcclellan@hargray.com
Subject: All required reviews have been returned for Manuscript ID BTXC-2016-0026

13-May-2016

Dear Dr Roger McClellan:

All required reviews have been returned by the reviewers for Manuscript ID BTXC-2016-0026 entitled "Glyphosate in the general population and in applicators: A critical review of studies on exposures" with Dr Ashley Roberts as contact author.

Please look at the reviews and make a decision by 27-May-2016.

Sincerely,
Mildred B Morgan
Critical Reviews in Toxicology Editorial Office mbmorgan@

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[REDACTED]>
Sent: Saturday, May 14, 2016 10:03 AM
To: Ashley Roberts
Cc: Mildred; Roger McClellan
Subject: Titles for Constellation of Glyphosate papers

Ashley:

As you coordinate the revision of the five glyphosate papers please give consideration to revising the titles. One option is to use a single master title like "Review of Potential Carcinogenicity of Glyphosate:" and assign the five papers sub- titles like ---- I. Overview and Summary Conclusions, II. Exposure Assessment, III. Animal Evidence , IV. Epidemiological Evidence and V. Mechanistic Evidence. This would parallel the IARC structure which is being critiqued. The current titles have been confusing to some reviewers.

As I have noted earlier, many of the reviewers of the 5 papers have called for greater clarity in presenting the approach used and conclusions drawn by IARC and then the comparison and contrasting of the approach and conclusions of the InterTek organized reviews.

Best regards,
Roger

Roger McClellan

From: John Acquavella <acquajohn@[REDACTED]>
Sent: Saturday, May 14, 2016 10:35 AM
To: Roger McClellan
Cc: mbmorgan@hargray[REDACTED]; ashley.roberts@infertek[REDACTED]
Subject: Re: Critical Reviews in Toxicology - Decision on Manuscript ID BTXC-2016-0029

Roger:

Thank you for the note. My affiliation is with Aarhus University. Like my co-authors, we can consult as we judge appropriate and our universities are not involved. I can see that my email signature can cause confusion and have revised it.

That being said, I will make sure that our disclosure of interests statement is clear - that we were all acting as independent consultants. We realize that this is a controversial area, but we hope that fair minded people will see the scientific value in our review - as all the reviewers did.

It is nice to know about your Aarhus connection. One of the great things about my professorship is spending time in residence in Aarhus. I go approximately 3 times a year to teach, advise students, and work with colleagues. The Department of Clinical Epidemiology is a great department and they have access to unparalleled national data sources for clinical epidemiology research. They are not political at all and actually value having faculty with a background in private industry. That's refreshing.

Regards,

John

John Acquavella, PhD FACE FISPE
Professor, Dept Clinical Epidemiology
Aarhus University, Denmark
+1 [REDACTED]
+1 9 [REDACTED]

On 5/14/16, 9:18 AM, "Roger McClellan" <[REDACTED]@att.net> wrote:

>John:

> I note from your e-mail you are using a combination title and address, ie Consultant and Professor. I think this will require greater clarity in the final papers. Am I correct in assuming this work was done as an independent consultant without any involvement of Aarhus University? I raise this because I can expect the critics of this and the other papers

Roger McClellan

From: onbehalfof+roger.o.mcclellan+[REDACTED]@manuscriptcentral.com on behalf of roger.o.mcclellan@[REDACTED]
Sent: Wednesday, May 25, 2016 5:01 PM
To: roger.o.mcclellan@[REDACTED]
Cc: mbmorgan@hargray[REDACTED]
Subject: Manuscript ID BTXC-2016-0029.R1 now in your Associate Editor Center

25-May-2016

Dear Dr McClellan:

The above manuscript, entitled "Glyphosate Epidemiology Expert Panel Review A weight of evidence systematic review of the relationship between glyphosate exposure and non-Hodgkin's lymphoma or multiple myeloma" with Professor John Acquavella as contact author, has been assigned to you and is awaiting reviewer selection. Please go to your Editor-in-Chief Center at <https://mc.manuscriptcentral.com/btxc> and select reviewers by 27-May-2016.

Sincerely,

Roger O. McClellan
Editor-in-Chief, Critical Reviews in Toxicology roger.o.mcclellan@[REDACTED]

Roger McClellan

From: Ashley Roberts Intertek <ashley.roberts@intertek [REDACTED]>
Sent: Monday, May 16, 2016 10:04 AM
To: roger.o.mcclellan@[REDACTED]; Judy Vowles Intertek
Cc: mbmorgan@hargray [REDACTED]
Subject: RE: Critical Reviews in Toxicology

Thank you Roger

Ashley Roberts, Ph.D.
Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Tel: +1 905-542-2900
Fax: +1 905-542-1011
E-mail: ashley.roberts@intertek [REDACTED]
2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

-----Original Message-----

From: onbehalfof+roger.o.mcclellan+[REDACTED]@manuscriptcentral.com
[mailto:onbehalfof+roger.o.mcclellan+[REDACTED]@manuscriptcentral.com] On Behalf Of roger.o.mcclellan@[REDACTED]
Sent: May-16-16 12:03 PM
To: Ashley Roberts Intertek; Judy Vowles Intertek
Cc: roger.o.mcclellan@[REDACTED]; mbmorgan@hargray [REDACTED]
Subject: Critical Reviews in Toxicology

16-May-2016

BTXC-2016-0025 - Glyphosate: Carcinogenic potential – A Critical review using four Expert Panels

Dear Dr Ashley Roberts:

By copy of this e-mail I am asking Mildred to provide you an additional set of comments on the summary paper. I strongly concur with the reviewer's suggestions. As you will note there is a strong consensus that the InterTek coordinated review and critique of the IARC review and classification of glyphosate needs to be very direct in comparing and contrasting the approach and results for IARC and the InterTek panels. I strongly support the inclusion in the summary paper of a table listing the participants in each InteTek Panel and a summary table comparing and contrasting key findings and conclusions of the IARC Panels and the InterTek panels with linkages to each of the detailed papers.

There may be one more set of comments on this paper. I will keep you posted.

Sincerely,
Dr Roger McClellan
Critical Reviews in Toxicology

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<http://www.intertek.com>

Roger McClellan

From: Whalley, Charles <Charles.Whalley@tandf[REDACTED]>
Sent: Friday, May 20, 2016 8:16 AM
To: Mildred Morgan; 'Roger McClellan'
Subject: RE: Glyphosate manuscripts in ScholarOne

Dear Mildred,

I see! I didn't realise they'd already had a decision, which is why I couldn't find them. I'm a little behind.

I am sorry that you're still having to work with your left hand, so I'm especially grateful for your response here. I do hope you are back to both hands soon.

Very best wishes,
Charles

From: Mildred Morgan [mailto:mbmorgan@hargray[REDACTED]]
Sent: 20 May 2016 15:07
To: Whalley, Charles; 'Roger McClellan'
Subject: RE: Glyphosate manuscripts in ScholarOne

Dear Charles:

All of the Glyphosate papers are loaded into Scholar One , they have all been reviewed and the comments sent back to authors for revision of the papers. Dr. Ashley Roberts has also received all of the comments.

I am still typing with only my left hand so it is a slow process. I am going to therapy 3 times a week. I will be so happy to be able to use both hands. Just going to take and patience.

Mildred

From: Whalley, Charles [mailto:Charles.Whalley@tandf[REDACTED]]
Sent: Friday, May 20, 2016 9:49 AM
To: Roger McClellan (roger.o.mcclellan@[REDACTED])
Cc: mbmorgan@hargray[REDACTED]
Subject: Glyphosate manuscripts in ScholarOne

Dear Roger and Mildred,

Am I right in thinking that the Glyphosate manuscripts from Dr Roberts' group are not currently loaded into the ScholarOne system?

Best wishes,
Charles

Charles Whalley - Managing Editor, Medicine & Health Science Journals
Taylor & Francis Group
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK
Direct line: [REDACTED]
Switchboard: [REDACTED]
[REDACTED]@tandf.co.uk

www.tandfonline.com

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Roger McClellan

From: Whalley, Charles <Charles.Whalley@tandf[REDACTED]>
Sent: Friday, May 20, 2016 9:00 AM
To: Roger McClellan
Cc: mbmorgan@hargray[REDACTED]
Subject: RE: Glyphosate manuscripts in ScholarOne

Dear Roger,

Many thanks for confirmation. I wasn't aware that a decision had already been returned on these manuscripts. I've got what I need to start preparing a quote for a possible supplement.

All best wishes as ever,
Charles

From: Roger McClellan [mailto:roger.o.mcclellan@[REDACTED]]
Sent: 20 May 2016 15:41
To: Whalley, Charles
Cc: mbmorgan@hargray[REDACTED]; Roger McClellan
Subject: Re: Glyphosate manuscripts in ScholarOne

Charles:

All five manuscripts have gone through a rigorous initial round of review including 10 reviewers on the Introduction and Summary paper. The comments have been positive and will help the authors further improve the constellation of five papers. Making revisions and ensuring the papers are appropriately cross linked and that references and Supplemental material are in order is going to be challenging for Ashley and his colleagues and will take some time.

I suspect the reference to Sponsor should note InterTek with reimbursement by Monsanto.

Best regards,
Roger

On Fri, 5/20/16, Whalley, Charles <[REDACTED]@tandf.co.uk> wrote:

Subject: Glyphosate manuscripts in ScholarOne
To: "Roger McClellan (roger.o.mcclellan@[REDACTED])" <roger.o.mcclellan@[REDACTED]>
Cc: "mbmorgan@hargray[REDACTED]" <mbmorgan@hargray[REDACTED]>
Date: Friday, May 20, 2016, 6:49 AM

Dear Roger
and Mildred,

Am I right
in thinking that the Glyphosate manuscripts from Dr
Roberts' group are not currently loaded into the
ScholarOne system?

Best
wishes,
Charles

Charles Whalley

Managing Editor, Medicine & Health Science
Journals

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Roger McClellan

From: Ashley Roberts Intertek <[REDACTED]@intertek.com>
Sent: Thursday, May 26, 2016 8:33 AM
To: roger.o.mcclellan@[REDACTED]
Cc: mbmorgan@hargray[REDACTED]
Subject: RE: Critical Reviews in Toxicology

Hi Roger,

I will call later today to discuss.

Best Wishes

Ashley

Ashley Roberts, Ph.D.
Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Tel: +1 [REDACTED]
Fax: +1 [REDACTED]
E-mail: [REDACTED]@intertek.com
2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

-----Original Message-----

From: onbehalfof+roger.o.mcclellan+[REDACTED]@manuscriptcentral.com
(mailto:onbehalfof+roger.o.mcclellan+[REDACTED]@manuscriptcentral.com) On Behalf Of roger.o.mcclellan [REDACTED]
Sent: May-25-16 6:58 PM
To: Ashley Roberts Intertek; Judy Vowles Intertek
Cc: roger.o.mcclellan@[REDACTED] mbmorgan@hargray [REDACTED]
Subject: Critical Reviews in Toxicology

25-May-2016

BTXC-2016-0026.R1 - Glyphosate in the general population and in applicators: A critical review of studies on exposures

Dear Dr Ashley Roberts:

Let's discuss how to better identify the Supplemental Material so it will stand alone and be informative to the reader. A brief paragraph to introduce it would be helpful to the reader.

A one or two sentence descriptor for each set of Supplemental Material that could be used at the end of the text would be useful.

Sincerely,
Dr Roger McClellan

Critical Reviews in Toxicology

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Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[REDACTED]>
Sent: Tuesday, July 5, 2016 3:31 PM
To: Roger McClellan; Ashley Roberts Intertek
Cc: Roger McClellan; Mildred
Subject: Re: Need for telephone conversation/ Followup

Ashley:

It is shown below - [REDACTED] Or you can reach me at my desk at [REDACTED] if I am at my desk, it is my fax line. Or call my cell phone at [REDACTED] I hope your having a great time in Nova Scotia, one of my favorite spots. I found a lot of McClellans and MacLellans there, almost all were six feet under.

Roger

On Tue, 7/5/16, Ashley Roberts Intertek <[REDACTED]@intertek.com> wrote:

Subject: Re: Need for telephone conversation/ Followup
To: "Roger McClellan" <roger.o.mcclellan@[REDACTED]>
Cc: "Roger McClellan" <roger.o.mcclellan@[REDACTED]>, "Mildred" <mbmorgan@hargray[REDACTED]>
Date: Tuesday, July 5, 2016, 2:17 PM

Hi Roger,

As I am on vacation, please
could you send me your telephone number so I can call you?

Thanks

Ashley

Sent from my BlackBerry 10 smartphone on the Bell network.

Original Message
From: Roger McClellan
Sent:
Tuesday, July 5, 2016 5:37 PM
To: Ashley
Roberts Intertek
Reply To: Roger
McClellan
Cc: Roger McClellan; Mildred
Subject: Re: Need for telephone conversation/ Followup

Ashley:

I am also
eager to get these papers wrapped up. I was hoping I could deal with one individual, you, rather than multiple authors. However, I understand you are away from your office for some time. There are several issues that need to be addressed.

First, the Acknowledgements

section and Declaration of Interest sections in all the papers need further attention. I want them to be as clear and transparent as possible. At the end of the day I want the most aggressive critics of Monsanto, your organization and each of the authors to read them and say - Damm, they covered all the points we intended to raise.

I was anticipating that each paper would include an Acknowledgements section that would read something like —"The authors gratefully acknowledge the extensive comments received from xx reviewers selected by the Editor and anonymous to the authors. These comments were very helpful in revising the paper." I am proud of the rigorous review given these papers and want to make certain that review is clear to all readers. The Acknowledgements sections should also identify any other reviewers of the paper and any editorial assistance.

The DOIs should start something like —" 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 remainder of the DOI should make clear how individuals were engaged, ie by Intertek. If you can say without consultation with Monsanto that would be great. If there was any review of the reports by Monsanto or their legal representatives that needs to be disclosed. Any previous appearances by individuals before regulatory agencies in the USA or abroad needs to be disclosed. The wording concerning involvement of employees of your firm and Can-Tox is not very clear and invites criticism, let it all hang out. Identify the individuals by name and note the nature of work done by the organization for Monsanto.

I want to be assured that all of the references in all the papers are clearly identified and can be made available to any interested person. Can your firm fill that role. I am concerned that in the summary paper key information is not directly referenced , rather reference is made to EPA documents. It is important to be as clear and transparent as possible. As I recall one paper refers to a "Confidential Document". Can that document be made available now?

As a summary point, did the review you conducted use ANY papers not referenced by IARC? If so, should that point be addressed in the summary paper and , perhaps, other papers as appropriate.

On a personal note I think the papers to a varying degree would benefit from very careful editing to minimize language that is combative. I had assumed that at a final stage all the papers would have been carefully edited by a professional editor.

Please give me a call at

██████████ to discuss how best to move forward.

Best regards, Roger

On Tue, 7/5/16, Ashley Roberts Intertek ██████████@intertek.com> wrote:

Subject: Re: Need
for telephone conversation
To: "Roger
McClellan" <██████████@att.net>
Date: Tuesday, July 5, 2016, 4:06 AM

Hi Roger

I am messaging you from a few days vacation I am taking in Nova Scotia.

I am getting a lot of pressure to publish the papers for a lot of reasons as you can imagine. Please could you let me know the changes you require that we spoke of while I was in China. Sorry to rush you on

this matter but these papers
will also
be useful for ECHA which is a European Agency
that is reviewing the safety of glyphosate. We would very
much like to share our
manuscripts with them to aid in their

deliberations.

I look
forward to receiving your reply.

Best Wishes

Ashley

Sent from my
BlackBerry 10 smartphone on the Bell network.
Original Message

From: Roger McClellan
Sent: Sunday, June
19, 2016 8:41 PM
To: Ashley Roberts
Intertek
Reply To: Roger McClellan
Cc: Mildred; Roger McClellan

Subject: Need for telephone conversation

Ashley:
I think it would be
useful if you and I were to have a

telephone conversation with regard to the glyphosate papers.
What is your schedule on Monday or
Wednesday and your
availability for a
call?

Do you have a professional editor
assisting with finalizing
these papers? You
reference in the DOIs that employees of

your firm previously did work for Monsanto. Can you provide
details, ie individuals and areas
of work and time period? I
note at least
one reference to a confidential report. Has

that now been disclosed. Is there any work that the Panels

used in drawing their conclusions
that is not now available?

I would have
been happier if all the paper had noted the

number of external reviewers and the value of the comments.

I am concerned that the authors
have chosen to not comply
with requests to
make it easier for the readers of identify

ALL the relevant literature. Why not bend over backwards to
address concerns? I am still concerned about the tone in
some places. Why
antagonize the readers? I am still not

clear as to the process used by all of the Panels. These
reports are essentially a rebuttal of IARC's process and
conclusions. There appears to
be a reluctance to be
absolutely clear in
presenting exactly what IARC concluded ,

the Panels conclusions and how they differ. Am I missing
something?

I look forward to
speaking with you.

Best regards,
Roger

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Subject: Re: Need for telephone conversation
To: "Roger McClellan" <roger.o.mcclellan@██████████>
Date: Tuesday, July 5, 2016, 4:06 AM

Hi Roger

I am messaging you from a few days vacation I am taking in Nova Scotia.

I am getting a lot of pressure to publish the papers for a lot of reasons as you can imagine. Please could you let me know the changes you require that we spoke of while I was in China. Sorry to rush you on this matter but these papers will also be useful for ECHA which is a European Agency that is reviewing the safety of glyphosate. We would very much like to share our manuscripts with them to aid in their deliberations.

I look forward to receiving your reply.

Best Wishes

Ashley

Sent from my BlackBerry 10 smartphone on the Bell network.

Original Message

From: Roger McClellan

Sent: Sunday, June 19, 2016 8:41 PM

To: Ashley Roberts Intertek

Reply To: Roger McClellan

Cc: Mildred; Roger McClellan

Subject: Need for telephone conversation

Ashley:

I think it would be useful if you and I were to have a telephone conversation with regard to the glyphosate papers. What is your schedule on Monday or Wednesday and your availability for a call?

Do you have a professional editor assisting with finalizing these papers? You reference in the DOIs that employees of your firm previously did work for Monsanto. Can you provide details, ie individuals and areas of work and time period? I note at least one reference to a confidential report. Has that now been disclosed. Is there any work that the Panels used in drawing their conclusions that is not now available?

I would have been happier if all the paper had noted the number of external reviewers and the value of the comments.

I am concerned that the authors have chosen to not comply with requests to make it easier for the readers of identify ALL the relevant literature. Why not bend over backwards to address concerns? I am still concerned about the tone in some places. Why antagonize the readers? I am still not clear as to the process used by all of the Panels. These reports are essentially a rebuttal of IARC's process and conclusions. There appears to be a reluctance to be absolutely clear in presenting exactly what IARC concluded, the Panels conclusions and how they differ. Am I missing something?

I look forward to speaking with you.

Best regards,

Roger

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Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[REDACTED]>
Sent: Thursday, July 7, 2016 9:09 AM
To: Ashley Roberts Intertek
Cc: Mildred; Roger McClellan
Subject: Re: Final Revisions

Ashley:

Thanks for the revised papers. I have started to review them. In the summary paper key information is presented in a paragraph beginning at line 127. This is now supported by a reference to a secondary document, ie EPA. Can you provide the primary references. I would personally like to know the reviewing pathologist and have a reference to that report, the other 3 pathologists and a reference to their report and the Pathology Working Group and a reference to their report. Can these be provided?

In the DOI reference is made to a key report Can-Tox was involved in preparing along with Gary Williams. Can that report be referenced? Perhaps it s already referenced in the text. Even if it is reference it again in the DOI.

I will be working through the others and will no doubt have additional comments.

Best regards, Roger

On Wed, 7/6/16, Ashley Roberts Intertek <[REDACTED]@intertek.com> wrote:

Subject: Final Revisions
To: "Roger McClellan" <roger.o.mcclellan@[REDACTED]>
Cc: "Mildred" <mbmorgan@hargray[REDACTED]>
Date: Wednesday, July 6, 2016, 5:16 PM

Dear Roger,

Please find attached the revised manuscripts as per your request below.

The changes can be seen as tracked changes for the sake of easy review. We have changed the DOI and made some slight editorial changes to the animal carcinogenicity paper.

I hope these address your concerns? I am currently on my way to Brussels so if these changes are acceptable, please could you confirm and provide me with a letter regarding our sharing these papers with ECHA.

Thanking you in anticipation.

Best Wishes

Ashley

PS. I noted that there was a McClellan street just outside of the town of Baddeck today. I am presuming some of your ancestors migrated to that part of Nova Scotia!!!

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

Tel: +1 [REDACTED]
Fax: + [REDACTED]
E-mail: [REDACTED]@intertek.com
2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

-----Original Message-----

From: Roger McClellan [mailto:roger.o.mcclellan@[REDACTED]]
Sent: July-05-16 4:35 PM
To: Ashley Roberts Intertek
Cc: Roger McClellan; Mildred
Subject: Re: Need for telephone conversation/ Followup

Ashley:

I am also eager to get these papers wrapped up. I was hoping I could deal with one individual, you, rather than multiple authors. However, I understand you are away from your office for some time. There are several issues that need to be addressed.

First, the Acknowledgements section and Declaration of Interest sections in all the papers need further attention. I want them to be as clear and transparent as possible. At the end of the day I want the most aggressive critics of Monsanto, your organization and each of the authors to read them and say - Damm, they covered all the points we intended to raise.

I was anticipating that each paper would include an Acknowledgements section that would read something like ---"The authors gratefully acknowledge the extensive comments received from xx reviewers selected by the Editor and anonymous to the authors. These comments were very helpful in revising the paper." I am proud of the rigorous review given these papers and want to make certain that review is clear to all readers. The Acknowledgements sections should also identify any other reviewers of the paper and any editorial assistance.

The DOIs should start something like --" 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 remainder of the DOI should make clear how individuals were engaged, ie by Intertek. If you can say without consultation with Monsanto that would be great. If there was any review of the reports by Monsanto or their legal representatives that needs to be disclosed. Any previous appearances by individuals before regulatory agencies in the USA or abroad needs to be disclosed. The wording concerning involvement of employees of your firm and Can-Tox is not very clear and invites criticism, let it all hang out. Identify the individuals by name and note the nature of work done by the organization for Monsanto.

I want to be assured that all of the references in all the papers are clearly identified and can be made available to any interested person. Can your firm fill that role. I am concerned that in the summary paper key information is not directly referenced, rather reference is made to EPA documents. It is important to be as clear and transparent as possible. As I recall one paper refers to a "Confidential Document". Can that document be made available now?

As a summary point, did the review you conducted use ANY papers not referenced by IARC? If so, should that point be addressed in the summary paper and, perhaps, other papers as appropriate.

On a personal note I think the papers to a varying degree would benefit from very careful editing to minimize language that is combative. I had assumed that at a final stage all the papers would have been carefully edited by a professional editor.

Please give me a call at [REDACTED] to discuss how best to move forward.

Best regards, Roger

On Tue, 7/5/16, Ashley Roberts Intertek <[REDACTED]@intertek.com> wrote:

Subject: Critical Reviews in Toxicology standing matter

To: "Roger McClellan" <roger.o.mcclellan@[REDACTED]>

Cc: "Mildred" <mbmorgan@hargray@[REDACTED]> "Whalley, Charles" <Charles.Whalley@tandf@[REDACTED]>

Date: Friday, July 8, 2016, 7:13 AM

Dear Roger and Mildred

Thank you for the phone call yesterday. It was lovely to speak to you both. After our conversation, I instructed the typesetter to follow the new guidelines for the presentation of supplemental material so we should soon start to see articles containing a 'Supplemental material' section, as shown in the sample Charles sent you.

I also wanted to follow up my message yesterday with some further information about the changes to journal standing matter I mentioned. These would be beneficial as we could potentially reduce the number of preliminary pages from four to two, freeing up a couple more pages in the journal budget for articles. The information on the standing matter has also been better organised and made clearer and more concise for readers.

I've attached descriptions of the two different templates and also explained a bit more about them below. If either of these appeal to you, I can ask the typesetter to create a journal-specific sample, which I can send to you for your review.

Please do let me know if you have any questions. I look forward to hearing your thoughts once you've had time to consider the various options.

Many thanks
and best wishes

Jenna

Option A

-
The subscriptions information page is removed.
Subscriptions information is merged with the text on the inside covers. The journal's aims and scope appear on the back cover.

-
We would have two preliminary pages if we were to adopt this option: the two table of contents pages.

Option B

-
The table of contents appears on the outside back cover of the journal and is continued onto the inside back cover.
The internal table of contents pages would therefore be removed.

Subscription information and typesetting and printing information would be added on page i of the journal.

We would have two preliminary pages: the subscriptions information page (p. i) and a blank page on the reverse of this (p. ii).

Jenna
Whittle
Production Editor,
Journals
Taylor & Francis

4 Park Square, Milton
Park, Abingdon, Oxon, OX14 4RN, UK

jenna.whittle@tandf

www.tandfonline.com

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Roger McClellan

From: Ashley Roberts Intertek <[REDACTED]@intertek.com>
Sent: Tuesday, July 12, 2016 3:50 AM
To: Roger McClellan
Subject: RE: Glyphosate papers -Frustration
Attachments: Genotoxicity Paper _Supplemental Info_Refs expanded_App B FINAL 2-25-16.....docx

Hi Roger,

Please find attached the changes requested to the genetox manuscript. Please let me know if this is now okay?

Best Wishes

Ashley

Ashley Roberts, Ph.D.
Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Tel: +1 [REDACTED]
Fax: +1 [REDACTED]
E-mail: [REDACTED]@intertek.com
2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

-----Original Message-----

From: Roger McClellan [mailto:roger.o.mcclellan@[REDACTED]]
Sent: July-08-16 2:34 PM
To: Ashley Roberts Intertek
Cc: Roger McClellan
Subject: Glyphosate papers -Frustration

Ashley:

When can you and I speak again about these papers. I have spent substantial time working on these papers and I am becoming increasingly frustrated. As an example --read the "revised" carcinogenicity paper. This paper is intended to critique the "animal evidence" that feeds in to the IARC classification. The IARC position should be clearly stated, indeed quoted, as a basis for the review. It is NOT.

Have you read the genotoxicity "revised" paper and the response to reviewers comments. Reviewer 1 calls for more details in Appendix B on identity of studies. The authors argue that was not requested in the earlier publication , why do we need to give it now? Do you agree with this approach to "stiffing" the reviewer?

These are just a couple of examples that heighten my frustration.

When can we speak about these matters?

Roger

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<http://www.intertek.com>

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[REDACTED]>
Sent: Thursday, July 14, 2016 1:12 PM
To: Mildred
Subject: Fw: RE: Glyphosate papers -Frustration
Attachments: Genotoxicity Paper _Supplemental Info_Refs expanded_App B FINAL 2-25-16.....docx

--- On Tue, 7/12/16, Ashley Roberts Intertek <ashley.roberts@intertek@[REDACTED]> wrote:

> From: Ashley Roberts Intertek [REDACTED]@intertek.com>
> Subject: RE: Glyphosate papers -Frustration
> To: "Roger McClellan" <roger.o.mcclellan@[REDACTED]>
> Date: Tuesday, July 12, 2016, 2:49 AM
> Hi Roger,
>
> Please find attached the
> changes requested to the genetox manuscript. Please let me know if
> this is now okay?
>
> Best Wishes
>
> Ashley
>
> Ashley
> Roberts, Ph.D.
> Senior Vice President
> Food & Nutrition Group
> Intertek Scientific & Regulatory
> Consultancy
> Tel: +1 [REDACTED]
> Fax: +1 [REDACTED]
> E-mail: [REDACTED]@intertek.com
> 2233 Argentia Road, Suite 201
> Mississauga, Ontario Canada L5N 2X7
>
>
> -----Original
> Message-----
> From: Roger McClellan
> [mailto:roger.o.mcclellan@[REDACTED]]
> Sent: July-08-16 2:34 PM
> To:
> Ashley Roberts Intertek
> Cc: Roger
> McClellan
> Subject: Glyphosate papers
> -Frustration

>
> Ashley:
> When can you and I speak again about these papers. I have spent
> substantial time working on these papers and I am becoming
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>
> Valued Quality. Delivered.
>
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>
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>

Roger McClellan

From: Ashley Roberts Intertek <[REDACTED]@intertek.com>
Sent: Saturday, July 16, 2016 8:26 AM
To: Roger McClellan
Subject: FW: Manuscript

Hi Roger,

I know you are off for a few days but I have had a question from one of the manuscript leaders and so I thought I better confirm with you.

The question is 1. Should I complete the copyright release form or does that go with the set of all publications?

I believe each person assigned the lead on the manuscript should do this but just thought I should get confirmation.

Thanks

Ashley

Ashley Roberts, Ph.D.
Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Tel: +1 [REDACTED]
Fax: +1 [REDACTED]
E-mail: [REDACTED]@intertek.com

2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

1. Should I complete the copyright release form or does that go with the set of all publications?
2. When the proofs arrive, the journal wants them returned in 48 hours. Knowing that our group never does anything in 48 hours, is there a standard method you suggest?

David

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Roger McClellan

From: John Acquavella <acquajohn@[REDACTED]>
Sent: Monday, July 18, 2016 1:56 PM
To: roger.o.mcclellan@[REDACTED]; ashley.roberts@intertek@[REDACTED]; judy.vowles@intertek@[REDACTED]
Cc: mbmorgan@hargray@[REDACTED]
Subject: Re: Critical Reviews in Toxicology - Decision on Manuscript ID BTXC-2016-0029.R1

Dr. McClellan:

I will be speaking at the Toxicology Forum on Tuesday, July 26. My topic is: Implications of the Use of Epidemiologic Data in Risk Analysis. Can I assume that I have your permission to mention some of the key thoughts from our recently accepted glyphosate epidemiology article and to cite it on my slides as: Acquavella et al. A weight of evidence systematic review of the relationship between glyphosate exposure and non-Hodgkin's lymphoma or multiple myeloma. Crit Rev Toxicol DOI 10.1080/10408444.2016.1214681.

Thank you for your consideration of this request.

Regards,

John

John Acquavella, PhD FACE FISPE
Professor, Dept Clinical Epidemiology
Aarhus University, Denmark
+1 [REDACTED]
+1 [REDACTED]

On 7/15/16, 1:30 PM, "Critical Reviews in Toxicology" <onbehalfof+roger.o.mcclellan@[REDACTED]@manuscriptcentral.com> wrote:

15-Jul-2016

Dear Professor Acquavella:

Ref: Glyphosate Epidemiology Expert Panel Review
A weight of evidence systematic review of the relationship between glyphosate exposure and non-Hodgkin's lymphoma or multiple myeloma

It was a pleasure to receive your revised manuscript and, especially, to note the careful attention you gave to the reviewers comments. In my opinion, the paper is now clearer and will be a valuable contribution to the literature on this widely used chemical. Hence, I am pleased to accept your paper in its current form which will now be forwarded to the publisher for copy editing and typesetting. This paper will be published in a Special Supplement of Critical Reviews in Toxicology along with four related papers.

In a letter to Ashley Roberts I have detailed the circumstances under which this and the other four papers in the Special Issue can be shared with regulatory authorities. Please be certain you adhere to that guidance.

You will receive proofs for checking, and instructions for transfer of copyright in due course.

The publisher also requests that proofs are checked and returned within 48 hours of receipt.

Thank you for your contribution to Critical Reviews in Toxicology and we look forward to receiving further submissions from you.

Sincerely,

Roger O. McClellan
Editor-in-Chief, Critical Reviews in Toxicology
roger.o.mcclellan@[REDACTED]

Visit www.informapharmascience.com and sign up for free eTOC alerts to all Informa Pharmaceutical Science journals

Roger McClellan

From: Whittle, Jenna <[REDACTED]@informa.com>
Sent: Monday, July 18, 2016 7:38 AM
To: Roger McClellan; Whalley, Charles
Cc: Mildred
Subject: RE: Critical Reviews in Toxicology - Decision on Manuscript ID BTXC-2016-0025.R1

Thanks for your messages, Roger. I confirm that the papers have arrived in production and I'll be in touch if I have any questions about them.

The publication date largely depends on how quickly authors can return corrections, assuming all the contractual arrangements are finalised shortly. However, all going well, I would estimate that mid-September seems likely and we will do our best to move things along as quickly as possible. Initial proofs of each article should be ready next week. Please do let me know if you have any questions.

Many thanks again and best wishes
Jenna

From: Roger McClellan [mailto:roger.o.mcclellan@[REDACTED]]
Sent: 16 July 2016 03:50
To: Whalley, Charles
Cc: Whittle, Jenna; Mildred; Roger McClellan
Subject: Fw: Critical Reviews in Toxicology - Decision on Manuscript ID BTXC-2016-0025.R1

Charles and Jenna:

Attached is the first of five letters accepting papers on the review of the potential carcinogenic hazard of Glyphosate (Roundup) to be published in a special supplement to Critical Reviews in Toxicology. Charles, I anticipate that you will finalize any necessary arrangements for publication of these five papers with any fees paid by Intertek or by Monsanto. I am assuming they will want open access to maximize the readership.

Jenna, please notify me as to the most likely production and publication schedule. The authors and sponsor are very eager to have these available on line at the earliest possible date.

I will be preparing a brief Editors note that will be placed in front of the five papers. I will try to get the piece to you at the earliest possible date.

As an aside, a total of 27 reviewers reviewed these papers with one paper reviewed by 5 individuals, three papers reviewed by 7 individuals and one paper reviewed by 10 individuals. Some individuals reviewed several papers and one individual reviewed all five papers. I doubt tht collectively any other pset of papers has been extensively reviewed.

Please let me know if you have any questions.

As a favor could one of you do a quick literature search using search terms like -- glyphosate, Roundup, cancer, carcinogenesis, genotoxicity, mechanisms of action, epidemiology, hazard and risk to see how many papers on these subjects have been published in last 10 years or 20 years.

How readily can you determine how many different references have been cited collectively in the 5 papers?

Thanks for your help on publishing what I think will be a highly cited collection of papers.

Best regards, Roger

--- On Fri, 7/15/16, Critical Reviews in Toxicology

<onbehalfof+roger.o.mcclellan@[REDACTED]@manuscriptcentral.com> wrote:

> From: Critical Reviews in Toxicology <onbehalfof+roger.o.mcclellan@manuscriptcentral.com>
> Subject: Critical Reviews in Toxicology - Decision on Manuscript ID BTXC-2016-0025.R1
> To: ashley.roberts@intertek, judy.vowles@intertek
> Cc: mbmorgan@hargray
> Date: Friday, July 15, 2016, 1:07 PM
> 15-Jul-2016

> Dear Dr Roberts:

> Ref: A Review of the Carcinogenic Potential of Glyphosate by
> Four Independent Expert Panels and Comparison to the IARC
> Assessment

> It was a pleasure to receive the revised manuscript and to
> note the careful attention given to the reviewers comments.
> In my opinion, the revisions were helpful in clarifying key
> points. This paper should be a valuable contribution to the
> literature on this widely used chemical. Hence, I am
> pleased to accept your paper in its current form which will
> now be forwarded to the publisher for copy editing and
> typesetting. It is understood that this paper will be
> published with four related papers in a Special Supplement
> to Critical Reviews in Toxicology.

> Recognizing the great interest of regulatory authorities in
> this and the related papers, I am extending permission to
> you to provide pre-publication copies of this and the four
> other papers to regulatory authorities and their advisors.
> It is understood these individuals will not reproduce or
> distribute these draft papers beyond the individuals who
> have need to review and cite the papers. Taylor and Francis
> will hold the copy right to the published papers. The papers
> should not be distributed further until you receive specific
> authorization from Mr Charles Whalley, the Managing Editor
> for CRT at T and F.

> You will receive proofs for checking, and instructions for
> transfer of copyright in due course.

> The publisher also requests that proofs are checked and
> returned within 48 hours of receipt.

> Thank you for your contribution to Critical Reviews in
> Toxicology and we look forward to receiving further
> submissions from you.

> Sincerely,

> Roger O. McClellan

- > Editor-in-Chief, Critical Reviews in Toxicology
- > roger.o.mcclellan@ [REDACTED]
- >
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- >
- >
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Roger McClellan

From: Ashley Roberts Intertek <ashley.roberts@intertek[REDACTED]>
Sent: Tuesday, July 19, 2016 1:47 PM
To: Roger McClellan
Subject: Re: Five Glyphosate Manuscripts

Hi Roger,

I have been actioned to ask you how much it would cost in addition to the cost of the publication of the journal, to have free access to the individual manuscripts? I think this service was provided previously for the Greim paper.

Please could you let me know what the additional cost for this service would be?

Thanking you in anticipation

Ashley

Sent from my BlackBerry 10 smartphone on the Bell network.

Original Message

From: Roger McClellan

Sent: Sunday, July 17, 2016 10:59 AM

To: Ashley Roberts Intertek

Reply To: Roger McClellan

Cc: Charles.Whalley@tandf[REDACTED]; Jenna.Whittle@informa[REDACTED]; Mildred; Roger McClellan

Subject: Re: FW:Five Glyphosate Manuscripts

Ashley:

I suggest the lead author for each of the Glyphosate papers complete the copyright assignment form for their paper and return them as requested. If this is not adequate I am sure you will hear from Jenna Whittle, the Production Editor for CRT, and/or Charles Whalley, the Managing Editor for CRT. Both are copied on this e-mail.

By copy of this e-mail I am asking Jenna to give the authors a week to approve the galleys for their paper. I encourage you to ask the lead author of each paper to take responsibility for review of the galley proofs for their paper. You may also want to ask that some one from the Intertek Editorial staff review all the galleys in view of the importance of these papers.

You should be aware that Charles is now on business travel and in the USA. Thus, you may not hear from him for a few days. You may want to alert Charles to your travel schedule to facilitate the two of you making contact on the Special Issue. In the meantime I am confident that Jenna will be moving the production forward in an expeditious manner.

Best regards,

Roger

On Sat, 7/16/16, Ashley Roberts Intertek <ashley.roberts@intertek[REDACTED]> wrote:

Subject: FW: Manuscript

To: "Roger McClellan" <roger.o.mcclellan@[REDACTED]>

Date: Saturday, July 16, 2016, 7:25 AM

Hi Roger,

I know you are off for a few days but I have had a question from one of the manuscript leaders and so I thought I better confirm with you.

The question is 1.
Should I complete the copyright release form or does that go with the set of all publications?

I believe each person assigned the lead on the manuscript should do this but just thought I should get confirmation.

Thanks

Ashley

Ashley Roberts,
Ph.D.

Senior Vice President

Food & Nutrition Group

Intertek Scientific
& Regulatory Consultancy

Tel: +1

Fax: +1

E-mail: ashley.roberts@intertek

2233 Argentia Road,
Suite 201

Mississauga, Ontario Canada L5N 2X7

1. Should I complete the copyright release form or does that go with the set of all publications?

2. When the proofs arrive, the journal wants them returned in 48 hours. Knowing that our group never does anything in 48 hours, is there a standard method you suggest?

David

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>
> From: Ashley Roberts
> Intertek
> Sent: Tuesday, July 19, 2016 3:47
> PM
> To: Roger McClellan
> Subject: Re: Five Glyphosate Manuscripts
>
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> Hi Roger,
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> I have been actioned to
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> manuscripts? I think this service was provided previously for the
> Greim paper.
>
> Please could you let me know
> what the
> additional cost for this service
> would be?
>
> Thanking you
> in
> anticipation
>
> Ashley
>
> Sent
> from my BlackBerry 10
> smartphone on the
> Bell network.
> Original
> Message
> From: Roger
> McClellan
> Sent: Sunday, July 17, 2016 10:59
> AM
> To: Ashley Roberts Intertek
> Reply To: Roger McClellan
>
> Cc:
> Charles.Whalley@tandf [REDACTED]
> Jenna.Whittle@informa [REDACTED]
> Mildred; Roger McClellan
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> Subject: Re:
> FW:Five Glyphosate
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> Ashley
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> Ashley
>
> Roberts,
> Ph.D.
>
> Senior Vice President
>
> Food & Nutrition Group
>
> Intertek Scientific
> &
> Regulatory
> Consultancy
>
>
> Tel: +1
> [REDACTED]
>
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>
> Fax: +1
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Mississauga, Ontario, ON L5N 2X7
Canada

Many thanks,

Keith

On 2016-07-19 11:35 AM, Jenna.Whittle@informa wrote:

19 Jul 2016

Keith Solomon,

Re: Glyphosate in the general population and in applicators: A critical review of studies on exposures

Production tracking number: ITXC 1214678

Thank you for submitting your paper, which has now been received by the Taylor & Francis production department. As production editor I will work with you to oversee the production of your article from manuscript to publication. My contact details are given at the end of this email.

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We will be sending proofs to you through our workflow system, CATS (Central Article Tracking System).

- The DOI of your paper is: 10.1080/10408444.2016.1214678. Once your article has published online, it will be available at the following permanent link:

<http://dx.doi.org/10.1080/10408444.2016.1214678>

- You can check the status of your paper online through the CATS system at: <https://cats.informa.com/PTS/in>

- Your User Name is: SLMNK6

• If you do not know your password, you may reset it here:
<http://cats.informa.com/PTS/forGottenPassword.do>

Yours sincerely,

Jenna Whittle

Taylor & Francis
4 Park Square
Milton Park
Abingdon
Oxfordshire
OX14 4RN
UNITED KINGDOM
Email: Jenna.Whittle@informa [REDACTED]

--

Keith R Solomon, Fellow ATS, Fellow SETAC, Prof. Emeritus (U of G)
Centre for Toxicology, School of Environmental Sciences
University of Guelph, 2120 Bovey Building
Gordon Street, Guelph, ON, N1G 2W1, Canada

[REDACTED] x [REDACTED]
Skype - [REDACTED] n
Fax: [REDACTED]
[REDACTED]@uoquelpb.ca

Centre for Toxicology
University of Guelph



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humans and the
environment with
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<http://www.intertek.com>

>
> -----Original
> Message-----
> From: Roger McClellan
> [mailto:roger.o.mcclellan@[REDACTED]]
> Sent: July-26-16 3:52 PM
> To:
> Ashley Roberts Intertek; Charles.Whalley@tandf@[REDACTED]
> Cc: Roger McClellan; Mildred
> Subject: Re: Five Glyphosate Manuscripts/ Need to Negotiate with
> Charles Whalley
>
> Ashley:
> I am
> traveling so I do not have access to all my records. I thought I had
> responded. You need to cover all business aspects of relationships
> with Critical Reviews in Toxicology with the journal's Managing
> Editor, Charles Whalley. I cover the science and he covers the
> business aspects of the journal. This should be covered in the
> contract for publishing the Special Issue. Charles, please let me know
> the status of the agreement between Taylor and Francis and/ Intertek
> and or Monsanto.
>
> Production is moving forward rapidly.
> Best regards, Roger
> -----
> On Tue, 7/26/16, Ashley Roberts Intertek <[REDACTED]@intertek.com>
> wrote:
>
> Subject: Re: Five
> Glyphosate Manuscripts
> To: "Roger
> McClellan" <roger.o.mcclellan@[REDACTED]>
> Date: Tuesday, July 26, 2016, 9:29 AM
>
> Hi Roger,
>
> I hope you had a good break? I
> was wondering if you have had a chance to consider my message below?
>
> I look
> forward to receiving
> your reply.
>
> Best Wishes
>
> Ashley
>
> Sent
> from my BlackBerry 10
> smartphone on the Bell network.
> Original Message

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[REDACTED]>
Sent: Wednesday, August 3, 2016 3:24 PM
To: Charles.Whalley@tandf@[REDACTED]
Cc: Roger McClellan
Subject: Fw: RE: Five Glyphosate Manuscripts/ Need to Negotiate with Charles Whalley

Charles:

Does T and F have a signed contract with Intertek/ Monsanto for the glyphosate Supplement?
Best regards, Roger

--- On Wed, 8/3/16, Ashley Roberts Intertek <[REDACTED]@intertek.com> wrote:

> From: Ashley Roberts Intertek <[REDACTED]@intertek.com>
> Subject: RE: Five Glyphosate Manuscripts/ Need to Negotiate with
> Charles Whalley
> To: "Roger McClellan" <roger.o.mcclellan@[REDACTED]>,
> "Charles.Whalley@tandf@[REDACTED]" <Charles.Whalley@tandf@[REDACTED]>
> Cc: "Mildred" <mbmorgan@hargray@[REDACTED]>
> Date: Wednesday, August 3, 2016, 11:18 AM Dear Roger/Charles,
>
> Please could you give me an
> update as to where we stand regarding the publications? I believe we
> have finalised all of the papers so are just awaiting to see the
> galley proofs. If you need me to pay for the printing of the journal
> etc, please send me the invoice as soon as you can. Regarding the
> free access to the manuscripts, please just add on what the additional
> cost for this function would be.
>
> I look forward to receiving an update as to next steps.
>
> Many Best
> Wishes
>
> Ashley
>
> Ashley Roberts, Ph.D.
> Senior Vice President
> Food
> & Nutrition Group
> Intertek Scientific
> & Regulatory Consultancy
> Tel: +1
> [REDACTED]
> Fax: +1 [REDACTED]
> E-mail: [REDACTED]@intertek.com
> 2233 Argentia Road, Suite 201
> Mississauga, Ontario Canada L5N 2X7
>

Roger McClellan

From: Whalley, Charles <Charles.Whalley@tand[REDACTED]>
Sent: Friday, August 5, 2016 6:02 AM
To: Ashley Roberts Intertek; Roger McClellan
Subject: RE: Welcome to Taylor & Francis Production: Critical Reviews in Toxicology 1214678

Dear Ashley,

Thanks for your email. As per our prior conversations, we had initially agreed with an online-only supplement, as this would be cheaper. The great majority of our readers and subscribers read the journal online, where they benefit from, amongst other things, supplemental material. The journal is only printed once a year, at the end of each volume, with print copies being sent to a relatively small proportion of our subscribers. Our current proposal assumes that the supplement issue would not be included in that end-of-year print volume; subscribers would be directed to the website. My apologies if this wasn't made clear, although I appreciate it's been a few months since we discussed these details.

I would, of course, be happy to include print for you, although this would be further additional cost, on top of the price sent to you recently to include Open Access. All that would entail would be inclusion in the print volume at the end of the year.

Let me know if you have any questions. I'm out of the office today and Monday but could call you on Tuesday.

Best wishes
Charles

From: Ashley Roberts Intertek [mailto:[REDACTED]@intertek.com]
Sent: 05 August 2016 12:32
To: Whalley, Charles; Roger McClellan
Subject: Fw: Welcome to Taylor & Francis Production: Critical Reviews in Toxicology 1214678

Dear Roger/Charles,

May be this is my misunderstanding but it was my impression that the articles were to be published in a stand alone paper back copy. Is this not the position?

Thanking you for your reply.

Best Wishes

Ashley

Sent from my BlackBerry 10 smartphone on the Bell network.

From: Whittle, Jenna <Jenna.Whittle@informa[REDACTED]>
Sent: Friday, August 5, 2016 8:15 AM
To: Keith Solomon
Cc: Ashley Roberts Intertek
Subject: RE: Welcome to Taylor & Francis Production: Critical Reviews in Toxicology 1214678

Dear Keith

Many thanks for your message and apologies for the delay in responding to your request to publish Figure 3 in colour.

Color figures will be reproduced in color in your online article free of charge. Although printing figures in color incurs a charge, your article is assigned for publication in a supplement that we believe will be published online only and not in print.

Please do let me know if you have any questions.

Best wishes

Jenna

Jenna Whittle
Production Editor, Journals
Taylor & Francis



Taylor & Francis Group
an informa business

4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK

jenna@tandf.co.uk
www.tandfonline.com

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From: Keith Solomon [mailto:[\[REDACTED\]@uoguelph.ca](mailto:[REDACTED]@uoguelph.ca)]
Sent: 20 July 2016 13:15
To: Whittle, Jenna
Cc: Ashley Roberts Intertek
Subject: Re: Welcome to Taylor & Francis Production: Critical Reviews in Toxicology 1214678

Jenna,

As requested, I attach the signed copyright form.

I will be fine with the proposed schedule.

I have spoken with the supporter of the research and we would like Fig 3 (only) to be printed in color. The invoice for this should be directed to:

Dr Ashley Roberts
Senior Vice President
Intertek Scientific & Regulatory Consultancy
E-Mail [\[REDACTED\]@intertek.com](mailto:[REDACTED]@intertek.com)
Work Address
2233 Argentia Road, Suite 201

Roger McClellan

From: Roger McClellan <[REDACTED]@att.net>
Sent: Friday, August 12, 2016 12:23 PM
To: Jenna.Whittle@informa[REDACTED]
Cc: roger.o.mcclellan[REDACTED]; Mildred; Charles.Whalley@tandf[REDACTED]
Subject: Re: Trivia versus substance: CRT standing matter

Jenna,

Please provide me an example of the type set version A for Volume 46. As the T and F staff consider changes for Critical Reviews in Toxicology I urge them to recognize the unique nature of the Journal.

Specifically, it is important to recognize that each annual issue, exclusive of Special Supplements, consists of 10 issues and a target of 920 pages. As I will note later, do the front and back cover count against the 920 page target. (I CAN NOT BELIEVE WE ARE WASTING TIME ON THIS KIND OF TRIVIA!!!!!!) The 10 issues in a sense become a legacy issue since all papers are published on-line when the final galley proofs are accepted. I am uncertain if a Table of Contents is created for each issue. Indeed, as I think about the matter it may be appropriate to consider creating a virtual Table of Contents that is 'built out' as new papers are accepted and published on line during the year.. For example, issues 1 through 9 contain 27 papers. As issue 10 is completed the number of papers in the regular issues of Volume 46 will increase to 29 or 30.

The only hard copies of Critical Reviews in Toxicology are now prepared and printed at year end. This started with Volume 44 in 2014. I note that Volume 44 did not have a Table of Contents. I now recall that being very inconvenient when I returned on several occasions to use the hard copy. Volume 45 (2015) has a Table of Contents at the front of the hard copy. This is convenient to use since the two pages are in consecutive order. By writing this memo I have answered one question. I am strongly opposed to placing the Table of Contents on the back cover (and presumably continuing it on the inside of the back cover) for a single annual hard copy of CRT. The approach of using the back cover for a Table of Contents may make sense for a multi-issue journal , it makes no sense for CRT. I question if the proposer of this approach is a scientific editor or author or user of journals. AS a scientist when I pick up a bound volume it is natural for me to go to the front to search for the Table of Contents.

As I write this e-mail I recall my anger a year ago at doing battle over a couple of pages of print in the journal. As a MANAGER, I have always viewed quantitative goals as targets that should be interpreted with the abundant use of common sense. I doubt that the financial success of T and F will turn on this issue. I urge that all of us focus on what makes sense.

Charles and Jenna, in the world of "bean counters" at T and F do the cover (front and back) and the back cover (front and back) count as part of the 920 pages assigned to CRT for 2016? If we collectively deliver less pages does some one get a BONUS or brownie points? What is your current production system for CRT? In printing hard copies does the press print 8 , 16 or 32 pages to the sheet or does the printing system work differently today? I note that the front and back cover are different weight paper than the rest of the Journal so they have to be printed separately.

Thanks for hearing me out.

Roger

PS I. In my opinion, the inability to focus on what is really important as opposed to trivia is a world wide phenomena. We need to return our focus to what will improve the scientific quality of CRT and it's profitability to T and F.

PS II. I do think it is important to list the membership of the Editorial Advisory Board at the front of the hard copy for historical reasons. Quite frankly, it probably does not make much difference what else is printed on the inside of the front cover or on either side of the back cover. Whatever is printed will soon be out dated and is not likely to be a primary reference source, ie folks will go elsewhere to obtain current information on subscriptions, instructions to authors, etc. The publication world is changing. Hard copies will probably be a thing of the past within a decade.

On Fri, 7/8/16, Whittle, Jenna <Jenna.Whittle@informa.com> wrote:

Roger McClellan

From: Whalley, Charles <Charles.Whalley@tandf[REDACTED]>
Sent: Thursday, August 18, 2016 8:21 AM
To: Roger McClellan
Subject: Glyphosate editorial

Dear Roger,

There's one more colleague I'd like to have a look at your editorial, but I wanted to raise something with you now. One of my colleagues has mentioned that, in the spirit of the editorial, it would be appropriate for us to include a Declaration of Interest statement from you. What do you think?

Best wishes,
Charles

Charles Whalley - Managing Editor, Medicine & Health Science Journals
Taylor & Francis Group
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK
Direct line: +[REDACTED]
Switchboard: +[REDACTED]
[REDACTED]@tandf.co.uk
www.tandfonline.com

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>

> From: Whalley,

> Charles

>

> Sent: 22 August 2016 15:55

>

> To: 'Ashley Roberts Intertek'

>

> Cc: Vasili, Temis

>

> Subject: Glyphosate supplement contract

>

>

>

>

> Dear Ashley,

>

> Please find attached a draft contract for your

> review. To summarise, this covers an Open Access online-only

> supplement in

> CRT, with 200 additional print copies of the

> supplement issue despatched in bulk to a single address

> (assuming St Louis, Missouri). (These print copies will not

> be sent to subscribers). The cost will be

> \$29,339 for the supplement plus \$1,306 for the

> print and delivery of the print issues, so

> \$30,645. We will issue a single invoice once the
> contract is signed.
>
> Please let me know if you have any questions
> regarding the contract. Once I hear you're happy, we
> will arrange for 2 print copies to be couriered to you for
> signature. These will
> need to be sent back to us for counter-signature, and then
> we will send one to you for your records.
>
> With that in mind, I will need to know from
> you:
>
> .
> The name
> and address to send the contracts
> .
> A contact
> number for the courier for this address
> .
> The name
> and address for the invoice
>
> I look forward to hearing from you on the
> above.
>

> Please be advised that I am out of the office,
> without an internet connection,
> 24th-30th Aug inclusive. I CC my
> Editorial Assistant, Temis Vasili, who will
> be able to cover for me in my absence. I don't
> anticipate my holiday to cause any delays here.

>

> Best wishes,

> Charles

>

> Charles Whalley

> -

> Managing Editor, Medicine & Health Science

> Journals

> Taylor & Francis

> Group

> 4 Park Square, Milton

> Park, Abingdon, Oxon, OX14 4RN, UK

> Direct line:

> + [REDACTED]

> Switchboard:

> + [REDACTED]

> charles.whalley@tandf [REDACTED]

>

> www.tandfonline.com

>

>

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>

>

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>

> <http://www.intertek.com>

>

▼
▼
▼
▼

Roger McClellan

From: Whalley, Charles <Charles.Whalley@tand[REDACTED]>
Sent: Wednesday, September 14, 2016 6:33 AM
To: Ashley Roberts Intertek
Cc: Vasili, Temis; Roger McClellan
Subject: RE: Glyphosate supplement

Dear Ashley,

Many thanks for this, which is very helpful. In advance of the final publication of these review papers, the authors are welcome to share their original accepted version of their manuscripts with the reporter you mention below, for the purposes of preparing their interview. We'd be pleased for any statement to link directly to the journal's website. I can send you the direct link to the articles once published, if that helps. They will, of course, be Open Access, so direct links will take readers straight to the full text.

Thanks also for sharing the wording of Monsanto's statement. Can I ask if we can see in advance any other statement, press release or promotional copy with references Taylor & Francis and/or CRT?

Finally, you've not mentioned anything on this front, but my colleagues in Marketing are eager to know of any social media plans, if any exist.

Best wishes,
Charles

From: Ashley Roberts Intertek [mailto:ashley.roberts@intertek[REDACTED]]
Sent: 13 September 2016 16:03
To: Whalley, Charles
Cc: Vasili, Temis; Roger McClellan
Subject: RE: Glyphosate supplement

Dear Charles/Roger,

In addition to the previous information that I sent to you regarding the promotion of the glyphosate publications, Monsanto has now updated this to include the following and they want to be transparent on what they are doing and to keep you in the loop on these matters.

For your information, they plan to help amplify the lack of carcinogenicity potential thorough, science-based review by: 1) helping coordinate an exclusive interview with Sir Colin Berry and a science reporter in advance of publication, 2) providing any inquiring media after publication with a Monsanto statement, and 3) directing interested media to the Critical Reviews in Toxicology website after publication. More details below.

1. The Sir Colin Berry exclusive interview will be with a science reporter from a mainstream media outlet in Europe. The reporter's story will be embargoed until after publication and the expert panels findings are publically available online. As part of this exclusive interview, we also think it would be beneficial to provide the reporter with an early version of the expert panel's report so the reporter has the information needed to write a detailed article. Please let us know if CRT supports this approach? if this is okay, Monsanto will suggest to Sir Colin that he share the early version of the report with the reporter during the interview.
2. For your reference, below is the Monsanto statement they plan to share on a reactive basis if they receive media inquiries after publication.

At Monsanto, we're fully confident in the safety profile of our products. Our confidence is based on rigorous internal safety assessments in addition to safety assessments by regulatory authorities, independent researchers and other experts around the world. In July 2015, Monsanto retained a scientific consultant to convene an expert panel to review the International Agency for Research on Cancer (IARC) monograph on glyphosate once it published. The charge to the experts was to take a thorough look at the data in the monograph, assess the scope of the research included or excluded, and publish their conclusions to allow for external review. The experts that make up the panel include medical doctors, cancer experts, and individuals who hold doctoral degrees and who are experts in public health. The experts have spent their careers as researchers at major universities and medical schools, at research institutions and as consultants. The panel's peer-reviewed findings recently were published in the journal Critical Reviews in Toxicology and are available here: [Monsanto will insert direct link here]. These findings by the panel come at an important time, after so much unnecessary confusion and concern has been caused by IARC's classification of glyphosate. The panel's findings are consistent with the conclusions of regulatory authorities around the world. In fact, since IARC classified glyphosate, regulatory authorities in Europe, Canada, Japan, New Zealand and Australia have publicly reaffirmed that glyphosate does not cause cancer. Additionally, in May 2016, the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) concluded that "glyphosate is unlikely to pose a carcinogenic risk to humans from exposure through the diet."

3. Lastly, after publication, Monsanto plan to proactively inform some reporters who have previously covered IARC's glyphosate monograph about the publication of the expert panel's findings. As such Monsanto plans to share a direct link to the Critical Reviews in Toxicology's website

Please let me know if this is acceptable to the journal.

Many best Wishes

Ashley

Ashley Roberts, Ph.D.
Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Tel: +1 [REDACTED]
Fax: +1 [REDACTED]
E-mail: [REDACTED]@intertek.com

2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

From: Whalley, Charles [mailto:Charles.Whalley@tandf [REDACTED]]
Sent: September-06-16 8:35 AM
To: Ashley Roberts Intertek
Cc: Vasili, Temis
Subject: RE: Glyphosate supplement contract

Dear Ashley,

Thanks for coordinating signature and return of contracts with Temis. I hope you've had a pleasant holiday.

Further to your response re promotion. I'd be grateful if Monsanto could provide:

- A draft of the press release before publication
- The names of the journalists who would receive the press release
- The names of the panellists who would be provided to these journalists for follow-up discussion
- Information on any social media promotion

Apologies for the quizzing, but we're anticipating a lot of interest in this supplement and so I'm eager that we're aware of any marketing in advance.

As for our promotion, I'll be able to confirm our plans after hearing from you on the above.

I'd be happy to discuss this with the appropriate person at Monsanto directly if that's easier for you.

All best wishes,
Charles

From: Ashley Roberts Intertek [mailto: [REDACTED]@intertek.com]
Sent: 23 August 2016 21:28
To: Whalley, Charles
Cc: Vasili, Temis
Subject: RE: Glyphosate supplement contract

Dear Charles,

Regarding the contract, I will respond to you tomorrow morning my time.

On the topic of promotion, I have spoken to Monsanto and they have indicated that if you are in agreement they would like to promote the publications. While nothing definite has been planned they were contemplating making a press release to some "friendly" journalists indicating when the report will be released with the time estimation for publication as well as provide some names of the panelists who they could contact for follow-up discussion. Beyond this initial action, no further thought has gone in to this and they were wondering if the Journal does any of their own kind of promotion.

If you could let me know if the above is acceptable, that would be great.

Many Thanks

Ashley

Ashley Roberts, Ph.D.
Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Tel: +1 [REDACTED]
Fax: +1 [REDACTED]
E-mail: [REDACTED]@intertek.com

2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

From: Whalley, Charles [mailto:Charles.Whalley@tandf [REDACTED]]
Sent: August-23-16 10:52 AM
To: Ashley Roberts Intertek
Cc: Vasili, Temis
Subject: RE: Glyphosate supplement contract

Dear Ashley,

Further to the below, it occurs to me that it would helpful and much appreciated if you could let me know on Intertek's and Monsanto's plans for promoting the supplement, if any, both with the print copies which we will

be producing and in any electronic or other communications/promotion. I look forward to hearing from you on this and the below.

Best wishes as ever,
Charles

From: Whalley, Charles
Sent: 22 August 2016 15:55
To: 'Ashley Roberts Intertek'
Cc: Vasili, Temis
Subject: Glyphosate supplement contract

Dear Ashley,

Please find attached a draft contract for your review. To summarise, this covers an Open Access online-only supplement in *CRT*, with 200 additional print copies of the supplement issue despatched in bulk to a single address (assuming St Louis, Missouri). (These print copies will not be sent to subscribers). The cost will be **\$29,339** for the supplement plus **\$1,306** for the print and delivery of the print issues, so **\$30,645**. We will issue a single invoice once the contract is signed.

Please let me know if you have any questions regarding the contract. Once I hear you're happy, we will arrange for 2 print copies to be couriered to you for signature. These will need to be sent back to us for counter-signature, and then we will send one to you for your records.

With that in mind, I will need to know from you:

- The name and address to send the contracts
- A contact number for the courier for this address
- The name and address for the invoice

I look forward to hearing from you on the above.

Please be advised that I am out of the office, without an internet connection, 24th-30th Aug inclusive. I CC my Editorial Assistant, Temis Vasili, who will be able to cover for me in my absence. I don't anticipate my holiday to cause any delays here.

Best wishes,
Charles

Charles Whalley - Managing Editor, Medicine & Health Science Journals
Taylor & Francis Group
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK
Direct line: [REDACTED]
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Roger McClellan

From: Whalley, Charles <[REDACTED]@tandf.co.uk>
Sent: Tuesday, August 23, 2016 2:33 AM
To: Roger McClellan
Cc: mbmorgan@hargray[REDACTED]
Subject: Editorial for special issue
Attachments: Special Supplemental Issue on Glyphosates Document for CRT_TF edits.docx

Dear Roger,

Please find attached your editorial for the glyphosate special issue, having been reviewed here. The only changes I've made are to the penultimate paragraph relating to the negotiations around the supplement.

I also note that the title for the supplement is 'An Independent Review of the Carcinogenic Potential of Glyphosate'

Best wishes,
Charles

Charles Whalley - Managing Editor, Medicine & Health Science Journals
Taylor & Francis Group
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK
Direct line: [REDACTED]
Switchboard: [REDACTED]
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Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[REDACTED]>
Sent: Wednesday, August 31, 2016 1:37 PM
To: Jenna.Whittle@informa[REDACTED]; Charles.Whalley@tand[REDACTED]
Cc: Roger McClellan; Mildred
Subject: Fw:Foreword for Special Glyphosates Supplement
Attachments: Special Supplemental Issue on Glyphosates 8 31 16 ROM.docx

Jenna and Charles:

Attached is the penultimate version of the Foreword for the Special Supplement. You will note it contains a Declaration of Interest. I welcome your comments on the DOI. I am uncertain if I have seen the Galleys on the two Williams etal papers. Can you send me the latest version. I assume they have been returned by Gary Williams. What is your current view of when the Supplement will be posted on line. I would prefer that it all be posted at the same time. A related question is how much space will be required to print the Abstracts in the hard copy issue of Volume 46.

Thanks for all your help on this special project.

Regards, Roger

--- On Wed, 8/31/16, Mildred Morgan <mbmorgan@hargray[REDACTED]> wrote:

> From: Mildred Morgan <mbmorgan@hargray[REDACTED]>
> Subject: Special Glyphosates Supplement
> To: "Roger McClellan" <roger.o.mcclellan@[REDACTED]>
> Date: Wednesday, August 31, 2016, 12:01 PM Attached.
>

Roger McClellan

From: Mildred Morgan <mbmorgan@hargray[REDACTED]>
Sent: Wednesday, August 31, 2016 5:39 AM
To: Roger McClellan
Subject: FW: CRT, sample cover

FYI. I don't know what affiliation you want to show for Vicki. Let me and Jenna know. She also asked whether you had any corrections.

MM

From: Whittle, Jenna [mailto:Jenna.Whittle@informa[REDACTED]]
Sent: Wednesday, August 31, 2016 3:53 AM
To: Mildred Morgan
Subject: RE: CRT, sample cover

Thanks for letting me know, Mildred. Please can you tell me what her affiliation is and I'll ensure that change is made? Do you know if Roger had any corrections?
Many thanks and best wishes
Jenna

Jenna Whittle
Production Editor
Taylor & Francis

4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK

From: [Mildred Morgan](#)
Sent: 30 August 2016 23:26
To: [Whittle, Jenna](#)
Subject: RE: CRT, sample cover

Hi Jenna,

On the CRT Sample cover you sent, be sure and include Vicki Delliarco to the list of CRT Board Members.

Mildred

From: Whittle, Jenna [mailto:[REDACTED]@informa.com]
Sent: Friday, August 19, 2016 1:15 PM
To: Roger McClellan
Cc: Mildred; Whalley, Charles
Subject: CRT, sample cover

Dear Roger, Mildred and Charles

Please find attached a sample cover with the layout changes discussed for your review. The subscriptions information has been reduced and added to the inside back cover, meaning that we no longer need a separate internal subscriptions page.

The print issue will feature a table of contents on pages i and ii. To give an idea of what this will look like, I've attached the table of contents from last year's volume – we can follow the same layout as this in the upcoming print issue.

Please do let me know if you have any feedback on this cover or, indeed, the style of the contents page and I can ask the typesetter to make adjustments.

Thanks and best wishes

Jenna

From: Roger McClellan [mailto:roger.o.mcclellan@██████████]
Sent: 12 August 2016 19:23
To: Whittle, Jenna
Cc: roger.o.mcclellan@██████████; Mildred; Whalley, Charles
Subject: Re: Trivia versus substance; CRT standing matter

Jenna,

Please provide me an example of the type set version A for Volume 46. As the T and F staff consider changes for Critical Reviews in Toxicology I urge them to recognize the unique nature of the Journal.

Specifically, it is important to recognize that each annual issue, exclusive of Special Supplements, consists of 10 issues and a target of 920 pages. As I will note later, do the front and back cover count against the 920 page target. (I CAN NOT BELIEVE WE ARE WASTING TIME ON THIS KIND OF TRIVIA!!!!!!) The 10 issues in a sense become a legacy issue since all papers are published on-line when the final galley proofs are accepted. I am uncertain if a Table of Contents is created for each issue. Indeed, as I think about the matter it may be appropriate to consider creating a virtual Table of Contents that is 'built out' as new papers are accepted and published on line during the year.. For example, issues 1 through 9 contain 27 papers. As issue 10 is completed the number of papers in the regular issues of Volume 46 will increase to 29 or 30.

The only hard copies of Critical Reviews in Toxicology are now prepared and printed at year end. This started with Volume 44 in 2014. I note that Volume 44 did not have a Table of Contents. I now recall that being very inconvenient when I returned on several occasions to use the hard copy. Volume 45 (2015) has a Table of Contents at the front of the hard copy. This is convenient to use since the two pages are in consecutive order. By writing this memo I have answered one question. I am strongly opposed to placing the Table of Contents on the back cover (and presumably continuing it on the inside of the back cover) for a single annual hard copy of CRT. The approach of using the back cover for a Table of Contents may make sense for a multi-issue journal, it makes no sense for CRT. I question if the proposer of this approach is a scientific editor or author or user of journals. AS a scientist when I pick up a bound volume it is natural for me to go to the front to search for the Table of Contents.

As I write this e-mail I recall my anger a year ago at doing battle over a couple of pages of print in the journal. As a MANAGER, I have always viewed quantitative goals as targets that should be interpreted with the abundant use of common sense. I doubt that the financial success of T and F will turn on this issue. I urge that all of us focus on what makes sense.

Charles and Jenna, in the world of "bean counters" at T and F do the cover (front and back) and the back cover (front and back) count as part of the 920 pages assigned to CRT for 2016? If we collectively deliver less pages does some one get a BONUS or brownie points? What is your current production system for CRT? In printing hard copies does the press print 8, 16 or 32 pages to the sheet or does the printing system work differently today? I note that the front and back cover are different weight paper than the rest of the Journal so they have to be printed separately.

Thanks for hearing me out.

Roger

PS I. In my opinion, the inability to focus on what is really important as opposed to trivia is a world wide phenomena. We need to return our focus to what will improve the scientific quality of CRT and it's profitability to T and F.

PS II. I do think it is important to list the membership of the Editorial Advisory Board at the front of the hard copy for historical reasons. Quite frankly, it probably does not make much difference what else is printed on the inside of the front cover or on either side of the back cover. Whatever is printed will soon be out dated and is not likely to be a primary reference source, ie folks will go elsewhere to obtain current information on subscriptions, instructions to authors, etc. The publication world is changing. Hard copies will probably be a thing of the past within a decade.

On Fri, 7/8/16, Whittle, Jenna <Jenna.Whittle@informa[REDACTED]> wrote:

Subject: Critical Reviews in Toxicology standing matter

To: "Roger McClellan" <roger.o.mcclellan@[REDACTED]>

Cc: "Mildred" <mbmorgan@hargray[REDACTED]>, "Whalley, Charles" <Charles.Whalley@tandf[REDACTED]>

Date: Friday, July 8, 2016, 7:13 AM

Dear Roger and Mildred

Thank you for the phone call yesterday. It was lovely to speak to you both. After our conversation, I instructed the typesetter to follow the new guidelines for the presentation of supplemental material so we should soon start to see articles containing a 'Supplemental material' section, as shown in the sample Charles sent you.

I also wanted to follow up my message yesterday with some further information about the changes to journal standing matter I mentioned. These would be beneficial as we could potentially reduce the number of preliminary pages from four to two, freeing up a couple more pages in the journal budget for articles. The information on the standing matter has also been better organised and made clearer and more concise for readers.

I've attached descriptions of the two different templates and also explained a bit more about them below. If either of these appeal to you, I can ask the typesetter to create a journal-specific sample, which I can send to you for your review.

Please do let me know if you have any questions. I look forward to hearing your thoughts once you've had time to consider the various options.

Many thanks
and best wishes

Jenna

Option A

The subscriptions information page is removed. Subscriptions information is merged with the text on the inside covers. The journal's aims and scope appear on the back cover.

We would have two preliminary pages if we were to adopt this option: the two table of contents pages.

Option B

The table of contents appears on the outside back cover of the journal and is continued onto the inside back cover. The internal table of contents pages would therefore be removed.

Subscription information and typesetting and printing information would be added on page i of the journal.

We would have two preliminary pages: the subscriptions information page (p. i) and a blank page on the reverse of this (p. ii).

Jenna
Whittle
Production Editor,
Journals
Taylor & Francis

4 Park Square, Milton
Park, Abingdon, Oxon, OX14 4RN, UK

jenna.whittle@tandf

www.tandfonline.com

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Roger McClellan

From: Whittle, Jenna <Jenna.Whittle@informa[REDACTED]>
Sent: Thursday, September 1, 2016 9:48 AM
To: Roger McClellan; Whalley, Charles
Cc: Roger McClellan; Mildred
Subject: RE: Foreword for Special Glyphosates Supplement

Dear Roger

I'll respond in more detail to your queries soon, but I wanted to let you know in the meantime that I've just sent you one of the Williams papers (Glyphosate rodent carcinogenicity bioassay expert panel review) after receiving it from the typesetter. Please let me know if you haven't received it. The other Williams proof is with the typesetter for amendment as we only received the author's corrections earlier this week. I'll send you the revised proof as soon as it is ready.

Best wishes

Jenna

Jenna Whittle
Production Editor
Taylor & Francis

4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK

From: [Roger McClellan](#)
Sent: 31 August 2016 20:37
To: [Whittle, Jenna](#); [Whalley, Charles](#)
Cc: [Roger McClellan](#); [Mildred](#)
Subject: Fw:Foreword for Special Glyphosates Supplement

Jenna and Charles:

Attached is the penultimate version of the Foreword for the Special Supplement. You will note it contains a Declaration of Interest. I welcome your comments on the DOI. I am uncertain if I have seen the Galleys on the two Williams et al papers. Can you send me the latest version. I assume they have been returned by Gary Williams. What is your current view of when the Supplement will be posted on line. I would prefer that it all be posted at the same time. A related question is how much space will be required to print the Abstracts in the hard copy issue of Volume 46.

Thanks for all your help on this special project.

Regards, Roger

--- On Wed, 8/31/16, Mildred Morgan <[mbmorgan@hargray\[REDACTED\]](mailto:mbmorgan@hargray[REDACTED])> wrote:

> From: Mildred Morgan <[mbmorgan@hargray\[REDACTED\]](mailto:mbmorgan@hargray[REDACTED])>
> Subject: Special Glyphosates Supplement
> To: "Roger McClellan" <[roger.o.mcclellan@\[REDACTED\]](mailto:roger.o.mcclellan@[REDACTED])>
> Date: Wednesday, August 31, 2016, 12:01 PM
> Attached.
>

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[REDACTED]>
Sent: Wednesday, September 7, 2016 12:48 PM
To: Charles.Whalley@tandf@[REDACTED] Jenna.Whittle@informa@[REDACTED]
Cc: Mildred; Roger McClellan
Subject: Re: Automatic reply: Proofs for Williams etal --FUNDING ?????/URGENT ATTENTION

Charles and Jenna:

As you are both aware, it is highly desirable that the five papers and my Foreword in the Glyphosate Special Supplemental Issue be posted on line at the earliest possible date. I note that Charles is out through September 22nd. Hence, it will not be possible to have a telephone conference call on September 8th to resolve the Funding entry issue.

My strong preference would be to publish the five papers and Foreword with the Declaration of Interest statements originally submitted. This approach is consistent with the other papers published in Volume 46. Is this approach acceptable to both of you and your supervisors?

Regards, Roger

On Wed, 9/7/16, Whalley, Charles <Charles.Whalley@tandf@[REDACTED]> wrote:

Subject: Automatic reply: Proofs for Williams etal --FUNDING ?????/URGENT
To: "Roger McClellan" <roger.o.mcclellan@[REDACTED]>
Date: Wednesday, September 7, 2016, 10:56 AM

#yiv5685896198
#yiv5685896198 --

_filtered #yiv5685896198 {font-family:Calibri;panose-1:2 15
5 2 2 2 4 3 2 4;}
_filtered #yiv5685896198 {font-family:Tahoma;panose-1:2 11
6 4 3 5 4 4 2 4;}
_filtered #yiv5685896198 {font-family:Verdana;panose-1:2 11
6 4 3 5 4 4 2 4;}
#yiv5685896198
#yiv5685896198 p.yiv5685896198MsoNormal, #yiv5685896198 li.yiv5685896198MsoNormal, #yiv5685896198
div.yiv5685896198MsoNormal
{margin:0cm;margin-bottom:.0001pt;font-size:11.0pt;}
#yiv5685896198 a:link, #yiv5685896198
span.yiv5685896198MsoHyperlink
{color:blue;text-decoration:underline;}
#yiv5685896198 a:visited, #yiv5685896198 span.yiv5685896198MsoHyperlinkFollowed
{color:purple;text-decoration:underline;}
#yiv5685896198 span.yiv5685896198EmailStyle17
{
}
#yiv5685896198 .yiv5685896198MsoChpDefault
{
}
_filtered #yiv5685896198 {margin:72.0pt 72.0pt 72.0pt 72.0pt;}
#yiv5685896198 div.yiv5685896198WordSection1
{
}
#yiv5685896198

Thank you for your email. I'm currently out of the office with intermittent email access, returning 22nd September.

Best wishes,
Charles

Charles Whalley

Managing Editor, Medicine & Health Science Journals Taylor & Francis Group

4 Park Square, Milton Park,

Abingdon, Oxon, OX14 4RN, UK

Direct line: [REDACTED]

Switchboard: [REDACTED]

charles.whalley@tandf [REDACTED]

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Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[REDACTED]>
Sent: Wednesday, September 7, 2016 3:10 PM
To: Charles.Whalley@tandf@[REDACTED]; JennaWhittle
Cc: Mildred; Roger McClellan
Subject: RE: Special Glyphosates Supplement--Need to resolveDOI versus DOI plus Funding

Jenna and Charles:

As I have noted in other e-mails the issue of potentially publishing separate "Funding" entries for each paper caught me totally by surprise. As I noted it is not necessary since funding of the management of the advisory committees and preparation of these five paper is clearly described in the papers and the DOIs. Let's get that matter settled soon!!!!
Regards, Roger

On Tue, 9/6/16, Whittle, Jenna <[REDACTED]@informa.com> wrote:

Subject: RE: Fw:Foreword for Special Glyphosates Supplement
To: "Roger McClellan" <roger.o.mcclellan@[REDACTED]>, "Whalley, Charles" <Charles.Whalley@tandf@[REDACTED]>
Cc: "Mildred" <mbmorgan@hargray@[REDACTED]>
Date: Tuesday, September 6, 2016, 2:12 AM

Dear Roger

I understand from Charles that this is the final version of the foreword, so I will send it off for copyediting and typesetting. You'll be sent the proofs for review/any corrections as soon as they're ready.

I've just received the corrected Williams proof from the typesetter so I will send it to you and the author shortly. Once the foreword is at revised proof stage, I can compile the issue. It should be fine to publish all the papers online at the same time. I can send you and Ashley the issue proofs for approval before we go to press.

We can probably expect each abstract to take up approximately half a page so we should allow around 3 pages for the supplement abstracts in the printed volume.

Please do let me know if you have any further questions.

Best wishes

Jenna

-----Original Message-----

From: Roger McClellan [mailto:roger.o.mcclellan@[REDACTED]]

Sent: 31 August 2016 20:37
To: Whittle, Jenna; Whalley, Charles
Cc: Roger McClellan; Mildred
Subject: Fw:Foreword for Special Glyphosates Supplement

Jenna and

Charles:

Attached is the penultimate version of the Foreword for the Special Supplement. You will note it contains a Declaration of Interest. I welcome your comments on the DOI. I am uncertain if I have seen the Galleys on the two Williams et al papers. Can you send me the latest version. I assume they have been returned by Gary Williams. What is your current view of when the Supplement will be posted on line. I would prefer that it all be posted at the same time. A related question is how much space will be required to print the Abstracts in the hard copy issue of Volume 46.

Thanks for all your help on this special project.

Regards, Roger

--- On Wed, 8/31/16, Mildred Morgan <mbmorgan@hargray[REDACTED]> wrote:

> From: Mildred Morgan <mbmorgan@hargray[REDACTED]>
> Subject: Special Glyphosates Supplement > To: "Roger McClellan" <roger.o.mcclellan@[REDACTED]> > Date: Wednesday, August 31, 2016, 12:01 PM Attached.
>

Roger McClellan

From: Whalley, Charles <Charles.Whalley@tandf[REDACTED]>
Sent: Friday, September 9, 2016 3:28 AM
To: Roger McClellan
Cc: Vasili, Temis
Subject: Previous highly cited glyphosate toxicity papers
Attachments: Glyphosate toxicity.docx

Dear Roger,

A month or so ago you asked if we could do some research on the citations to previously published articles on glyphosate. I attach the details that Temis has put together on this. It seems most of the highly cited articles on environmental/aquatic toxicity, and that there has been a steady increase in publications on this topic, peaking a few years ago.

Let me know if you've any questions.

Best wishes,
Charles

Charles Whalley - Managing Editor, Medicine & Health Journals
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Roger McClellan

From: Whalley, Charles <Charles.Whalley@tandf[REDACTED]>
Sent: Monday, September 12, 2016 5:24 PM
To: Roger McClellan; Whittle, Jenna
Cc: Mildred B. Morgan
Subject: RE: Funding Entry

Dear Roger,

Thanks for this. Jenna is going to check in with her manager and the typesetter on this, but we should be able to take that section out from the template for CRT. It's popped in at a bad time, as we're so close to finishing this supplement, but won't be difficult to resolve. Our policy on Declarations of Interest hasn't changed.

I'd be happy to discuss this over the phone once I'm back. As you've seen, I'm travelling until Thursday 22nd, at a clinical toxicology meeting in Boston, but will see emails.

Best wishes as ever,
Charles

From: Roger McClellan [mailto:roger.o.mcclellan@[REDACTED]]
Sent: 08 September 2016 00:29
To: Whittle, Jenna
Cc: Whalley, Charles; Roger McClellan; Mildred B. Morgan
Subject: Funding Entry

Charles and Jenna:

Jenna, I appreciate being given some background on the use of a "Funding" entry on papers published by T&F. This is the first time I have heard anything about the use of a "Funding" entry. Thus, I was surprised when it first showed up in galleys.

Perhaps you can provide me some additional details about this entry. I am confident that many authors publishing in CRT will be confused since funding sources have routinely been included in the mandatory Declaration of Interest (DOI) statements that CRT has been using for several years.

As you know, CRT has been a leader in championing a mandatory DOI. The DOI was created since it was apparent that the usual statements about "Conflicts of Interest" were not adequate. It is my personal opinion that statements such as "The authors have no conflict of interest to declare" are virtually useless. That is the case since conflicts of interest are in the eye of the beholder, not the declarer.

As you are aware, the typical DOI for a CRT review paper covers funding. However, the typical DOI includes substantially more information that allows a reader to form an opinion as to potential conflicts of interest. In short, statements about funding are a useful step in the right direction but are not adequate for CRT.

In my opinion, the issue of funding for a paper reporting original research findings is very different than for review papers such as those published in CRT. I suspect the T&F procedures on creating the "Funding" entry are oriented primarily to papers reporting original research findings. Perhaps you

can share with me the internal T&F procedures used to create "Funding" entries. From the several funding entries I have read, it appears T&F uses information provided by authors and some independent data bases. What are these data bases?

As you know, the funding of preparation of review papers can be very complex along with their authorship. Some authors are from academic institutions while other authors are employed by industrial firms, government agencies or consulting firms. Many papers have authors from all of the above sectors. Preparation of reviews may be self-funded by the author's employer or sponsorship by government or private sector grants or contracts. In some cases a consulting firm or trade association may be involved. I suggest that the T&F personnel involved in creating "Funding" entries review the DOIs for all of the papers published in CRT in 2016. This will give them an appreciation of the complexity of these matters. In particular, it will become apparent from this review that "funding" must be considered in the context of other elements of a DOI.

For now, I suggest that CRT continues to use DOIs of the kind used in 2016. In addition, I would welcome in the future, T&F personnel reviewing prospective DOIs to verify that funding has been adequately addressed within the DOI. This approach may help us improve the DOIs in CRT review papers and avoid the confusion of introducing a separate "Funding" entry for each paper.

I look forward to your feedback on this important issue.

Best Regards,

Roger

Roger McClellan

From: Whalley, Charles <Charles.Whalley@tandf[REDACTED]>
Sent: Monday, September 12, 2016 5:26 PM
To: Roger McClellan; Whittle, Jenna
Cc: Mildred
Subject: RE: Publication Options for your Article

Dear Roger,

Thanks for this. It is indeed an automated email. We will make the article free-to-view at no cost.

Best wishes,
Charles

From: Roger McClellan [mailto:roger.o.mcclellan@[REDACTED]]
Sent: 09 September 2016 16:19
To: Whittle, Jenna; Whalley, Charles
Cc: Mildred; Roger McClellan
Subject: Re: Publication Options for your Article

Jenna anCharles:

I recognize this is a form letter. Please coordinate the handling of details related to publishing this Foreword to the Special Glyphosate Issue. I assume any costs are covered within the agreement between T and F and Intertek or as an internal T and F cost.

Regards, Roger

On Fri, 9/9/16, Jenna.Whittle@informa[REDACTED] <cats@taylorandfrancis.com> wrote:

Subject: Publication Options for your Article
To: roger.o.mcclellan@[REDACTED]
Date: Friday, September 9, 2016, 2:33 AM

Roger McClellan

roger.o.mcclellan@att.net

06 Sep 2016

Your article listed below is currently in production with Taylor & Francis.

Journal: ITXC, Critical Reviews in Toxicology

Manuscript ID: 1234117

Manuscript Title: Evaluating the Potential Carcinogenic Hazard of Glyphosate

By: McClellan

We are delighted that you have chosen to publish your

paper in Critical Reviews in Toxicology. This email is to inform you of the publication options available to you.

Standard publication route

Your paper will be published in the journal, and made available online permanently for subscribers and licensed institutions throughout the world, including provision of online access through developing world initiatives. You will also receive a link via email that you can send on to 50 colleagues who can download the paper free of charge. After the appropriate publisher embargo period, you may deposit the Accepted Manuscript into an institutional or subject repository (Green Open Access). (See <http://journalauthors.tandf.co.uk/publication/rapidonlinepublication.asp> for further information.) If we do not hear from you, your article will be published on this basis.

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If you have questions about Open Access please contact openaccess@tandf.co.uk or visit <http://journalauthors.tandf.co.uk/preparation/OpenAccess.asp> for further information.

Yours sincerely,
Jenna Whittle
Taylor & Francis
4 Park Square
Milton Park
Abingdon
Oxfordshire

OX14 4RN
UNITED KINGDOM
Email: [REDACTED]@informa.com

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[REDACTED]>
Sent: Tuesday, September 13, 2016 9:12 AM
To: Charles.Whalley@tandf[REDACTED]
Cc: Roger McClellan; Mildred
Subject: Fw: RE: Glyphosate supplement

Charles:

Are you available to discuss by telephone later today. Are you in the USA today? Do you have the tel # for Vasili? What is his position at T and F?

Regards, Roger

--- On Tue, 9/13/16, Ashley Roberts Intertek <ashley.roberts@intertek@[REDACTED]> wrote:

> From: Ashley Roberts Intertek <ashley.roberts@intertek@[REDACTED]>
> Subject: RE: Glyphosate supplement
> To: "Whalley, Charles" <Charles.Whalley@tandf@[REDACTED]>
> Cc: "Vasili, Temis" <Temis.Vasili@informa@[REDACTED]>, "Roger McClellan"
> <roger.o.mcclellan@[REDACTED]>
> Date: Tuesday, September 13, 2016, 8:03 AM
>
>
>
>
>
>
>
>
> Dear Charles/Roger,
>
> In addition to the previous
> information that I sent to you regarding the promotion of the
> glyphosate publications, Monsanto has now updated this to include the
> following and they want to be transparent on what they are doing and
> to keep you in the loop on these matters.
>
> For your information, they plan to
> help amplify the lack of carcinogenicity potential thorough,
> science-based review by: 1) helping coordinate an exclusive interview
> with Sir Colin Berry and a science reporter in advance of
> publication, 2) providing any inquiring media after publication with a
> Monsanto statement, and 3) directing interested media to the Critical
> Reviews in Toxicology website after publication. More details below.
>
>
> 1.
> The Sir Colin Berry exclusive interview will be with a science
> reporter from a mainstream media outlet in Europe.
> The reporter's story will be embargoed until after publication and the

> expert panels findings are publically available online. As part of
> this exclusive interview, we also think it would be beneficial to
> provide the reporter with an early version of the expert panel's
> report so the reporter has the information needed to write a detailed
> article.
> Please let us know if CRT supports this approach? if this is okay,
> Monsanto will suggest to Sir Colin that he share the early version of
> the report with the reporter during the interview.
>
>
> 2.
> For your reference, below is the Monsanto statement they plan to share
> on a reactive basis if they receive media inquiries after publication.
>
> At Monsanto, we're fully
> confident in the safety profile of our products. Our confidence is
> based on rigorous internal safety assessments in addition to safety
> assessments by regulatory authorities, independent researchers and
> other experts around the world. In July 2015, Monsanto retained a
> scientific consultant to convene an expert panel to review the
> International Agency for Research on Cancer (IARC) monograph on
> glyphosate *once it published*. The charge to the experts was to take a
> thorough look at the data in the monograph, assess the scope of the
> research included or excluded, and publish their conclusions to allow
> for external review. The experts that make up the panel include
> medical doctors, cancer experts, and individuals who hold doctoral
> degrees and who are experts in public health. The experts have spent
> their careers as researchers at major universities and medical
> schools, at research institutions and as consultants. The panel's
> peer-reviewed findings recently were published in the journal
> Critical Reviews in Toxicology and are available here: [Monsanto will
> insert direct link here]. These findings by the panel come at an
> important time, after so much unnecessary confusion and concern has
> been caused by IARC's classification of glyphosate. The panel's
> findings are consistent with the conclusions of regulatory authorities
> around the world. In fact, since IARC classified glyphosate,
> regulatory authorities in Europe, Canada, Japan, New Zealand and
> Australia have publicly reaffirmed that glyphosate does not cause
> cancer. Additionally, in May 2016, the Joint FAO/WHO Meeting on
> Pesticide Residues (JMPR) concluded that "glyphosate is unlikely to
> pose a carcinogenic risk to humans from exposure through the diet."
>
> 3.
> Lastly, after publication, Monsanto plan to proactively inform some
> reporters who have previously covered IARC's glyphosate monograph
> about the publication of the expert panel's findings. As such Monsanto
> plans to share a direct link to the Critical Reviews in Toxicology's
> website.
>
> Please let me know if this is
> acceptable to the journal.
>

> Many best Wishes
>
> Ashley
>
>
> Ashley Roberts,
> Ph.D.
>
> Senior Vice President
>
> Food & Nutrition Group
>
> Intertek Scientific
> & Regulatory Consultancy
>
> Tel: +1 [REDACTED]
>
>
> Fax: +1 [REDACTED]
>
> E-mail: ashley.roberts@intertek [REDACTED]
>
> 2233 Argentia Road,
> Suite 201
>
> Mississauga, Ontario Canada L5N 2X7
>
>
>
> From: Whalley,
> Charles [mailto:Charles.Whalley@tandf [REDACTED]]
>
> Sent: September-06-16 8:35 AM
>
> To: Ashley Roberts Intertek
>
> Cc: Vasili, Temis
>
> Subject: RE: Glyphosate supplement
> contract
>
>
>
> Dear Ashley,
>
> Thanks for coordinating signature and
> return of contracts with Temis. I hope you've had a pleasant holiday.
>
> Further to your response re
> promotion, I'd be grateful if Monsanto could

> provide:
> .
> A draft of the press release before
> publication
> .
> The names of the journalists who
> would receive the press release
> .
> The names of the panellists who would
> be provided to these journalists for follow-up discussion .
> Information on any social media promotion
>
> Apologies for the quizzing, but
> we're anticipating a lot of interest in this supplement and so I'm
> eager that we're aware of any marketing in advance.
>
> As for our promotion, I'll be
> able to confirm our plans after hearing from you on the above.
>
> I'd be happy to discuss this
> with the appropriate person at Monsanto directly if that's easier for
> you.
>
> All best wishes,
> Charles
>
>
>
>
> From: Ashley
> Roberts Intertek [mailto:ashley.roberts@intertek[REDACTED]]
>
>
> Sent: 23 August 2016 21:28
>
> To: Whalley, Charles
>
> Cc: Vasili, Temis
>
> Subject: RE: Glyphosate supplement
> contract
>
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> Dear Charles,
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> Many Thanks

>
> Ashley

>
> Ashley Roberts,
> Ph.D.

>
> Senior Vice President

>
> Food & Nutrition Group

>
> Intertek Scientific
> & Regulatory Consultancy

>
> Tel: +1

> [REDACTED]

>
> Fax: +1 [REDACTED]

>
> E-mail: ashley.roberts@intertek [REDACTED]

>
> 2233 Argentia Road,
> Suite 201

>
> Mississauga, Ontario Canada L5N 2X7

>
>

>
>

> From: Whalley,
> Charles [mailto:Charles.Whalley@tandf [REDACTED]]

>
>

> Sent: August-23-16 10:52 AM

>
>

> To: Ashley Roberts Intertek

>
>

> Cc: Vasili, Temis

>
> Subject: RE: Glyphosate supplement
> contract
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> Dear Ashley,
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> electronic or other communications/promotion. I look forward to
> hearing from you on this and the below.
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> Best wishes as ever,
> Charles
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>
>
> From: Whalley,
> Charles
>
> Sent: 22 August 2016 15:55
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> To: 'Ashley Roberts Intertek'
>
> Cc: Vasili, Temis
>
> Subject: Glyphosate supplement contract
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> Please find attached a draft contract for your review. To summarise,
> this covers an Open Access online-only supplement in CRT, with 200
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>
> Charles Whalley
> -
> Managing Editor, Medicine & Health Science Journals Taylor & Francis
> Group
> 4 Park Square, Milton
> Park, Abingdon, Oxon, OX14 4RN, UK
> Direct line:
> [REDACTED]
> Switchboard:
> [REDACTED]
> charles.whalley@tandf [REDACTED]
>
> www.tandfonline.com
>
>
> Taylor & Francis
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> no. 1072954
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- > this for any purpose nor disclose its contents to any other person.
- > <http://www.intertek.com>
- >
- >
- >
- >
- >

Roger McClellan

From: Whalley, Charles <Charles.Whalley@tandf [REDACTED]>
Sent: Tuesday, September 13, 2016 9:29 AM
To: Roger McClellan
Cc: Mildred
Subject: RE: RE: Glyphosate supplement

Dear Roger,

I'm currently in Boston, and will be heading off to set up my booth for the conference in a moment. T&F does not provide me with a mobile phone, so we'll have to continue by email until I return to the office on 22nd Sept. Did you have any concerns with Monsanto's Marketing plans, or just questions about timelines?

For your reference, Temis' number for her desk is + [REDACTED] (Vasili is her surname; our email addresses show as 'surname, first name'.) She is an Editorial Assistant, and helps me in the management and administration of all of my journals, as well as supporting some other members of my team. Editorial Assistant is the entry-level role in our department, although Temis is more experienced than most, having previously worked at another publisher and with a background in neuroscience.

Best wishes as ever,
Charles

From: Roger McClellan [mailto:roger.o.mcclellan@ [REDACTED]]
Sent: 13 September 2016 16:12
To: Whalley, Charles
Cc: Roger McClellan; Mildred
Subject: Fw: RE: Glyphosate supplement

Charles:
Are you available to discuss by telephone later today. Are you in the USA today? Do you have the tel # for Vasili? What is his position at T and F?
Regards, Roger

--- On Tue, 9/13/16, Ashley Roberts Intertek < [REDACTED]@intertek.com> wrote:

> From: Ashley Roberts Intertek <ashlev.roberts@intertek.com>
> Subject: RE: Glyphosate supplement
> To: "Whalley, Charles" <Charles.Whalley@tandf [REDACTED]>
> Cc: "Vasili, Temis" < [REDACTED]@informa.com>, "Roger McClellan" <roger.o.mcclellan@ [REDACTED]>
> Date: Tuesday, September 13, 2016, 8:03 AM
>
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- > For your information, they plan to
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- > science-based review by: 1) helping coordinate an exclusive
- > interview with Sir Colin Berry and a science reporter
- > in advance of publication, 2) providing any inquiring media
- > after publication with a Monsanto statement, and 3)
- > directing interested media to the Critical Reviews in
- > Toxicology website after publication. More details below.
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- > science reporter from a mainstream media outlet in Europe.
- > The reporter's story will be embargoed until after
- > publication and the expert panels
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- > provide the reporter with an early version of the expert
- > panel's report so the reporter has the information
- > needed to write a detailed article.
- > Please let us know if CRT supports this approach? if this
- > is okay, Monsanto will suggest to Sir Colin that he share
- > the early version of the report with the reporter during the
- > interview.
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- > For your reference, below is the Monsanto statement they
- > plan to share on a reactive basis if they receive media
- > inquiries after publication.
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- > At Monsanto, we're fully
- > confident in the safety profile of our products. Our
- > confidence is based on rigorous internal safety assessments
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- > researchers and other experts around the world. In July
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> direct link here]. These findings by the panel come at an
> important time, after so much unnecessary confusion and
> concern has been caused by IARC's classification
> of glyphosate. The panel's findings are consistent
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> carcinogenic risk to humans from exposure through the
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> Ashley

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> Mississauga, Ontario Canada L5N 2X7
>
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>
> From: Whalley,
> Charles [mailto:Charles.Whalley@tandf] [REDACTED]
>
> Sent: September-06-16 8:35 AM
>
> To: Ashley Roberts Intertek
>
> Cc: Vasili, Temis
>
> Subject: RE: Glyphosate supplement
> contract
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> Dear Ashley,
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> Thanks for coordinating signature and
> return of contracts with Temis. I hope you've had a
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> A draft of the press release before
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> Information on any social media
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> able to confirm our plans after hearing from you on the
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> I'd be happy to discuss this
> with the appropriate person at Monsanto directly if
> that's easier for you.
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> All best wishes,
> Charles
>
>
>
> From: Ashley
> Roberts Intertek [mailto:██████████@intertek.com]
>
>
> Sent: 23 August 2016 21:28
>
> To: Whalley, Charles
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> Cc: Vasili, Temis
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> Subject: RE: Glyphosate supplement
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> [REDACTED]

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> Fax: +1

> [REDACTED]

> E-mail: [REDACTED]@intertek.com

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> Suite 201

>
> Mississauga, Ontario Canada L5N 2X7

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> From: Whalley,
> Charles [mailto:Charles.Whalley@tandf [REDACTED]]

>
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> Sent: August-23-16 10:52 AM

>
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> Cc: Vasili, Temis

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> Sent: 22 August 2016 15:55

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>
> Charles Whalley
> .
> Managing Editor, Medicine & Health Science
> Journals
> Taylor & Francis
> Group
> 4 Park Square, Milton
> Park, Abingdon, Oxon, OX14 4RN, UK
> Direct line:
> [REDACTED]
> Switchboard:
> [REDACTED]
> charles.whalley@tandf.com [REDACTED]
>
> www.tandfonline.com
>
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> <http://www.intertek.com>

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>
>
>
>

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[REDACTED]>
Sent: Tuesday, September 13, 2016 9:50 AM
To: Charles.Whalley@tandf.[REDACTED]
Cc: mbmorgan@hargray.[REDACTED]; roger.o.mcclellan@[REDACTED]; Jenna.Whittle@informa.[REDACTED]
Subject: RE: RE: Glyphosate supplement/ Followup

Charles:

I have no problems with the Monsanto Proposal. My concern is with removal of the special entry for Funding and the inter-related issue of schedule. I want this Special Supplement Issue to be identical in format to earlier regular issues in Vol 46. I see no need to change horses in mid stream since the DOI of the accepted papers covered funding.

Later we can discuss why the T and F folks got a "bee in their bonnet" over funding , especially since CRT had been a leader on the disclosure issue.

Roger

On Tue, 9/13/16, Whalley, Charles <Charles.Whalley@tandf.[REDACTED]> wrote:

Subject: RE: RE: Glyphosate supplement
To: "Roger McClellan" <roger.o.mcclellan@[REDACTED]>
Cc: "Mildred" <mbmorgan@hargray.[REDACTED]>
Date: Tuesday, September 13, 2016, 8:29 AM

#yiv1006742520
#yiv1006742520 --

_filtered #yiv1006742520 {font-family:Calibri;panose-1:2 15 5 2 2 2 4 3 2 4;}
_filtered #yiv1006742520 {font-family:Tahoma;panose-1:2 11 6 4 3 5 4 4 2 4;}
#yiv1006742520
#yiv1006742520 p.yiv1006742520MsoNormal, #yiv1006742520 li.yiv1006742520MsoNormal, #yiv1006742520 div.yiv1006742520MsoNormal
{margin:0cm;margin-bottom:.0001pt;font-size:12.0pt;}
#yiv1006742520 a:link, #yiv1006742520 span.yiv1006742520MsoHyperlink
{color:blue;text-decoration:underline;}
#yiv1006742520 a:visited, #yiv1006742520 span.yiv1006742520MsoHyperlinkFollowed
{color:purple;text-decoration:underline;}
#yiv1006742520 span.yiv1006742520EmailStyle17
{color:#1F497D;}
#yiv1006742520 .yiv1006742520MsoChpDefault
{font-size:10.0pt;}
_filtered #yiv1006742520 {margin:72.0pt 72.0pt 72.0pt 72.0pt;}
#yiv1006742520 div.yiv1006742520WordSection1
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[mailto:roger.o.mcclellan@[REDACTED]]

Sent: 13 September 2016 16:12

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> From: Ashley Roberts Intertek <ashley.roberts@intertek@[REDACTED]>

> Subject: RE: Glyphosate supplement

> To: "Whalley, Charles" <Charles.Whalley@tandf@[REDACTED]>

> Cc: "Vasili, Temis" <Temis.Vasili@informa[REDACTED]> "Roger McClellan" <roger.o.mcclellan[REDACTED]>

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> Ashley Roberts,
> Ph.D.
>
> Senior Vice President
>
> Food & Nutrition Group
>
> Intertek Scientific
> & Regulatory Consultancy
>
> Tel: +1
> [REDACTED]
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> Fax: +1 [REDACTED]
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> E-mail: [REDACTED]@intertek [REDACTED]
>
> 2233 Argentia Road,
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>
> Mississauga, Ontario Canada L5N 2X7
>
>
>
>

> From: Whalley,
> Charles [mailto:Charles.Whalley@tandf[REDACTED]]

>

> Sent: September-06-16 8:35 AM

>

> To: Ashley Roberts Intertek

>

> Cc: Vasili, Temis

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> Subject: RE: Glyphosate supplement

> contract

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>

> From: Ashley

> Roberts Intertek [mailto:ashley.roberts@intertek] [REDACTED]

>

>

> Sent: 23 August 2016 21:28

>

> To: Whalley, Charles

>

> Cc: Vasili, Temis

>

> Subject: RE: Glyphosate supplement

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> spoken to Monsanto and they have indicated that if you are

> in agreement they would like to promote the

> publications. While nothing definite has been planned

> they were contemplating

> making a press release to some "friendly"

> journalists indicating when the report will be released with

> the time estimation for publication as well as provide some

> names of the panelists who they could contact for follow-up

> discussion. Beyond this initial

> action, no further thought has gone in to this and they

> were wondering if the Journal does any of their own kind of

> promotion.

>

> If you could let me know if the above

> is acceptable, that would be great.

>

> Many Thanks

>

> Ashley

>

>

> Ashley Roberts,

> Ph.D.

>

> Senior Vice President

>

> Food & Nutrition Group

>

> Intertek Scientific

> & Regulatory Consultancy

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> E-mail: [REDACTED]@intertek.com

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> Suite 201

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> Mississauga, Ontario Canada L5N 2X7

>

>

>

>

> From: Whalley,

> Charles (mailto:Charles.Whalley@tandf[REDACTED])

>

>

> Sent: August-23-16 10:52 AM

>

> To: Ashley Roberts Intertek

>

> Cc: Vasili, Temis

>

> Subject: RE: Glyphosate supplement

> contract

>

>

>

> Dear Ashley,

>

> Further to the below, it occurs to me

> that it would helpful and much appreciated if you could let

> me know on Intertek's and Monsanto's plans for

> promoting the supplement,

> if any, both with the print copies which we will be

> producing and in any electronic or other

> communications/promotion. I look forward to hearing from you

> on this and the below.

>

> Best wishes as ever,

> Charles

>

>

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[REDACTED]>
Sent: Tuesday, September 20, 2016 2:21 PM
To: ashley.roberts@intertek [REDACTED]; roger.o.mcclellan@[REDACTED]; JennaWhittle
Cc: Charles.Whalley@tandf [REDACTED]; Mildred Morgan; judy.vowles@intertek [REDACTED]
Subject: Re: CRT supplement 1, final files for approval/ Changes to 3 DOIs

Jenna:

To provide consistency across all five papers the DOIs on 3 papers need to be expanded.
Solomon: Add at beginning of DOI --"The employment affiliation of the author is shown on the cover page. However, it should be recognized that the author participated in their view process and preparation of this paper as an independent professional and not as a representative of his employer."
Brusick et al.: Add 2 sentences to beginning of DOI identical to the Williams et al papers.
Acquavella et al: Add 2 sentences to beginning of DOI identical to first 2 sentences of Williams et al papers.
In my opinion, with these changes, the papers are now ready for on-line posting. I assume that Dr Roberts concurs.
Please acknowledge receipt and note when papers will be posted.
Thanks for your help on this special issue.
Roger

On Tue, 9/20/16, Whittle, Jenna <Jenna.Whittle@informa[REDACTED]> wrote:

Subject: CRT supplement 1, final files for approval
To: "Ashley Roberts Intertek" <ashley.roberts@intertek [REDACTED]> "Roger McClellan" <roger.o.mcclellan@[REDACTED]>
Cc: "Whalley, Charles" <Charles.Whalley@tandf [REDACTED]>, "Mildred Morgan" <mbmorgan@hargray [REDACTED]>
"judy.vowles@intertek [REDACTED]" <judy.vowles@intertek [REDACTED]>
Date: Tuesday, September 20, 2016, 9:51 AM

Dear Roger and Ashley

As discussed, please find attached the final print files for the supplement. Please could you review these files and let me know if they have your approval for publication.

In addition, as a number of changes had to be made to the Declaration of interest sections, I would be grateful if you could check these in particular to ensure that they are correct and complete.

Many thanks for all your help with this. Please do let me know if you have any questions.

Best wishes

Jenna

Jenna
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Roger McClellan

From: Larry Kier <ldkier@██████████>
Sent: Tuesday, September 20, 2016 1:26 PM
To: Roger O. McClellan
Subject: Quotes in SAP Letter

Dear Roger:

It's been a while and I hope you are doing well.

As you are probably aware the EPA will be convening a FIFRA SAP in October to review glyphosate carcinogenicity.

I am preparing a letter for submission to the SAP which briefly presents the conclusions of the glyphosate genotoxicity Expert Panel report and provides relevant material from the report to comment on the Charge Questions relevant to genotoxicity evaluation submitted to the SAP.

I would like to use brief (one or two sentences each) direct quotes from the report in this letter to make sure there is as accurate a representation as possible.

It's my understanding that the report will be published online this week and will be open access but I wanted to check with you to make sure it's ok to use direct quotes from the publication in the letter.

Thanks and best regards,

Larry Kier

This e-mail message may contain privileged and/or confidential information, and is intended to be received only by persons entitled to receive such information. If you have received this e-mail in error, please notify the sender immediately. Please delete it and all attachments from any servers, hard drives or any other media. Other use of this e-mail by you is strictly prohibited.

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[REDACTED]>
Sent: Tuesday, September 20, 2016 2:50 PM
To: Larry Kier
Cc: ashley.roberts@intertek [REDACTED] mbmorgan@hargray [REDACTED] Roger McClellan
Subject: Re: Quotes in SAP Letter/ Yes

Larry

Great to hear from you. Yes, the Special Glyphosate Issue should be posted on line in a matter of days. You are certainly free to make direct quotes, with appropriate attribution, from the paper in your letter and oral presentation, if you make one. In some cases you may even want to make direct quotes from your earlier papers which were provided to IARC prior to their review. To cover all the options you may wish to make direct quotes from the original papers published by you and others.

You should be aware that in the past some EPA Offices have raised issues about citing review papers. If you want more details I suggest you contact Barbara Beck and/or Sam Cohen.

Best regards,
Roger

On Tue, 9/20/16, Larry Kier <ldkier@[REDACTED]> wrote:

Subject: Quotes in SAP Letter
To: "Roger O. McClellan" <roger.o.mcclellan@[REDACTED]>
Date: Tuesday, September 20, 2016, 12:25 PM

Dear Roger: It's been a while and I hope you are doing well. As you are probably aware the EPA will be convening a FIFRA SAP in October to review glyphosate carcinogenicity. I am preparing a letter for submission to the SAP which briefly presents the conclusions of the glyphosate genotoxicity Expert Panel report and provides relevant material from the report to comment on the Charge Questions relevant to genotoxicity evaluation submitted to the SAP.

I would like to use brief (one or two sentences each) direct quotes from the report in this letter to make sure there is as accurate a representation as possible. It's my understanding that the report will be published online this week and will be open access but I wanted to check with you to make sure it's ok to use direct quotes from the publication in the letter.

Thanks and best regards, Larry Kier ----- This e-mail message may contain privileged and/or confidential information, and is intended to be received only by persons entitled to receive such information. If you have received this e-mail in error, please notify the sender immediately. Please delete it and all attachments from any servers, hard drives or any other media. Other use of this e-mail by you is strictly prohibited.

Roger McClellan

From: Ashley Roberts Intertek <[REDACTED]@intertek.com>
Sent: Thursday, September 22, 2016 10:41 AM
To: Whittle, Jenna
Cc: Roger McClellan; Mildred Morgan; Whalley, Charles
Subject: RE: Final changes

Many Thanks Jenna.

Ashley Roberts, Ph.D.
Senior Vice President, Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Health, Environmental and Regulatory Services
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Skype: [REDACTED]
2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

From: Whittle, Jenna [mailto:Jenna.Whittle@informa[REDACTED]]
Sent: September-22-16 12:37 PM
To: Ashley Roberts Intertek
Cc: Roger McClellan; Mildred Morgan; Whalley, Charles
Subject: RE: Final changes

Hi Ashley

I unfortunately can't give a specific date for publication as this depends on whether further corrections will be required to the next set of final files. The corrected files should hopefully arrive by the end of the day UK time on Monday if the typesetter doesn't have any difficulty incorporating the corrections. We also need to allow time for you to check the final files and for all the quality control checks here to take place so I'm afraid publication on Monday is unlikely. Hopefully it shouldn't be too much later in the week if no further corrections are required.

Best wishes
Jenna

From: Ashley Roberts Intertek [mailto:ashley.roberts@intertek[REDACTED]]
Sent: 22 September 2016 16:48
To: Whittle, Jenna
Cc: Roger McClellan; Mildred Morgan; Whalley, Charles
Subject: RE: Final changes
Importance: High

Hi Jenna,

Could you let me know with the changes we made if we are still aiming for a Monday publication?

Many Thanks

Ashley

Ashley Roberts, Ph.D.
Senior Vice President, Food & Nutrition Group
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Skype: [REDACTED]
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Mississauga, Ontario Canada L5N 2X7

From: Whittle, Jenna [<mailto:Jenna.Whittle@informa.com>] [REDACTED]
Sent: September-21-16 12:12 PM
To: Ashley Roberts Intertek
Cc: Roger McClellan; Mildred Morgan; Whalley, Charles
Subject: RE: Final changes

Thank you for sending me your final amendments, Ashley. I'll arrange for them to be incorporated and I will let you know if I have any questions. For Roger's reference, I've attached your other emails detailing the other corrections.

These are more extensive changes than we would normally expect at this stage in the production process (reorganising the order of various sections, etc.) and so the typesetter will need more time to incorporate them accurately. I'm concerned that errors could be accidentally introduced while they make these amendments, despite their best efforts, so I will send you another final file for approval before we go to press. This should hopefully be on or by Monday 26th. Please note that only major errors that would otherwise result in an erratum or corrigendum should be corrected at that stage to avoid delays.

If you have any questions, please do not hesitate to contact me.

Best wishes

Jenna

From: Ashley Roberts Intertek [<mailto:ashley.roberts@intertek.com>] [REDACTED]
Sent: 21 September 2016 16:57
To: Whittle, Jenna
Subject: Final changes

Hi Jenna,

These are the last of the typos changes we found in the manuscripts as outlined on the various page numbers

1. Need to reorder within the summary document so the sections follow the same sequence as the chapters - Introduction, Exposure, Epidemiology, Rodent bioassay, and Genotoxicity
2. Page 8, second column, bullet point "c.", "(positive trend $p < 0.05$)" should be "positive trend ($p < 0.05$)"
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4. Page 48, last line of first column, "...low observed adverse effect..." should be "**lowest** observed adverse effect"
5. Page 49, second column, third complete paragraph, "IARC did not comment on the absence of hemangiosarcomas in the Nufarm (2009)...." should be "IARC did not comment on the absence of hemangiosarcomas in Nufarm (2009)" (delete "the" from original text)
6. Page 59, second column, 4 lines up from bottom, "high degree of and standard for detailed" should be "high degree of, and standard for, detailed" (added commas)
7. Page 63, first column, second complete paragraph "25.0 µM" should be "25.0 µm" (small "m" for micrometer)
8. Page 65, the "in vivo" in the title heading "Chromosomal effects in vivo" needs to be italicized.
9. Page 65 second column, 17 lines up from the bottom "Another positive publication Amer et al. (2006)" should be "Another positive publication (Amer et al. 2006)" (change position of bracket)

If you have any questions, please let me know.

Best Wishes

Ashley

From: Whittle, Jenna [<mailto:Jenna.Whittle@informa>]
Sent: September-21-16 10:38 AM
To: Ashley Roberts Intertek
Subject: RE: A few changes

Thanks for these, Ashley. Just to confirm the changes to pp. 49 and 50, please can you check that this is correct:

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. Here, again the level of significance in common tumors is $p < .005$. The following islet cell adenoma 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.

Thanks and best wishes

Jenna

From: Ashley Roberts Intertek [mailto:ashley.roberts@intertek] [REDACTED]

Sent: 21 September 2016 14:25

To: Whittle, Jenna

Subject: A few changes

Hi Jenna,

The following typos and changes need to be made to the following papers

- Page 2, lines 19 and 24 – change “glyphosates” (plural) to “glyphosate” (singular) paper #1 Rogers Foreword
- Page 32, Table 4 Title – should be “Validity considerations for glyphosate studies (add the word “for”) Paper #3 Epidemiology

For the summary paper #2 and the animal bioassay paper #4 the following error was picked up.

As outlined below the study identified as “the first study” is actually “the second study” and vice-versa in the discussion of “Pancreatic tumors in rats”, here is how the text should read on the bottom of page 9/top of page 10. I highlighted words which need to change:

In the ~~second~~ first study Sprague-Dawley rats received doses of 0, 30 (3), 100 (10), and 300 (31 mg/kg bw/day) ppm in the diet for 26 months. No pancreatic islet carcinomas were observed. Adenomas were found having a positive trend ($p < .05$) in the study. ~~Here again~~ The level of significance for an increase in common tumors in the trend test should be $p < .005$. The tumor incidences for controls, low, mid, and high doses respectively were: 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. This incidence demonstrates no dose-response pattern, and an absence of pre-neoplastic effects. In addition, in the second study in males, the adenomas did not progress to carcinomas.

In the ~~first~~ second study Sprague-Dawley rats received 0, 2000, 8000, and 20,000ppm 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 (2), 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, 0/59. 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 here again the level of significance 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) not evaluated by IARC, similarly did not show pancreatic islet cell tumors. Based on this information the Expert Panel concludes that there is no evidence that glyphosate induces islet cell tumors in the pancreas.

The same changes will need to be done on the bottom of page 49 and top of page 50 of the animal bioassay paper #4. Here the changes are slightly simpler – the text needs to be moved as shown above, and the only word-changing is “first” to “second” and “second” to “first” (2 times in that paragraph).

Please let me know if you need clarification on any of the above?

Best Wishes

Ashley

Ashley Roberts, Ph.D.

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Mississauga, Ontario Canada L5N 2X7

From: Whittle, Jenna [mailto:Jenna.Whittle@informa[REDACTED]]

Sent: September-20-16 12:52 PM

To: Ashley Roberts Intertek; Roger McClellan
Cc: Whalley, Charles; Mildred Morgan; Judy Vowles Intertek
Subject: CRT supplement 1, final files for approval

Dear Roger and Ashley

As discussed, please find attached the final print files for the supplement. Please could you review these files and let me know if they have your approval for publication.

In addition, as a number of changes had to be made to the Declaration of interest sections, I would be grateful if you could check these in particular to ensure that they are correct and complete.

Many thanks for all your help with this. Please do let me know if you have any questions.

Best wishes

Jenna

Jenna Whittle
Production Editor, Journals
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Roger McClellan

From: Whittle, Jenna <[REDACTED]@informa.com>
Sent: Monday, September 26, 2016 8:07 AM
To: Ashley Roberts Intertek
Cc: Roger McClellan; Mildred Morgan; Whalley, Charles
Subject: Supplement proofs - update

Dear all

I have just received the final proofs from the typesetter, but the tables in the Williams et al. paper haven't been renumbered and repositioned following the changes requested to the article structure, so I will need to request another updated proof from the typesetter. I'm afraid this means that there will be a delay in sending you the final proof for approval – please accept my apologies for this. I will be in touch again as soon as I can.

Best wishes

Jenna

From: Ashley Roberts Intertek [mailto:ashley.roberts@intertek.[REDACTED]]
Sent: 22 September 2016 17:41
To: Whittle, Jenna
Cc: Roger McClellan; Mildred Morgan; Whalley, Charles
Subject: RE: Final changes

Many Thanks Jenna.

Ashley Roberts, Ph.D.
Senior Vice President, Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Health, Environmental and Regulatory Services
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Sent: September-22-16 12:37 PM
To: Ashley Roberts Intertek
Cc: Roger McClellan; Mildred Morgan; Whalley, Charles
Subject: RE: Final changes

Hi Ashley

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Sent: 22 September 2016 16:48
To: Whittle, Jenna
Cc: Roger McClellan; Mildred Morgan; Whalley, Charles
Subject: RE: Final changes
Importance: High

Hi Jenna,

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Many Thanks

Ashley

Ashley Roberts, Ph.D.
Senior Vice President, Food & Nutrition Group
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Sent: September-21-16 12:12 PM
To: Ashley Roberts Intertek
Cc: Roger McClellan; Mildred Morgan; Whalley, Charles
Subject: RE: Final changes

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Best wishes

Jenna

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Sent: 21 September 2016 16:57
To: Whittle, Jenna
Subject: Final changes

Hi Jenna,

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If you have any questions, please let me know.

Best Wishes

Ashley

From: Whittle, Jenna [mailto: [REDACTED]@informa.com]
Sent: September-21-16 10:38 AM
To: Ashley Roberts Intertek
Subject: RE: A few changes

Thanks for these, Ashley. Just to confirm the changes to pp. 49 and 50, please can you check that this is correct:

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. Here, again the level of significance in common tumors is $p < .005$. The following islet cell adenoma 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.

Thanks and best wishes

Jenna

From: Ashley Roberts Intertek [mailto: [REDACTED]@intertek.com]
Sent: 21 September 2016 14:25
To: Whittle, Jenna
Subject: A few changes

Hi Jenna,

The following typos and changes need to be made to the following papers

- Page 2, lines 19 and 24 – change “glyphosates” (plural) to “glyphosate” (singular) paper #1 Rogers Foreword
- Page 32, Table 4 Title – should be “Validity considerations for glyphosate studies (add the word “for”) Paper #3 Epidemiology

For the summary paper #2 and the animal bioassay paper #4 the following error was picked up.

As outlined below the study identified as “the first study” is actually “the second study” and vice-versa in the discussion of “Pancreatic tumors in rats”, here is how the text should read on the bottom of page 9/top of page 10. I highlighted words which need to change:

In the ~~second~~ first study Sprague-Dawley rats received doses of 0, 30 (3), 100 (10), and 300 (31 mg/kg bw/day) ppm in the diet for 26 months. No pancreatic islet carcinomas were observed. Adenomas were found having a positive trend ($p < .05$) in the study. ~~Here again –~~ The level of significance for an increase in common tumors in the trend test should be $p < .005$. The tumor incidences for controls, low, mid, and high doses respectively were: 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. This incidence demonstrates no dose-response pattern, and an absence of pre-neoplastic effects. In addition, in the second study in males, the adenomas did not progress to carcinomas.

In the ~~first~~ second study Sprague-Dawley rats received 0, 3000, 8000, and 20,000ppm 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 (2), 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, 0/59. 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 here again the level of significance 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) not evaluated by IARC, similarly did not show pancreatic islet cell tumors. Based on this information the Expert Panel concludes that there is no evidence that glyphosate induces islet cell tumors in the pancreas.

The same changes will need to be done on the bottom of page 49 and top of page 50 of the animal bioassay paper #4. Here the changes are slightly simpler – the text needs to be moved as shown above, and the only word-changing is “first” to “second” and “second” to “first” (2 times in that paragraph).

Please let me know if you need clarification on any of the above?

Best Wishes

Ashley
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From: Whittle, Jenna [mailto:[REDACTED]@informa.com]
Sent: September-20-16 12:52 PM
To: Ashley Roberts Intertek; Roger McClellan
Cc: Whalley, Charles; Mildred Morgan; Judy Vowles Intertek
Subject: CRT supplement 1, final files for approval

Dear Roger and Ashley

As discussed, please find attached the final print files for the supplement. Please could you review these files and let me know if they have your approval for publication.

In addition, as a number of changes had to be made to the Declaration of interest sections, I would be grateful if you could check these in particular to ensure that they are correct and complete.

Many thanks for all your help with this. Please do let me know if you have any questions.

Best wishes

Jenna

Jenna Whittle
Production Editor, Journals
Taylor & Francis



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Roger McClellan

From: Whittle, Jenna <[REDACTED]@informa.com>
Sent: Tuesday, September 27, 2016 10:34 AM
To: Roger McClellan
Subject: RE: CRT supplement (46.S1) - final files for approval/ Approved

Thanks Roger. I will do.

From: Roger McClellan [mailto:roger.o.mcclellan@[REDACTED]]
Sent: 27 September 2016 16:34
To: ashley.roberts@intertek [REDACTED]; Whittle, Jenna <[REDACTED]@informa.com>
Cc: ashley.roberts@intertek [REDACTED]; roger.o.mcclellan@[REDACTED]; Whalley, Charles <Charles.Whalley@tandf[REDACTED]>; Mildred Morgan <mbmorgan@hargray.com>
Subject: Re: CRT supplement (46.S1) - final files for approval/ Approved

Jenna

The final files look great!!! Please proceed with posting on-line as soon as you have approval from Charles. I note that Ashley has approved the files. Please send an electronic linkage to the Special Issue, a linkage I can share with others. Thanks for your assistance with this major project.

Regards, Roger

On Tue, 9/27/16, Whittle, Jenna <[REDACTED]@informa.com> wrote:

Subject: CRT supplement (46.S1) - final files for approval
To: "Roger McClellan" <roger.o.mcclellan@[REDACTED]>, "Ashley Roberts Intertek" <[REDACTED]@intertek.com>
Cc: "Whalley, Charles" <Charles.Whalley@tandf[REDACTED]>, "Mildred Morgan" <mbmorgan@[REDACTED]>
Date: Tuesday, September 27, 2016, 6:41 AM

Dear Ashley and Roger
Please find attached the
final files for the supplement. Apologies again for the
delay.

Please could you review
these files and let me know if they have your approval for
publication.
Thanks and best wishes

Jenna

Jenna
Whittle
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Roger McClellan

From: Ashley Roberts Intertek <ashley.roberts@intertek [REDACTED]>
Sent: Tuesday, September 27, 2016 10:36 AM
To: Whittle, Jenna; Roger McClellan
Cc: Whalley, Charles; Mildred Morgan
Subject: RE: CRT supplement (46.S1) - final files for approval

Thank you Jenna

Ashley Roberts, Ph.D.
Senior Vice President, Food & Nutrition Group
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Interested in learning about regulatory approvals in China? Stop by Booth PP170 to meet Sandy Lin, Director, China office.	Wine & Cheese Reception October 6th, 2016 3:30-4:30 Booth PP170	
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From: Whittle, Jenna [mailto:Jenna.Whittle@informa.com]
Sent: September-27-16 12:33 PM
To: Ashley Roberts Intertek; Roger McClellan
Cc: Whalley, Charles; Mildred Morgan
Subject: RE: CRT supplement (46.S1) - final files for approval

Thanks for checking the files, Ashley. After Charles has confirmed we can proceed with publication, I'll send the issue to press. It should appear on the journal website approximately 24 hours after this.

Best wishes
Jenna

From: Ashley Roberts Intertek [mailto:[REDACTED]@intertek.com]
Sent: 27 September 2016 15:55
To: Whittle, Jenna <Jenna.Whittle@informa.com>; Roger McClellan <roger.o.mcclellan@[REDACTED]>
Cc: Whalley, Charles <Charles.Whalley@tandf.com>; Mildred Morgan <mbmorgan@hargray.com>
Subject: RE: CRT supplement (46.S1) - final files for approval

Hi Jenna,

We have checked the final files and we are good to go.

So, please take this as an approval for publication. As a result, could you let me know when they will go on line?

Many Thanks for your hard work on this matter.

Best Wishes

Ashley

Ashley Roberts, Ph.D.
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Stop by Booth PP170 to meet Sandy Un, Director, China office.

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October 6th, 2016
3:30-4:30
Booth PP170

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From: Whittle, Jenna [mailto:[REDACTED]@informa.com]
Sent: September-27-16 9:41 AM
To: Roger McClellan; Ashley Roberts Intertek
Cc: Whalley, Charles; Mildred Morgan
Subject: CRT supplement (46.S1) - final files for approval
Importance: High

Dear Ashley and Roger

Please find attached the final files for the supplement. Apologies again for the delay.

Please could you review these files and let me know if they have your approval for publication.

Thanks and best wishes

Jenna

Jenna Whittle
Production Editor, Journals
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Roger McClellan

From: Whalley, Charles <[REDACTED]@tandf.co.uk>
Sent: Thursday, September 29, 2016 1:45 AM
To: Roger McClellan
Cc: mbmorgan@hargray[REDACTED] Whittle, Jenna; Vasili, Temis
Subject: CRT Supplement now published

Dear Roger,

I note that the glyphosate supplement is now published online and all showing as Open Access. The full table of contents is accessible at the following link: <http://tandfonline.com/toc/itxc20/46/sup1?nav=tocList> This has been a considerable amount of work on all sides so I'm delighted to see it come to fruition

I'm in the office today if you wanted to follow up on this by phone. Between 3:30 and 4pm UK time I shall be on the phone (incidentally to a toxicologist at the University of New Mexico), but otherwise I should be available and at my desk.

Very best wishes,
Charles

Charles Whalley - Managing Editor, Medicine & Health Journals

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Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[REDACTED]>
Sent: Thursday, September 29, 2016 12:34 PM
To: bolt@ifado[REDACTED]; rcc0022@auburn[REDACTED]; scohen@unmc[REDACTED]; dellarcov@gmail[REDACTED];
rdavid_dorman@ncsu[REDACTED]; f.guengerich@vanderbilt[REDACTED]; gunnar.johanson@[REDACTED];
s.tsuda@iwate-u.ac[REDACTED]; david.warheit@gmail[REDACTED]
Cc: Charles Whalley; Roger McClellan; Mildred B. Morgan
Subject: SPECIAL ISSUE: GLYPHOSATE

CRT Board of Directors

The Special Issue of Critical Reviews in Toxicology (CRT), Vol. 46, entitled "An Independent Review of the Carcinogenic Potential of Glyphosate" has been published on-line and can be accessed via the following link: <http://tandfonline.com/toc/itxc20/46/sup1?nav=tocList>. As you will note, the issue includes a brief foreword I prepared and five papers prepared by the Panel. I call your attention to the comprehensive "Declaration of Interests" statement for each of the papers. Such DOI statements routinely accompany each article published in CRT. In my opinion, these statements are among the most comprehensive published today in scientific journals.

You will also note the papers were extensively reviewed by a total of 27 independent reviewers, including a number of you serving on the CRT Editorial Advisory Board. Several of you reviewed all five papers. The review comments proved very useful to the authors and contributed to the overall quality of the published papers.

I expect the papers in the Special Issue will be widely read and cited. As you will note, the papers are available on open access which should encourage readership.

I extend a special note of thanks to you for your valuable advice concerning these papers and the Special Issue. Your advice contributed to the quality of the rigorous review process used and the scientific quality of the Issue.

If you know of individuals who would like to prepare a set of papers on a single lengthy paper for publication as a Special Issue of CRT, please have them contact me with regard to scientific details concerned with publication of such issues. If the material is deemed scientifically appropriate for a Special Issue, I will refer the individual to Charles Whalley, the Managing Editor for CRT to discuss costs and business details associated with publication of a Special Issue.

Roger

--- On Sat, 10/15/16, Nebert, Daniel (nebertdw) <NEBERTDW@UCMAIL.UC [REDACTED]> wrote:

> From: Nebert, Daniel (nebertdw) <NEBERTDW@UCMAIL.UC [REDACTED]>
> Subject: An Independent Review of the Carcinogenic Potential of
> Glyphosate
> To: "Abdel-Malek, Zalfa (abdelmza)" <ABDELMZA@UCMAIL.UC [REDACTED]>
> "Bernstein, Jonathan (bernstja)" <BERNSTJA@UCMAIL.UC [REDACTED]> "Bingham,
> Eula (binghael)" <BINGHAEL@UCMAIL.UC [REDACTED]> "BOL-Bermudez, Mei-Ling
> (bermudmn)" <bermudmn@mail.uc [REDACTED]> "BOL-Frank, Evan (franken)"
> <franken@mail.uc [REDACTED]> "BOL-Hsieh, Heidi (hsiehhi)"
> <hsiehhi@mail.uc [REDACTED]> "BOL-Krishan, Mansi (krishami)"
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> <mille3dl@mail.uc [REDACTED]> "BOL-Vonhandorf, Andrew (vonhanap)"
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> "CHM-Mersha, Tesfaye (Tefaye.Mersha)" <Tefaye.Mersha@cchmc [REDACTED]>
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> "CHM-Ryan, Patrick (Patrick.Ryan)" <Patrick.Ryan@cchmc [REDACTED]> "Choubey,
> Divaker (choubedr)" <choubedr@ucmail.uc [REDACTED]> "Nebert, Daniel
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> "Huang, Shouxiong (huangsx)" <huangsx@ucmail.uc [REDACTED]> "Hugo, Eric
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> <abbyleaajo@ [REDACTED]>, "Kadekaro, Ana Luisa (kadekaal)"
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> <medvedm@UCMAIL.UC [REDACTED]> "Meller, Jaroslaw (mellerj)"
> <mellerj@ucmail.uc [REDACTED]> "Miller, Marian (millermn)"
> <millermn@ucmail.uc [REDACTED]> "Ovesen, Jerald (overseji)"
> <overseji@UCMAIL.UC [REDACTED]> "Papautsky, Ian (papauti)"

- >
- > The issue begins with a brief
- > foreword by Roger O McClellan,
- > DVM,
- > MMS, DSc[Honorary], Diplomate-ABT, followed by five papers prepared by
- > the Glyphosphate Panel. It is especially worth noting the
- > comprehensive "Declaration of Interests"
- > statements for each of the papers. Such DOI statements routinely
- > accompany each article published in CRT. These strong statements are
- > probably among the most comprehensive published today in scientific
- > journals.
- >
- >
- > It is also worth noting that the
- > papers were extensively reviewed by a total of 27 independent
- > Reviewers; several individuals reviewed all five papers..!! The
- > Reviewers' comments proved very useful to the authors and contributed
- > to increasing the overall quality of the published papers and the
- > entire Special Issue.
- >
- > It is my understanding that the US
- > Environmental Protection Agency (EPA) will be holding a 3-day meeting
- > later this month focusing on Glyphosate. The papers in this Special
- > Issue are available (open access) which should encourage readership.
- > I understand that the European Food Safety Authority (EFSA) has become
- > quite interested in Glyphosate. Also, the broader issue of how the
- > International Agency for Research on Cancer (IARC) approaches
- > evaluating the "carcinogenic hazard" of various agents is becoming
- > of increasing concern and interest.
- >
- > DwN
- >
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- > <http://tandfonline.com/toc/itxc20/46/sup1?nav=tocList>
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- (14) All communications with any of the authors of Williams, et al., *A Review of the Carcinogenic Potential of Glyphosate by Four Independent Expert Panels and Comparison to the IARC Assessment* 46 Crit. Rev. Toxicol. 3-20 (2016), including all communications with any of the authors of the four companion papers by the Intertek Expert Panel, related to GBs, AMPA, and/or surfactants for GB's.

Response:

As noted above, the primary communications between authors and the Editor are initially conducted electronically using the Manuscript Central/Scholar One system provided by the publisher, Taylor and Francis. After critical review and acceptance by the Editor-in-Chief, the accepted manuscripts are electronically transferred to the Central Article Tracking System (CATS) operated by Taylor and Francis. The CATS system is used for processing of the accepted manuscripts, including production of galley proofs for review and approval by the authors before proceeding to on-line publication. CATS is maintained and used by Taylor and Francis to publish the approximate 2600 journals in its portfolio.

As Editor-in-Chief, I do not maintain files to duplicate the CATS system.

- (16) All communications and documents related to the three corrigenda and “expression of concern” published in *Critical Reviews in Toxicology* on September 26, 2018 regarding the five manuscripts by the Intertek Expert panel.

Response:

As noted in the response to Item 16 “Expression of Concern” and five Corrigenda have now been published on-line in the Taylor and Francis web site for *Critical Reviews in Toxicology*. All of the communications and documents in my possession related to this matter have been provided in the Response to Item 15.

- (17) Communications and documents related to any medical literature, studies, journal articles, tests, and/or scientific analyses related to the potential adverse human health effects of GBFs, AMPA, and/or surfactants for GBFs for which You were involved with the peer-review process. This request includes drafts

Response:

I do not recall my involvement in the peer-review process related to potential adverse human health effects of GBFs, AMPA, and/or surfactants for GBFs that relate to any medical literature, studies, journal articles, tests, and/or scientific analyses other than those discussed above related to manuscripts published in Critical Reviews in Toxicology which I serve as Editor-in-Chief.

- (18) All communications related to the de-classified internal Monsanto documents dubbed the "Monsanto Papers."

Response:

Reference has been made to the "Monsanto Papers" during the investigation described above in to the manner in which the five papers published in the Special Supplement to Volume 46 (2016) of Critical Reviews in Toxicology. I am not aware of any other communications to me or from me involving the "Monsanto Papers."

(19) Documents relied on or reviewed to prepare for this Deposition.

Response:

I have not relied on any documents, other than those referenced above, responding to this Subpoena and preparing for my deposition.

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.

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

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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.

Commented [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 m³ 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 m² 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 1.04×10^{-5} 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.

Commented [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 2.25×10^{-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.

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

Commented [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

Commented [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.

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 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 studies were considered by authoritative bodies to have met the guidelines for a carcinogenicity bioassay in mice (ICH 1997; US EPA 1990).

Commented [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

Commented [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 ...

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

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

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

Commented [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?

Commented [wh12]: YES IT WAS IMORTAT IN THE DECISION AND SHOULD BE INCLUDED

Commented [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), several conclusions were drawn, including:

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

Commented [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

Commented [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.

Commented [wh17]: JOHN IS WRONG - IT IS THERE - IT IS THE 3 ONE MENTIONED BY HILL

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

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

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.

Commented [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.

Commented [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.

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.

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

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).

Commented [JA22]: Seems repetitive to say this again

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.

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

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

Commented [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.

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

Commented [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).

Commented [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.

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

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

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.~~

Commented [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~~: "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). 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 conclusions 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 hepatocellular 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 (2%), 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 ($P = 0.031$)."^o 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

Commented [wh32]: I WOULD LEAVE THE DELETED PHRASE IN – IT IS GIVES CLARITY ABOUT IARC'S APPROACH – THIS IS NOT INFLAMMATORY, IT IS DESCRIPTIVE

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 support for revise 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 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 evidence 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 than 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.~~

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~~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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(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 absentweak, lackings consistency, and there as no a-dose-response effect;

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(iii) the strength-of-association of pancreatic islet-cell adenomas in male SD rats is weakabsent, not seen in the majority of rat studies, lackings 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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With respect to the cancer bioassay data, the Expert Panel 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. (2016) 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%.

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~~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:

~~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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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. The Expert Panel's review of the glyphosate epidemiologic literature and the application of commonly applied causal principles ~~did~~ 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 600 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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Tables

Table 1. Tumor Incidence/number of animals examined (mg/kg bw/day)*

	Males				Females			
	0	100	300	1000	0	100	300	1000
Haemangiosarcomas	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

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

Tumors	Dose (ppm)			
	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 <i>In Vitro</i>		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 <i>In Vivo</i>	IARC Monograph 112	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 <i>In Vitro</i>		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
Mammalian <i>In Vivo</i>		SCE	None	3/0	2/0	ND	5/0
		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
Human <i>In Vivo</i>	Dominant Lethal	High	0/1	ND	ND	0/1	
	Chromosome Aberrations	High	ND	0/1	ND	0/1	
High Weight Combined Totals (IARC results only)		Micronucleus	High	ND	0/3	ND	0/3
				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.]

Commented [jv51]: footnotes missing from table

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 <i>In Vitro</i>	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 <i>In Vivo</i>	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 <i>in vitro</i> and <i>in vivo</i> .	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 <i>in vitro</i> and <i>in vivo</i> .	Conflicting and/or non-reproducible responses in the same test or test category both <i>in vitro</i> and <i>in vivo</i>
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

1 st 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