JECH Online First, published on March 3, 2016 as 10.1136/jech-2015-207005

Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA)

Christopher J Portier,[1] Bruce K Armstrong,[2] Bruce C Baguley,[3] Xaver Baur,[4] Igor Belyaev,[5] Robert Bellé,[6] Fiorella Belpoggi,[7] Annibale Biggeri,[8] Maarten C Bosland,[9] Paolo Bruzzi,[10] Lygia Therese Budnik,[11] Merete D Bugge,[12] Kathleen Burns,[13] Gloria M Calaf,[14] David O Carpenter,[15] Hillary M Carpenter,[16] Lizbeth López-Carrillo,[17] Richard Clapp,[18] Pierluigi Cocco,[19] Dario Consonni,[20] Pietro Comba,[21] Elena Craft,[22] Mohamed Aqiel Dalvie,[23] Devra Davis,[24] Paul A Demers,[25] Anneclaire J De Roos,[26] Jamie DeWitt,[27] Francesco Forastiere,[28] Jonathan H Freedman,[29] Lin Fritschi,[30] Caroline Gaus,[31] Julia M Gohlke,[32] Marcel Goldberg,[33] Eberhard Greiser,[34] Johnni Hansen,[35] Lennart Hardell,[36] Michael Hauptmann,[37] Wei Huang,[38] James Huff,[39] Margaret O James,[40] C W Jameson,[41] Andreas Kortenkamp,[42] Annette Kopp-Schneider,[43] Hans Kromhout,[44] Marcelo L Larramendy,[45] Philip J Landrigan,[46] Lawrence H Lash,[47] Dariusz Leszczynski,[48] Charles F Lynch,[49] Corrado Magnani,[50] Daniele Mandrioli,[51] Francis L Martin,[52] Enzo Merler,[53] Paola Michelozzi,[54] Lucia Miligi,[55] Anthony B Miller,[56] Dario Mirabelli,[57] Franklin E Mirer,[58] Saloshni Naidoo,[59] Melissa J Perry,[60] Maria Grazia Petronio,[61] Roberta Pirastu,[62] Ralph J Portier,[63] Kenneth S Ramos,[64] Larry W Robertson,[65] Theresa Rodriguez,[66] Martin Röösli,[67] Matt K Ross,[68] Deodutta Roy,[69] Ivan Rusyn,[70] Paulo Saldiva,[71] Jennifer Sass,[72] Kai Savolainen,[73] Paul T J Scheepers,[74] Consolato Sergi,[75] Ellen K Silbergeld,[76] Martyn T Smith,[77] Bernard W Stewart,[78] Patrice Sutton,[79] Fabio Tateo,[80] Benedetto Terracini,[81] Heinz W Thielmann,[82] David B Thomas,[83] Harri Vainio,[84] John E Vena,[85] Paolo Vineis,[86] Elisabete Weiderpass,[87] Dennis D Weisenburger,[88] Tracey J Woodruff,[89] Takashi Yorifuji,[90] Il Je Yu,[91] Paola Zambon,[92] Hajo Zeeb,[93] Shu-Feng Zhou[94]

The International Agency for Research on Cancer (IARC) Monographs Programme identifies chemicals, drugs, mixtures, occupational exposures, lifestyles and personal habits, and physical and biological agents that cause cancer in humans and has evaluated about 1000 agents since 1971. Monographs are written by ad hoc Working Groups (WGs) of international scientific experts over a period of about 12 months ending in an eight-day meeting. The WG evaluates all of the publicly available scientific information on each substance and, through a transparent and rigorous process,[1] decides on the degree to which the scientific evidence supports that substance's potential to cause or not cause cancer in humans.

For Monograph 112,[2] 17 expert scientists evaluated the carcinogenic hazard for four insecticides and the herbicide glyphosate.[3] The WG concluded that the data for glyphosate meet the criteria for classification as a *probable human carcinogen*.

The European Food Safety Authority (EFSA) is the primary agency of the European Union for risk assessments regarding food safety. In October 2015, EFSA reported[4] on their evaluation of the Renewal Assessment Report[5] (RAR) for glyphosate that was prepared by the Rapporteur Member State, the German Federal Institute for Risk Assessment (BfR). EFSA concluded that 'glyphosate is unlikely to pose a carcinogenic hazard to humans and the evidence does not support classification with regard to its carcinogenic potential'. Addendum 1 (the BfR Addendum) of the RAR[5] discusses the scientific rationale for differing from the IARC WG conclusion.

Serious flaws in the scientific evaluation in the RAR incorrectly characterise the potential for a carcinogenic hazard from exposure to glyphosate. Since the RAR is the basis for the European Food Safety Agency (EFSA) conclusion,[4] it is critical that these shortcomings are corrected.

THE HUMAN EVIDENCE

EFSA concluded 'that there is very limited evidence for an association between glyphosate-based formulations and non-Hodgkin lymphoma (NHL), overall inconclusive for a causal or clear associative relationship between glyphosate and cancer in human studies'. The BfR Addendum (p. ii) to the EFSA report explains that 'no consistent positive association was observed' and 'the most powerful study showed no effect'. The IARC WG concluded there is *limited evidence of carcinogenicity in humans* which means "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."[1]

The finding of *limited evidence* by the IARC WG was for NHL, based on high-quality case–control studies, which are particularly valuable for determining the carcinogenicity of an agent because their design facilitates exposure assessment and reduces the potential for certain biases. The Agricultural Health Study[6] (AHS) was the only cohort study available providing information on the carcinogenicity

For numbered affiliations see end of article.

Correspondence to Dr Christopher J Portier, Environmental Health Consultant, Thun, CH-3600, Switzerland; cportier@me.com

Copyright Article author (or their employer) 2016. Produced by BMJ Publishing Group Ltd under licence.

of glyphosate. The study had a null finding for NHL (RR 1.1, 0.7–1.9) with no apparent exposure–response relationship in the results. Despite potential advantages of cohort versus case–control studies, the AHS had only 92 NHL cases in the unadjusted analysis as compared to 650 cases in a pooled case–control analysis from the USA.[7] In addition, the median follow-up time in the AHS was 6.7 years, which is unlikely to be long enough to account for cancer latency.[8]

The RAR classified all of the case–control studies as 'not reliable,' because, for example, information on glyphosate exposure, smoking status and/or previous diseases had not been assessed. In most cases, this is contrary to what is actually described in the publications. Well-designed case–control studies are recognised as strong evidence and routinely relied on for hazard evaluations.[9 10] The IARC WG carefully and thoroughly evaluated all available epidemiology data, considering the strengths and weaknesses of each study. This is key to determining that the positive associations seen in the case–control studies are a reliable indication of an association and not simply due to chance or methodological flaws. To provide a reasonable interpretation of the findings, an evaluation needs to properly weight studies according to quality rather than simply count the number of positives and negatives. The two meta-analyses cited in the IARC Monograph[11] are excellent examples of objective evaluations and show a consistent positive association between glyphosate and NHL.

The final conclusion[5] (Addendum 1, p.21) that "there was no unequivocal evidence for a clear and strong association of NHL with glyphosate" is misleading. IARC, like many other groups, uses three levels of evidence for human cancer data.[1] *Sufficient evidence* means 'that a causal relationship has been established' between glyphosate and NHL. BfR's conclusion is equivalent to deciding that there is not *sufficient evidence*. Legitimate public health concerns arise when 'causality is credible', that is, when there is *limited evidence of carcinogenicity*.

EVIDENCE FROM ANIMAL CARCINOGENICITY STUDIES

EFSA concluded 'No evidence of carcinogenicity was confirmed by the majority of the experts (with the exception of one minority view) in either rats or mice due to a lack of statistical significance in pairwise 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 (MTD), lack of preneoplastic lesions and/or being within historical control range'. The IARC WG review found a significant positive trend for renal tumours in male CD-1 mice,[12] a rare tumour, although no comparisons of any individual exposure group to the control group were statistically significant. The WG also identified a significant positive trend for hemangiosarcoma in male CD-1 mice,[13] again with no individual exposure group significantly different from controls. Finally, the WG also saw a significant increase in the incidence of pancreatic islet cell adenomas in two studies in male Sprague-Dawley rats.[14–16] In one of these rat studies, thyroid gland adenomas in females and liver adenomas in males were also increased. By the IARC review criteria,[1] this constitutes *sufficient evidence* in animals.

The IARC WG reached this conclusion using data that were publicly available in sufficient detail for independent scientific evaluation (a requirement of the IARC Preamble[1]). On the basis of the BfR Addendum, it seems there were three additional mouse studies and two additional rat studies that were unpublished and available to EFSA. Two of the additional studies were reported to have a significant trend for renal tumours, one in CD-1 mice (Sugimoto. *18-Month Oral Oncogenicity Study in Mice*. Unpublished, designated ASB2012–11493 in RAR. 1997), and one in Swiss-Webster mice (Unknown. *A chronic feeding study of glyphosate (roundup technical) in mice*. Unpublished, designated ABS2012–11491 in RAR. 2001). One of these studies (Sugimoto. Unpublished, 1997) also reported a significant trend for hemangiosarcoma. The RAR also reported two studies in CD-1 mice showing significant trends for malignant lymphoma (Sugimoto. Unpublished, 1997; Unknown. *Glyphosate Technical: Dietary Carcinogencity Study in the Mouse*. Unpublished, designated ABS2012–11492 in RAR. 2009).

The RAR dismissed the observed trends in tumour incidence because there are no individual treatment groups that are significantly different from controls and because the maximum observed response is reportedly within the range of the historical control data (Table 5.3–1, p.90). Care must be taken in using historical control data to evaluate animal carcinogenicity data. In virtually all guidelines,[1 17 18] scientific reports[19] and publications[20–23] on this issue, the recommended first choice is the use of concurrent controls and trend tests, even in the EC regulations cited in the RAR[18] (see p.375). Trend tests are more powerful than pairwise comparisons, particularly for rare tumours where data are sparse. Historical control data should be from studies in the same time frame, for the same animal strain, preferably from the same laboratory or the same supplier and preferably reviewed by the same pathologist.[17 18] While the EFSA final peer review[4] mentions the use of historical control data from the original laboratory, no specifics are provided and the only referenced historical control data[24] are in the BfR addendum.[5] One of the mouse studies[12] was clearly done before this historical control database was developed, one study (Sugimoto. Unpublished, 1997) used Crj:CD-1 mice rather than Crl:CD-1 mice, and one study[13] did not specify the substrain and was reported in 1993 (probably started prior to 1988). Hence, only a single study (Unknown. Unpublished, 2009) used the same mouse strain as the cited historical controls, but was reported more than 10 years after the historical control data set was developed.

The RAR dismissed the slightly increased tumour incidences in the studies considered because they occurred "only at dose levels at or above the limit dose/maximum tolerated dose (MTD)", and because there was a lack of preneoplastic lesions. Exceeding the MTD is demonstrated by an increase in mortality or other serious toxicological findings at the highest dose, not by a slight reduction in body weight. No serious toxicological findings were reported at the highest doses for the mouse studies in the RAR. While some would argue that these high doses could cause cellular disruption (eg, regenerative hyperplasia) leading to cancer, no evidence of this was reported in any study. Finally, a lack of preneoplastic lesions for a significant neoplastic finding is insufficient reason to discard the finding.

MECHANISTIC INFORMATION

The BfR Addendum dismisses the IARC WG finding that 'there is strong evidence that glyphosate causes genotoxicity' by suggesting that unpublished evidence not seen by the IARC WG was overwhelmingly negative and that, since the reviewed studies were not done under guideline principles, they should get less weight. To maintain transparency, IARC reviews only publicly available data. The use of confidential data submitted to the BfR makes it impossible for any scientist not associated with BfR to review this conclusion. Further weakening their interpretation,

the BfR did not include evidence of chromosomal damage from exposed humans or human cells that were highlighted in Tables 4.1 and 4.2 of the IARC Monograph [3]

The BfR confirms (p.79) that the studies evaluated by the IARC WG on oxidative stress were predominantly positive but does not agree that this is strong support for an oxidative stress mechanism. They minimise the significance of these findings predominantly because of a lack of positive controls in some studies and because many of the studies used glyphosate formulations and not pure glyphosate. In contrast, the WG concluded that (p.77) 'Strong evidence exists that glyphosate, AMPA and glyphosate-based formulations can induce oxidative stress'. From a scientific perspective, these types of mechanistic studies play a key role in distinguishing between the effects of mixtures, pure substances and metabolites.

Finally, we strongly disagree that data from studies published in the peer-reviewed literature should automatically receive less weight than guideline studies. Compliance with guidelines and Good Laboratory Practice does not guarantee validity and relevance of the study design, statistical rigour and attention to sources of bias.[25 26] The majority of research after the initial marketing approval, including epidemiology studies, will be conducted in research laboratories using various models to address specific issues related to toxicity, often with no testing guidelines available. Peer-reviewed and published findings have great value in understanding mechanisms of carcinogenicity and should be given appropriate weight in an evaluation based on study quality, not just on compliance with guideline rules.

GENERAL COMMENTS

Science moves forward on careful evaluations of data and a rigorous review of findings, interpretations and conclusions. An important aspect of this process is transparency and the ability to question or debate the findings of others. This ensures the validity of the results and provides a strong basis for decisions. Many of the elements of transparency do not exist for the RAR.[5] For example, citations for almost all references, even those from the open scientific literature, have been redacted. The ability to objectively evaluate the findings of a scientific report requires a complete list of cited supporting evidence. As another example, there are no authors or contributors listed for either document, a requirement for publication in virtually all scientific journals where financial support, conflicts of interest and affiliations of authors are fully disclosed. This is in direct contrast to the IARC WG evaluation listing all authors, all publications and public disclosure of pertinent conflicts of interest prior to the WG meeting.[27]

Several guidelines have been devised for conducting careful evaluation and analysis of carcinogenicity data, most after consultation with scientists from around the world. Two of the most widely used guidelines in Europe are the OECD guidance on the conduct and design of chronic toxicity and carcinogenicity studies[17] and the European Chemicals Agency Guidance on Commission Regulation (EU) No 286/2011;[18] both are cited in the RAR. The methods used for historical controls and trend analysis are inconsistent with these guidelines.

Owing to the potential public health impact of glyphosate, which is an extensively used pesticide, it is essential that all scientific evidence relating to its possible carcinogenicity is publicly accessible and reviewed transparently in accordance with established scientific criteria.

SUMMARY

The IARC WG concluded that glyphosate is a 'probable human carcinogen', putting it into IARC category 2A due to *sufficient evidence* of carcinogenicity in animals, *limited evidence* of carcinogenicity in humans and *strong* evidence for two carcinogenic mechanisms.

- The IARC WG found an association between NHL and glyphosate based on the available human evidence.
- The IARC WG found significant carcinogenic effects in laboratory animals for rare kidney tumours and hemangiosarcoma in two mouse studies and benign tumours in two rat studies.
- The IARC WG concluded that there was strong evidence of genotoxicity and oxidative stress for glyphosate, entirely from publicly available research, including findings of DNA damage in the peripheral blood of exposed humans.

The RAR concluded[5] (Vol. 1, p.160) that 'classification and labelling for carcinogenesis is not warranted' and 'glyphosate is devoid of genotoxic potential'.

- EFSA[4] classified the human evidence as 'very limited' and then dismissed any association of glyphosate with cancer without clear explanation or justification.
- Ignoring established guidelines cited in their report, EFSA dismissed evidence of renal tumours in three mouse studies, hemangiosarcoma in two mouse studies and malignant lymphoma in two mouse studies. Thus, EFSA incorrectly discarded all findings of glyphosate-induced cancer in animals as chance occurrences.
- EFSA ignored important laboratory and human mechanistic evidence of genotoxicity.
- EFSA confirmed that glyphosate induces oxidative stress but then, having dismissed all other findings of possible carcinogenicity, dismissed this finding on the grounds that oxidative stress alone is not sufficient for carcinogen labelling.

The most appropriate and scientifically based evaluation of the cancers reported in humans and laboratory animals as well as supportive mechanistic data is that glyphosate is a *probable human carcinogen*. On the basis of this conclusion and in the absence of evidence to the contrary, it is reasonable to conclude that glyphosate formulations should also be considered likely human carcinogens. The CLP Criteria[18] (Table 3.6.1, p.371) allow for a similar classification of Category 1B when there are 'studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals'.

In the RAR, almost no weight is given to studies from the published literature and there is an over-reliance on non-publicly available industry-provided studies using a limited set of assays that define the minimum data necessary for the marketing of a pesticide. The IARC WG evaluation of *probably carcinogenic to humans* accurately reflects the results of published scientific literature on glyphosate and, on the face of it, unpublished studies to which EFSA refers.

Most of the authors of this commentary previously expressed their concerns to EFSA and others regarding their review of glyphosate[28] to which EFSA has published a reply.[29] This commentary responds to the EFSA reply.

The views expressed in this editorial are the opinion of the authors and do not imply an endorsement or support for these opinions by any organisations to which they are affiliated.

Author affiliations
[1]Environmental Health Consultant, Thun, Switzerland
[2]The University of Sydney, Sydney, New South Wales, Australia
[3]The University of Auckland, Auckland, New Zealand
[4]Charité University Medicine Berlin, Berlin, Germany
[5]Cancer Research Institute, Bratislava, Slovak Republic
[6]Sorbonne Universités, UPMC Univ Paris 06, UMR8227, Roscoff, France

[7]CesareMaltoni Cancer Research Center, Bentivoglio (Bologna), Italy
[8]Institute for Cancer Prevention and Research, University of Florence, Italy
[9]University of Illinois at Chicago, Chicago, Illinois, USA
[10]National Cancer Research Institute, San Martino—IST Hospital, Genoa, Italy
[11]University of Hamburg, Hamburg, Germany
[12]STAMI, National Institute of Occupational Health, Oslo, Norway
[13]Sciencecorps, Lexington, Massachusetts, USA
[14]Instituto de Alta Investigación, Universidad de Tarapacá, Arica, Chile
[15]Institute for Health and the Environment, University at Albany, Rensselaer, New York, USA
[16]Toxicologist, Maplewood, Minnesota, USA
[17]National Institute of Public Health, Cuernavaca, Morelos, Mexico
[18]Boston University School of Public Health, Boston, Massachusetts, USA
[19]Department of Public Health, Clinical and Molecular Medicine, University of Cagliari, Cagliari, Italy
[20]Department of Preventive Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[21]Department of Environment and Primary Prevention, IstitutoSuperiore di Sanità, Rome, Italy
[22]Environmental Defense Fund, Austin, Texas, USA
[23]Center for Environmental and Occupational Health, University of Cape Town, Cape Town, South Africa
[24]Environmental Health Trust, Jackson Hole, Wyoming, USA and The Hebrew University Hadassah School of Medicine, Jerusalem, Israel.
[25]Dalla Lana School of Public Health, University of Toronto, Canada
[26]Department of Environmental and Occupational Health, Drexel University, Philadelphia, Pennsylvania, USA
[27]Brody School of Medicine, East Carolina University, Greenville, North Carolina, USA
[28]Department of Epidemiology, Lazio Regional Health Service, Rome, Italy
[29]University of Louisville School of Medicine, Louisville, Kentucky, USA
[30]School of Public Health, Curtin University, Perth, Western Australia, Australia
[31]Department of Environmental Toxicology, The University of Queensland, Brisbane, Australia
[32]Department of Population Health Sciences, Virginia Tech, Blacksburg, Virginia, USA
[33]Paris Descartes University, France
[34]Epi.Consult GmbH, Musweiler, Germany
[35]Danish Cancer Society Research Center, Copenhagen, Denmark
[36]University Hospital, Orebra, Sweden
[37]Biostatistics Branch, Netherlands Cancer Institute, Amsterdam, The Netherlands
[38]Faculty of Department of Occupational and Environmental Health, Peking Univ School of Public Health, Beijing, China
[39]National Institute for Environmental Health Sciences, Research Triangle Park, North Carolina, USA
[40]University of Florida, Gainesville, Florida, USA
[41]CWJ Consulting, LLC, Cape Coral, Florida, USA
[42]Institute of Environment, Health and Societies, Brunel University London, London, UK
[43]Division of Biostatistics, German Cancer Research Center, Heidelberg, Germany
[44]Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands
[45]National Council of Scientific and Technological Research, National University of La Plata, Argentina
[46]Arnhold Institute for Global Health, Icahn School of Medicine at Mount Sinai, New York, USA
[47]Department of Pharmacology, Wayne State University School of Medicine, Detroit, Michigan, USA
[48]Department of Biosciences, University of Helsinki, Helsinki, Finland
[49]Department of Epidemiology, University of Iowa, Iowa City, Iowa, USA
[50]Cancer Epidemiology Unit, University of Eastern Piedmont, Novara, Italy
[51]Cesare Maltoni Cancer Research Center, Bentivoglio (Bologna), Italy
[52]Centre for Biophotonics, Lancaster University, UK
[53]Department of Prevention, Occupational Health Unit, National Health Service, Padua, Italy
[54]Department of Epidemiology Lazio Region, Rome, Italy
[55]Occupational and Environmental Epidemiology Unit, ISPO-Cancer Prevention and Research Institute, Florence, Italy
[56]Dalla Lana School of Public Health, University of Toronto, Canada
[57]Unit of Cancer Epidemiology, University of Turin and CPO-Piemonte, Torino, Italy
[58]Department of Environmental and Occupational Health Sciences, City University of New York School of Public Health, USA
[59]School of Nursing and Public Health, University of KwaZulu-Natal, Durban, South Africa
[60]Department of Environmental and Occupational Health, Milken Institute School of Public Health, The George Washington University, Washington DC, USA
[61]Health and Environment-Department of Prevention, Local Health Authority-Empoli, Florence, Italy
[62]Department of Biology and Biotechnology "Charles Darwin", Sapienza Rome University, Italy
[63]Department of Environmental Sciences, School of the Coast & Environment, Louisiana State University, Baton Rouge, Los Angeles, USA
[64]Center for Applied Genetics and Genomic Medicine, University of Arizona Health Sciences, Tucson, Arizona, USA
[65]Iowa Superfund Research Program and the Interdisciplinary Graduate Program in Human Toxicology, University of Iowa, Iowa City, Iowa, USA
[66]Center for Research in Health, Work and Environment (CISTA), National Autonomous University of Nicaragua (UNAN-León), León, Nicaragua
[67]Swiss Tropical and Public Health Institute, Associated Institute of the University of Basel, Basel, Switzerland
[68]College of Veterinary Medicine, Mississippi State University, Mississippi State, USA
[69]Department of Environmental and Occupational Health, Florida International University, Miami, Florida, USA
[70]Department of Veterinary Integrative Biosciences, Texas A&M University, College Station, Texas, USA
[71]Faculty of Medicine, University of São Paulo, São Paulo, Brazil
[72]Natural Resources Defense Council and George Washington University, Washington DC, USA
[73]Nanosafety Research Centre, Finnish Institute of Occupational Health, Helsinki, Finland
[74]Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands
[75]Department of Pathology, University of Alberta, Edmonton, Alberta, Canada
[76]Department of Environmental Health Sciences, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA
[77]School of Public Health, University of California, Berkeley, California, USA
[78]Faculty of Medicine, University of New South Wales, Randwick, New South Wales Australia
[79]Program on Reproductive Health and the Environment, University of California, San Francisco, California, USA
[80]Istituto di Geosceinze e Georisorse (CNR), Padova, Italy
[81]University of Torino, Torino, Italy
[82]German Cancer Research Center, Heidelberg and Faculty of Pharmacy, Heidelberg University, Germany
[83]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, Washington, USA
[84]Faculty of Public Health, Kuwait University, Kuwait City, Kuwait
[85]Department of Public Health Sciences, Medical University of South Carolina, Charleston, South Carolina, USA
[86]Department of Environmental Epidemiology, Imperial College London, London, UK
[87]Department of Research, Cancer Registry of Norway, Institute of Population-Based Cancer Research, Oslo, Norway; Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, The Arctic University of Norway, Tromsø, Norway; Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; and Genetic Epidemiology Group, Folkhälsan Research Center, Helsinki, Finland.
[88]Department of Pathology, City of Hope Medical Center, Duarte, California, USA
[89]Program on Reproductive Health and the Environment, University of California, San Francisco, USA
[90]Okayama University, Okayama, Japan
[91]Institute of Nanoproduct Safety Research, Hoseo University, Asan, The Republic of Korea
[92]University of Padua, Padova, Italy
[93]Department of Prevention and Evaluation, Leibniz-Institute for Prevention Research and Epidemiology, Bremen, Germany
[94]College of Pharmacy, University of South Florida, Tampa, Florida, USA

Contributors All authors to this commentary have participated in its development and approve the content. MCB, FF, LF, CWJ, HK, TR, MKR, IR and CS were all participants in the IARC WG. CJP was an Invited Specialist in the IARC WG. Many of the remaining authors have also served on IARC Working Groups that did not pertain to glyphosate.

Competing interests CJP, MTS and DDW are providing advice to a US law firm involved in glyphosate litigation. CJP also works part-time for the Environmental Defense Fund on issues not related to pesticides.

Provenance and peer review Commissioned; externally peer reviewed.

OPEN ACCESS

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

To cite Portier CJ, Armstrong BK, Baguley BC, *et al*. *J Epidemiol Community Health* Published Online First: [*please include* Day Month Year] doi:10.1136/jech-2015-207005

J Epidemiol Community Health 2016;**0**:1–5. doi:10.1136/jech-2015-207005

REFERENCES

1 IARC. *Preamble to the IARC Monographs*. 2006. http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf

2 Guyton KZ, Loomis D, Grosse Y, *et al*. Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. *Lancet Oncol* 2015;16:490–1.
3 IARC Working Group. Glyphosate. In: *Some organophosphate insecticides and herbicides: diazinon, glyphosate, malathion, parathion, and tetrachlorvinphos*. Vol 112. IARC Monogr Prog, 2015:1–92.
4 European Food Safety Authority. Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate. *EFSA J* 2015;13:4302.
5 European Food Safety Authority. *Final Addendum to the Renewal Assessment Report*. 2015. http://registerofquestions.efsa.europa.eu/roqFrontend/outputLoader?output=ON-4302
6 De Roos AJ, Blair A, Rusiecki JA, *et al*. Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. *Environ Health Perspect* 2005;113:49–54.
7 De Roos AJ, Zahm SH, Cantor KP, *et al*. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. *Occup Environ Med* 2003;60:E11.
8 Weisenburger DD. Pathological classification of non-Hodgkin's lymphoma for epidemiological studies. *Cancer Res* 1992;52(19 Suppl):5456s–62s; discussion 5462s-5464s.
9 Checkoway H, Pearce N, Kriebel D. Research methods in occupational epidemiology. 2nd edn. *Monographs in epidemiology and biostatistics*. New York: Oxford University Press, 2004:xiv, 372 p.
10 Rothman KJ, Greenland S, Lash TL. *Modern epidemiology*. 3rd edn. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2008:x, 758 p.
11 Schinasi L, Leon ME. Non-Hodgkin lymphoma and occupational exposure to agricultural pesticide chemical groups and active ingredients: a systematic review and meta-analysis. *Int J Environ Res Public Health* 2014;11:4449–527.
12 EPA. *Glyphosate; EPA Reg. # 524–308; mouse oncogenicity study*. 1985. V. Accession No. 251007–014. Tox review 004370. p.
13 JMPR. FAO plant production and protection paper, 178, 2004—pesticide residues in food—2004. *Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and WHO the Core Assessment Group*; Vol 178. Geneva, Switzerland: World Health Organization/Food and Agriculture Organization, 2004:95–169.
14 EPA. *Second peer review of Glyphosate*. 19911–19.
15 EPA. *Glyphosate—EPA Registration No. 524–308–2-Year Chronic Feeding/Oncogenicity Study in Rats with Technical Glyphosate*, I. William Dykstra. Toxicology Branch, Editor. 1991. V. MRID 416438–01 Tox review 008897. p.
16 EPA. *Glyphosate; 2-Year Combined Chronic Toxicity/Carcinogenicity Study in Sprague-Dawley Rats—List A Pesticide for Reregistration*, B. William Dykstra. Toxicology, Editor. 1991. V. MRID 416438–01. Tox review 008390. 1–29.
17 OECD. *Guidance Document 116 on the Conduct and Design of Chronic Toxicity and Carcinogenicity Studies*, H.a.S.P. Environment, Editor. Paris: OECD, 2012.
18 European Chemicals Agency. *Guidance on the Application of the CLP Criteria: Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures*. Helsinki, Finland: European Chemicals Agency, 2015.
19 NRC Committee to Review the Styrene Assessment in The National Toxicology Program 12th Report on Carcinogens. *Review of the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens: Workshop Summary*; Washington DC: National Academies Press, 2014.
20 Keenan C, Elmore S, Francke-Carroll S, *et al*. Best practices for use of historical control data of proliferative rodent lesions. *Toxicol Pathol* 2009;37:679–93.
21 Haseman JK, Boorman GA, Huff J. Value of historical control data and other issues related to the evaluation of long-term rodent carcinogenicity studies. *Toxicol Pathol* 1997;25:524–7.
22 Greim H, Gelbke HP, Reuter U, *et al*. Evaluation of historical control data in carcinogenicity studies. *Hum Exp Toxicol* 2003;22:541–9.
23 Haseman JK, Huff J, Boorman GA. Use of historical control data in carcinogenicity studies in rodents. *Toxicol Pathol* 1984;12:126–35.
24 Giknis M, Clifford C. *Spontaneous Neoplastic Lesions in the Crl:CD-1(ICR)BR Mouse*. Charles River Laboratories; 2000.
25 Myers JP, vom Saal FS, Akingbemi BT, *et al*. Why public health agencies cannot depend on good laboratory practices as a criterion for selecting data: the case of bisphenol A. *Environ Health Perspect* 2009;117:309–15.
26 Buonsante VA, Muilerman H, Santos T, *et al*. Risk assessment's insensitive toxicity testing may cause it to fail. *Environ Res* 2014;135:139–47.
27 IARC Monograph 112. *List of Working Group Participants*. IARC Monogr Eval Carcinog Risks Hum 2015 26 March, 2015 [cited 2015 24 November]. http://monographs.iarc.fr/ENG/Meetings/vol112-participants.pdf
28 Portier CJ, *et al*. *Open Letter: Review of the Carcinogenicity of Glyphosate by EFSA and BfR*. 2015 [cited 2016 1/18/2016]. http://www.efsa.europa.eu/sites/default/files/Prof_Portier_letter.pdf
29 Url B. Response to Open Letter: Review of the Carcinogenicity of Glyphosate by EFSA and BfR. 2016. 1/13/2016. http://www.efsa.europa.eu/sites/default/files/EFSA_response_Prof_Portier.pdf