Viewpoint: Weaponized incompetence? The ethical and science contradictions of the International Agency for Research on Cancer’s controversial ‘probable carcinogen’ assessment of glyphosate

Abstract

A plaintiff lawyer in a recent glyphosate litigation produced an International Agency for Research on Cancer (IARC) document claiming that glyphosate was on the Monograph 112 agenda one year before the Monograph 112 Working Group met in March 2015, in keeping with proper IARC procedures. A chronology of actual events, documented by entries on the IARC website in 2014, demonstrates that this is not true. In fact, IARC only added glyphosate later in 2014 to the proposed monograph, first said in March to be titled ‘Some Pesticides and Related Chemicals’, a few months later with title changed to ‘Some Organophosphate Insecticides’, and finally in July with the final title ‘Some Organophosphate Insecticides and Herbicides’. In addition to the deceptive document, flaws in the scientific deliberations of the Working Group and questionable application of a chemoinformatics tool to justify evaluation of glyphosate indicate that IARC fell short of its stated scientific standards with Monograph 112.

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Introduction

In March 2015, IARC announced that it considered the phosphonate herbicide, glyphosate, to be a probable human carcinogen. IARC’s determination led to the initiation of numerous U.S. lawsuits, first in California, and then in other states, claiming that Roundup, an herbicide containing glyphosate, causes NHL. The IARC classification differed from glyphosate safety conclusions by regulatory bodies worldwide, conclusions reached both before and after March 2015, but U.S. Roundup litigation has continued unabated.

Because of publications pointing out scientific errors in the IARC Monographs Program evaluation of glyphosate (Eur J Cancer Prev 2018;27:82-87; Regul Toxicol Pharmacol 2018;98:A1-A4; Clin Lymphoma Myeloma Leuk 2022;22:e1050), I have now been deposed three times as a non-retained expert witness related to U.S. lawsuits regarding Roundup and NHL risk. At the last deposition in March 2023 I was shown a Call for Experts document for IARC Monograph 112 by a plaintiff lawyer.
IARC MONOGRAPHS - UPCOMING MEETINGS

Volume 112 - Call for Experts

Volume 112: Some Organophosphate Insecticides and Herbicides: Diazinon, Guthion, Malathion, Parathion, and Tetrachlorvinphos
Lyon, France
3-10 March 2015

CALL FOR EXPERTS
Closing date: 30 July 2014
Within 1 month of the closing date, IARC will send preliminary invitations to the experts selected. Names and principal affiliations will be available on this website.

Thank you for your interest in the IARC Monographs.

Kate Guyton, Responsible Officer for Volume 112
Kurt Straif, Head of the IARC Monographs programme

Posted 12 March 2014

Top and bottom of Call for Experts announcement that IARC claims they posted on 12 March 2014 except they never did

Hidden process to include glyphosate in an insecticide monograph

This document is attributed to Kate Guyton, Responsible Officer for Volume 112, and Kurt Straif, Head of the IARC Monographs programme, and is dated 12 March 2014. The title of Monograph 112 is reported on the document to be the final Monograph 112 title, Some Organophosphate Insecticides and Herbicides, with all four organophosphate insecticides and glyphosate listed as agents that were evaluated. The date on the document contradicted evidence provided by David Zaruk indicating that glyphosate, at least, had not been added to the Monograph 112 agenda by the middle of July 2014. This prompted an investigation reported below into the chronology of the reporting of agents included on the agenda of Monograph 112.

The document in question was obtained via the Wayback Machine, which periodically visits websites worldwide and archives any documents that have been posted or modified on each website since the last visit. The first indication that something is awry is the date that the document was archived by the Wayback Machine (as indicated in the URL November 2, 2017). That is, the document was not archived until three years and eight months after the alleged posting date of March 12, 2014. To investigate this apparent anomaly, documents related to Monograph 112 that were both posted by IARC in 2014 and archived by the Wayback Machine in 2014 were examined.

The first mention of Monograph 112 appears to have been posted on March 12 and archived on March 15. The 2013 in the date heading this announcement appears to be a typo. The title of Monograph 112 on this actual March 12 post on the IARC website is stated to be Some Pesticides and Related Chemicals. Unlike the title on the Call for Experts document shown at the deposition (and allegedly also dated March 12) there is no list of specific pesticides to be evaluated.
The second mention of Monograph 112 on the IARC website in 2014 was archived on April 5. Once again, the title of the Monograph is reported to be “Some Pesticides and Related Chemicals”. In spite of this general and nonspecific title, the Call for Experts, Call for Data, and Request for Observer Status links on this IARC website entry take one to documents attributed to Drs. Guyton and Straif that are dated 12 March 2014 and contain the final Monograph 112 title with a list of all five agents evaluated. Each of these documents was archived by the Wayback Machine on November 2, 2017. Whatever documents were originally linked to by this post that was archived on April 5 no longer exist on the IARC website.
To introduce an additional oddity, two of the four organophosphate insecticides included on the Monograph 112 agenda (diazinon and malathion) were not recommended (with high priority) for consideration by the IARC Monographs Program until an Advisory Group meeting held April 7-9 of 2014, and glyphosate was recommended as a medium priority agent at the same meeting. That is, the alleged 12 March agenda in the documents under investigation named three specific pesticides one month before they were recommended for consideration by the Monographs Program. The announcement in *Lancet Oncology* (2014;15:683-684) of the Advisory Group recommendations was published in print in June. The announcement was published online on May 6, 2014, and the title given for Monograph 112 in the "Upcoming meetings" section on the right margin is still "Some Pesticides and Related Chemicals". Thus, the title of Monograph 112 as reported in official IARC publications up to at least May 6, 2014 did not provide any information about specific agents to be evaluated, contrary to the documents dated 12 March 2014 that are under investigation.

The third 2014 mention of Monograph 112 on the IARC website was archived on May 28. The title of Monograph 112 is still reported to be "Some Pesticides and Related Chemicals", and again with links to the alleged 12 March documents that name all five pesticides included on the final agenda of Monograph 112.
On the next actual 2014 mention of Monograph 112 on the IARC website, which was archived on June 15 (image below), the title has changed to “Some Organophosphate Insecticides”. Again, the Upcoming Meeting link takes one to the entry archived on July 16 (at least now with the same title). No specific insecticides were listed on the actual entry on the IARC website.

The next mention of Monograph 112 on the IARC website is the above-noted entry archived on July 16, with the title of Monograph 112 stated to be “Some Organophosphate Insecticides”. A paper reporting the results of Monograph 110 (Lancet Oncology 2014;15:924-925) was published in print in August. The paper was published online on July 11, 2014, and the “Upcoming meetings” section on the left margin confirms that the title at that time was “Some Organophosphate Insecticides”, with no specific insecticides listed. There still would be no clue from IARC announcements that glyphosate, which is neither an insecticide nor an organophosphate, would be included in Monograph 112.

Finally, the first actual acknowledgment on the IARC website in 2014 of glyphosate (or specific insecticides) being on the Monograph 112 agenda was archived on July 28 (image below). Thus, glyphosate was not publicly reported as an agent to be evaluated in Monograph 112 until shortly before the Call for Experts period ended on July 30. That is, researchers around the world with particular experience and expertise in glyphosate toxicology and health effects would have been unlikely to notice the late change in the Monograph 112 title in time to respond successfully to the Call for Experts.
The first mention of glyphosate being included in Monograph 112 was not in March as IARC claims but just before the deadline for expert nominations.

Flaws in IARC’s process

The Preamble of Monograph 112 states that agents to be reviewed in a given monograph are to be announced on the Monographs Program website approximately one year in advance of the corresponding Working Group meeting. The Call for Experts document for Monograph 112 shown at my deposition was apparently created in late July to cover for that fact that the agents to be reviewed were not announced in a timely fashion. The peculiar rush to evaluate glyphosate, an agent of low toxicity that was recommended only as a medium priority agent at the April 2014 Advisory Group meeting, has never been adequately explained.

Although the focus above is on glyphosate, there is no evidence on the IARC website of when the four organophosphate insecticides were first publicly announced as being on the Monograph 112 agenda. When the announced title changed to “Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos” in June one might have inferred from the April 2014 Advisory Group meeting that diazinon and malathion, recommended as high priority agents for IARC consideration, would be included, but three other organophosphate insecticides (chlorpyrifos, fonofos, and terbufos) were, like glyphosate, proposed as medium priority agents by the April Advisory Group, but were not included in Monograph 112. IARC should clarify the timing of the announcement of each agent included on the Monograph 112 agenda, and explain the deviation from standard IARC Monographs Program procedures put in place to guarantee the integrity of the carcinogen classification process.

Flaws in the scientific deliberations

In addition to deviating from standard procedures in the year leading up to the Monograph 112 Working
Group meeting in March 2015, it is also the case that the Working Group deviated in its glyphosate deliberations from the clearly stated (in the Monograph Preamble) criteria for concluding that there was sufficient evidence of carcinogenicity in experimental animals. The IARC paper summarizing Monograph 112 findings (Lancet Oncology 2015;16:490-491) states that the conclusion that there was sufficient evidence that glyphosate was an animal carcinogen was based on a positive trend in renal tubule carcinoma in male mice, a positive trend for hemangiosarcoma in male mice, and increased pancreatic islet-cell adenomas in male rats in two studies. The paper also mentions a positive finding in an initiation-promotion study in mice, but the Working Group concluded that this study was poorly designed, and was an inadequate study for the evaluation of glyphosate.

Neither the renal tubule carcinoma trend in male mice nor the pancreatic islet-cell adenoma increase in male rats is significant using an appropriate statistical method (Eur J Cancer Prev 2018;27:82-87; Regul Toxicol Pharmacol 2018;98:A1-A4), but even if one accepts the Working Group conclusion regarding pancreatic islet-cell adenomas in male rats, this finding is irrelevant to a conclusion that there is sufficient evidence of carcinogenicity in animals. The Preamble clearly states that a conclusion of sufficient evidence of carcinogenicity in experimental animals must be based on a finding of increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms. An increase in pancreatic islet-cell adenomas would not meet the stated criteria.

Interestingly, the only pancreatic islet-cell carcinoma in one of the two rat studies for which the Working Group concluded (based on a significant increase in the lowest dose group compared to control) that there was a glyphosate-associated increase in adenomas occurred in the control group, so that the tumor rate in the lowest of three glyphosate exposure levels is no longer significantly elevated in the analysis of adenomas and carcinomas combined. The only finding relevant to the stated criteria for concluding sufficient evidence of glyphosate carcinogenicity in animals in the rodent studies relied upon by IARC is the positive trend in hemangiosarcoma in male mice. The trend was observed only in one of two studies in CD-1 mice, and was not supported by the hemangiosarcoma rates in females in the same study or in males or females in the other study. A positive finding in a single study with one sex of one animal species does not meet the Preamble criteria for concluding sufficient evidence of carcinogenicity in experimental animals.

Flawed chemoinformatics approach

The failure to follow Monographs Program procedures and criteria and the erroneous scientific deliberations on glyphosate by the Monograph 112 Working Group are troubling, particularly in view of the apparent rush to evaluate glyphosate less than one year after it was recommended by an Advisory Group as a medium priority agent for future consideration.

A post hoc attempt by IARC to justify the selection of agents evaluated in Monographs 112 and 113 by use of chemoinformatics (Environ Health Perspect 2016;124:1823-1829) leaves questions about the scientific basis with regard to glyphosate. Glyphosate did not stand out in the chemoinformatics approach, but apparently was selected for evaluation in Monograph 112 in large part because of its high production volume and widespread use.
An IARC meta-analysis (Int J Environ Res Public Health 2014;11:4449-4527) that reported a significant increase for glyphosate in a subgroup analysis (i.e., B-cell lymphoma) was cited in the chemoinformatics paper as providing scientific support for the evaluation of glyphosate. This marginally significant finding, which would not remain significant after any reasonable adjustment for the multiple comparisons (i.e., there were statistical analyses of multiple pesticides and pesticide classes, applied to incidence of various lymphoma subtypes in addition to NHL overall), was based on two studies. One study was a Swedish case-control study (Int J Cancer 2008;123:1657-1663) for which there is strong empirical evidence of information and selection bias (Risk Anal 2020;40:696-704), and the other is a large European case-control study (Occup Environ Med 2013;70:91-98) with few glyphosate-exposed subjects (4 cases and 2 controls) that concluded that there was no support to a role of occupational exposure to several specific agrochemicals in the aetiology of B-cell lymphoma, and limited support in the aetiology of CLL (only one of the four B-cell cases exposed to glyphosate was a CLL). The stated rationale for evaluating glyphosate was scientifically weak.

Conclusion

In view of the departure from stated IARC procedures and criteria in Monograph 112 and the seriously flawed scientific deliberations by the Working Group on glyphosate, the IARC glyphosate classification, which stands alone among evaluations of glyphosate worldwide, should be retracted. There is no credible evidence that glyphosate causes cancer in rodents (Toxicol Sci 2020;175:156-167) or humans (Risk Anal 2020;40:696-704; Cancer Causes Control 2021;32:409-414). The continued refusal of IARC Monographs Program staff to respond to legitimate criticism of the IARC classification of glyphosate as a probable human carcinogen is untenable, and lends credence to concerns that the IARC Monographs Program is unduly influenced by outside considerations other than the mandate to protect humans from cancer risks.

Robert Tarone was a Research Mathematical Statistician at the U.S. National Cancer Institute for 28 years and Biostatistics Director at the International Epidemiology Institute for 14 years. He retired in June 2016 and has received no pay for his scientific efforts since his retirement. He was coauthor of IARC Scientific Publication No. 79 on the design and statistical analysis of animal carcinogenicity studies. Find Robert on X @roberttarone

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