Glyphosate difficulties - need for impartial research and public funding

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Porto, Feb 28th, 2020
The Glyphosate Case
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International Agency for Research on Cancer

World Health Organization

20 March 2015

IARC Monographs Volume 112: evaluation of five organophosphate insecticides and herbicides

Lyon, France, 20 March 2015 – The International Agency for Research on Cancer (IARC), the specialized cancer agency of the World Health Organization, has assessed the carcinogenicity of five organophosphate pesticides. A summary of the final evaluations together with a short rationale have now been published online in The Lancet Oncology, and the detailed assessments will be published as Volume 112 of the IARC Monographs.

What were the results of the IARC evaluations?

The herbicide glyphosate and the insecticides malathion and diazinon were classified as probably carcinogenic to humans (Group 2A).

The insecticides tetrachlorvinphos and parathion were classified as possibly carcinogenic to humans (Group 2B).
Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA)


supports that substance’s potential to cause or not cause cancer in humans.

For Monograph 112,17 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 reported8 on their evaluation of the Renewal Assessment Report5 (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 RAR7 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 with the exception of non-Hodgeklin lymphoma (NHL)’.
The Glyphosate Case

Prior IARC Evaluations of Pesticides

75 pesticides and pesticide classes have been evaluated 1971-2014.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Number</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>1</td>
<td>Arsenic and arsenical compounds, including pesticides (1980, 2012)</td>
</tr>
<tr>
<td>Group 2A</td>
<td>4</td>
<td>Non-arsenical insecticides, occupational exposure in spraying (1991) &amp; 3 others upgraded from 2B</td>
</tr>
<tr>
<td>Group 2B</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>49</td>
<td>Includes 2 downgraded from 2B</td>
</tr>
</tbody>
</table>

Implication: Human data are inadequate for most pesticides evaluated to date.
There is sufficient evidence that financial conflicts of interest is able to affect reviews outcome, including systematic reviews and meta-analysis.

Systematic Reviews and Meta-Analysis authors often fail to disclose their financial conflicts of interest.

An increasing number of systematic reviews methods have been proposed in environmental and occupational health and many of them do not address the issue of financial conflict of interest of the authors.


Yank V, Rennie D, Bero LA. Financial ties and concordance between results and conclusions in meta-analyses: retrospective cohort study. BMJ. 2007;335:1202-1205
The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses.

Ioannidis JP.

Abstract

POLICY POINTS: Currently, there is massive production of unnecessary, misleading, and conflicted systematic reviews and meta-analyses. Instead of promoting evidence-based medicine and health care, these instruments often serve mostly as easily produced publishable units or marketing tools. Suboptimal systematic reviews and meta-analyses can be harmful given the major prestige and influence these types of studies have acquired. The publication of systematic reviews and meta-analyses should be realigned to remove biases and vested interests and to integrate them better with the primary production of evidence.

CONTEXT: Currently, most systematic reviews and meta-analyses are done retrospectively with fragmented published information. This article aims to explore the growth of published systematic reviews and meta-analyses and to estimate how often they are redundant, misleading, or serving conflicted interests.

METHODS: Data included information from PubMed surveys and from empirical evaluations of meta-analyses.

FINDINGS: Publication of systematic reviews and meta-analyses has increased rapidly. In the period January 1, 1986, to December 4, 2015, PubMed tags 266,782 items as "systematic reviews" and 58,611 as "meta-analyses." Annual publications between 1991 and 2014 increased 2,728% for systematic reviews and 2,635% for meta-analyses versus only 153% for all PubMed-indexed items. Currently, probably more systematic reviews of trials than new randomized trials are published annually. Most topics addressed by meta-analyses of randomized trials have overlapping, redundant meta-analyses; same-topic meta-analyses may exceed 20 sometimes. Some fields produce massive numbers of meta-analyses; for example, 185 meta-analyses of antidepressants for depression were published between 2007 and 2014. These meta-analyses are often produced either by industry employees or by authors with industry ties and results are aligned with sponsor interests. China has rapidly become the most prolific producer of English-language, PubMed-indexed meta-analyses. The most massive presence of Chinese meta-analyses is on genetic associations (63% of global production in 2014), where almost all results are misleading since they combine fragmented information from mostly abandoned era of candidate genes. Furthermore, many contracting companies working on evidence synthesis receive industry contracts to produce meta-analyses, many of which probably remain unpublished. Many other meta-analyses have serious flaws. Of the remaining, most have weak or insufficient evidence to inform decision making. Few systematic reviews and meta-analyses are both non-misleading and useful.

CONCLUSIONS: The production of systematic reviews and meta-analyses has reached epidemic proportions. Possibly, the large majority of produced systematic reviews and meta-analyses are unnecessary, misleading, and/or conflicted.
Conclusion

In conclusion, we found marginally significant positive meta-RRs for the association between glyphosate use and risk of NHL and MM, and statistically null associations with HL and leukemia. A statistically significant positive meta-RR for B-cell lymphoma, but not other NHL subtypes, was calculated based on only two studies. Combining these results with recognition of the methodological weaknesses of the small number of existing studies and an overall body of literature that is not strong, consistent, temporally unambiguous, or indicative of a positive biological gradient, we determined that no causal relationship has been established between glyphosate exposure and risk of NHL, HL, MM, leukemia, or any subtype of LHC.

Acknowledgments

The authors thank John Acquavella and Thomas Sorahan for their thoughtful comments on earlier drafts of this manuscript, and Bernard Beckerman for his technical review of the tables.

Funding

This work was supported by Monsanto Company, the original producer and marketer of glyphosate formulations.
Relationship between Research Outcomes and Risk of Bias, Study Sponsorship, and Author Financial Conflicts of Interest in Reviews of the Effects of Artificially Sweetened Beverages on Weight Outcomes: A Systematic Review of Reviews

Daniele Mandrioli, Cristin E Keams, Lisa A. Bero

Published: September 8, 2016 • http://dx.doi.org/10.1371/journal.pone.0162198

Abstract

Background

Artificially sweetened beverage consumption has steadily increased in the last 40 years. Several reviews examining the effects of artificially sweetened beverages on weight outcomes have discrepancies in their results and conclusions.

Included in the Following Collection

Diabetes Prevention
Reviews performed by authors that had a financial conflict of interest with the food industry were more likely to have favorable conclusions (18/22) than reviews performed by authors without conflicts of interest (4/9), RR: 7.36 (95% CI: 1.15 to 47.22).
Authors of 42% (13/31) of reviews had conflicts of interest that were not disclosed in the article;

Most of these (n = 8) were in reviews that also had no disclosed funding sources
ICMJE Form for Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in six parts.

Zhang L, Rana I, Shaffer RM, Taioli E, Sheppard L.

Abstract
Glyphosate is the most widely used broad-spectrum systemic herbicide in the world. Recent evaluations of the carcinogenic potential of glyphosate-based herbicides (GBHs) by various regional, national, and international agencies have engendered controversy. We investigated whether there was an association between high cumulative exposures to GBHs and increased risk of non-Hodgkin lymphoma (NHL) in humans. We conducted a new meta-analysis that includes the most recent update of the Agricultural Health Study (AHS) cohort published in 2018 along with five case-control studies. Using the highest exposure groups when available in each study, we report the overall meta-relative risk (meta-RR) of NHL in GBH-exposed individuals was increased by 41% (meta-RR = 1.41, 95% confidence interval, CI: 1.13-1.75). For comparison, we also performed a secondary meta-analysis using high-exposure groups with the earlier AHS (2005) and we calculated a meta-RR for NHL of 1.45 (95% CI: 1.11-1.91), which was higher than the meta-RRs reported previously. Multiple sensitivity tests conducted to assess the validity of our findings did not reveal meaningful differences from our primary estimated meta-RR. To contextualize our findings of an increased NHL risk in individuals with high GBH exposure, we reviewed publicly available animal and mechanistic studies related to lymphoma. We documented further support from studies of malignant lymphoma incidence in mice treated with pure glyphosate, as well as potential links between glyphosate / GBH exposure and immunosuppression, endocrine disruption, and genetic alterations that are commonly associated with NHL or lymphomagenesis. Overall, in accordance with findings from experimental animal and mechanistic studies, our current meta-analysis of human epidemiological studies suggests a compelling link between exposures to GBHs and increased risk for NHL.

KEYWORDS: Carcinogenesis; Glyphosate; Meta-analysis; Pesticide; Ranger pro; Roundup

GLOBAL GLYPHOSATE STUDY
Questions

“Have glyphosate and GBHs been tested at currently admitted doses and at real-world levels of exposure?”

“Do glyphosate and its formulations have different effects?”

“What are the possible effects of GBHs other than cancer?”

The Global Glyphosate Study

- In 2016 the Ramazzini Institute started the Pilot Phase of the Global Glyphosate Study, involving multiple independent Institutions and Universities in Europe and the U.S.

- The Pilot Study aimed to obtain general information as to whether GBHs at currently admitted doses might be toxic at various stages of early life (newborn, infancy and adolescence), and to identify early markers of exposure and effect, before proceeding to a more comprehensive long-term study.

- The €300,000 Pilot Study was funded by 30,000 members of the public in Italy, who are associates of the Ramazzini Institute.
Glyphosate Pilot Study: the RI Partners

✓ University of Bologna (Dpt. of Agriculture, Dpt. Veterinary Medicine and Dpt. of Economics, Management and Statistics), Italy

✓ Italian National Institute of Health, Dpt. of Food Safety and Veterinary Public Health Rome, Italy

✓ Genoa Hospital San Martino, Environmental Carcinogenesis Unit, Genoa, Italy

✓ Mount Sinai School of Medicine, New York, NY, USA

✓ George Washington University, Washington, DC, USA
**Glyphosate Pilot Study: Study Design**

<table>
<thead>
<tr>
<th>GROUP</th>
<th>COMPOUND</th>
<th>DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Drinking water</td>
<td>Control</td>
</tr>
<tr>
<td>II</td>
<td>Glyphosate</td>
<td>US ADI (1.75 mg/kg bw/day)</td>
</tr>
<tr>
<td>III</td>
<td>Roundup</td>
<td>US ADI (1.75 mg/kg bw/day)</td>
</tr>
</tbody>
</table>

- **Route of Administration:** The test substances have been administered ad libitum in drinking water to Sprague Dawley rats.

- **Test Substances:** Glyphosate (purity > 99.5%) and its formulation Roundup Bioflow (MON 52276, containing glyphosate [41.5%], water [42.5%] and surfactant [16%]).

- **Dose:** the U.S. Environmental Protection Agency’s acceptable daily dietary exposure level of glyphosate (cRfD) - 1.75 mg/kg bw/day.
# Glyphosate Pilot Study: Study Design

<table>
<thead>
<tr>
<th>Breeders</th>
<th>Offspring</th>
<th>Treatment</th>
<th>End of the experiment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Animals</strong></td>
<td><strong>Group</strong></td>
<td><strong>Animals a</strong></td>
<td><strong>Compound</strong></td>
</tr>
<tr>
<td>Sex</td>
<td>No.</td>
<td>N.</td>
<td>Sex</td>
</tr>
<tr>
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<td>I</td>
<td>F</td>
<td>8</td>
<td>I</td>
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<tr>
<td></td>
<td>M</td>
<td>8</td>
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<td></td>
<td>F+M</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>F</td>
<td>8</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>8</td>
<td></td>
</tr>
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<td>F+M</td>
<td>16</td>
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<tr>
<td>III</td>
<td>F</td>
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<td>III</td>
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<td></td>
<td>M</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F+M</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>M+F</td>
<td>48</td>
<td>M+F</td>
</tr>
</tbody>
</table>

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*No more than 2 sisters and 2 brothers per litter*

*Test compounds are administered *ad libitum* in drinking water*

*Doses are calculated considering the Glyphosate US ADI (1.75 mg/kg bw/day)*

*Solutions are administered to dams starting from the 6<sup>th</sup> day of pregnancy*

*Animals are treated until the landmarks of sexual development are acquired (PND 73 ± 2).*

*Animals are treated from embryonic life (GD 6) indirectly from dams milk until PND 28 ± 2, then directly for 90 days after weaning (until PND 125 ± 2).*
Biomarkers of Exposure: Glyphosate Trend

Glyphosate trend in Female Urine

A: Dams
B: 6-week cohort
C: 13-week cohort

(mg/kg)

Control Glyphosate Roundup

A B C

A B C
Glyphosate Pilot Study: Microbiome

**Dams**
- G to R:
  - BM: 0.89
  - GD5: 0.65
  - GD13: 0.24
  - LD7: 0.63
  - LD14: 0.64
  - PND7: 0.019
  - PND14: 0.34
  - PND31: 0.032
  - PND57: 0.001
  - PND125: 0.001

- R to C:
  - BM: 0.37
  - GD5: 0.6
  - GD13: 0.48
  - LD7: 0.99
  - LD14: 0.16
  - PND7: 0.4
  - PND14: 0.96
  - PND31: 0.001
  - PND57: 0.16
  - PND125: 0.019

- G to C:
  - BM: 0.17
  - GD5: 0.82
  - GD13: 0.33
  - LD7: 0.43
  - LD14: 0.39
  - PND7: 0.028
  - PND14: 0.57
  - PND31: 0.017
  - PND57: 0.016
  - PND125: 0.029

**Pups**
- G to R:
  - BM: 0.89
  - GD5: 0.65
  - GD13: 0.24
  - LD7: 0.63
  - LD14: 0.64
  - PND7: 0.019
  - PND14: 0.34
  - PND31: 0.032
  - PND57: 0.001
  - PND125: 0.001

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  - PND7: 0.028
  - PND14: 0.57
  - PND31: 0.017
  - PND57: 0.016
  - PND125: 0.029

- Treatment:
  - Glyphosate
  - Roundup
  - Water
In pups, anogenital distance (AGD) at PND 4 was statistically significantly increased both in Roundup-treated males and females and in glyphosate-treated males.

Age at first estrous (FE) was significantly delayed in the Roundup-exposed group.

Serum testosterone concentration significantly increased in Roundup-treated female offspring from the 13-week cohort compared to control animals.

Roundup exposure was also associated with altered testosterone metabolism in both males and females, where a statistically significant decrease in DHT/TT ratio was observed in the longest treated group (13-week).
Glyphosate Pilot Study: Genotoxicity

- A statistically significant increase in the micronuclei frequency in male and female rats treated with Roundup in the 6 weeks cohort.
Glyphosate Pilot Study: Limitations

- Only one dose
- Limited number of animals
- Limited number of endpoints
- Chronic effects, including cancer, could not be addressed
Glyphosate Pilot Study: Remarks

- Four peer-reviewed manuscripts from the Pilot Study are available online in the international scientific journal Environmental Health.

- GBHs at currently admitted doses were able to alter certain important biological parameters, mainly relating to sexual development, genotoxicity and the alteration of the intestinal microbiome.

- GBHs exposure might lead to bioaccumulation of glyphosate in relation to the duration of the exposure.

- Glyphosate and its formulations might have different effects, as exemplified by the effects of the mixed formulation on the microbiome.

A long-term study is now necessary to extend and confirm the initial evidence that has emerged in the Pilot Study.
The need for independent research on the health effects of glyphosate-based herbicides

Glyphosate, formulated as Roundup, is the world's most widely used herbicide. Glyphosate is used extensively on genetically modified (GM) food crops designed to be resistant to glyphosate. The widespread use of glyphosate raises concerns about its potential health effects. Independent research is necessary to evaluate the health impacts of exposure to glyphosate.

The Ramazzini Institute 13-week pilot study on glyphosate and Roundup administered at human-equivalent dose to Sprague Dawley rats: effects on the microbiome

Qixing Mao, Fabiana Manservisi, Simona Panzacchi, Daniele Mandrioli, Ilaria Menghetti, Andrea Vornoli, Luciano Bua, Laura Falchioni, Corina Lesspeur, Jia Chen, Fiorella Belagaggi

The Ramazzini Institute 13-week pilot study glyphosate-based herbicides administered at human-equivalent dose to Sprague Dawley rats: effects on development and endocrine system

Fabiana Manservisi, Corina Lesspeur, Simona Panzacchi, Daniele Mandrioli, Laura Falchioni, Luciano Bua, Marco Manservisi, Marcella Spinaci, Giovanna Gallo, Alberto Mantovani, Stefano Lorenzetti, Rossella Miglio, Anderson Martino Andrade, David Mebjurg Kristensen, Melissa J. Perry, Shanna H. Swan, Jia Chen & Fiorella Belagaggi
Glyphosate Pilot Study: Results Presented to the EU Parliament

Philippe LAMBERTS - Greens/EFA Co-Chair, Marco AFFRONTE, Fiorella BELPOGGI, and Daniele MANDRIOLI

2018-05-16 | 10:30 to 11:00 | Recorded
Long-Term Study: The Ramazzini Integrated Experimental Design (RIED)

Traditionally, separate studies are conducted to evaluate these effects

Number of animals

- The RIED aims to maximize the endpoints measured for each animal, thus reducing the overall number of animals produced/utilized, in accordance with the 3Rs.

- **Reduction up to 33% in animal use** as compared to current use of separate guidelines experiments.

- Animal Study Application approved by the Italian Ministry of Health.
Crowdfunding Campaign

WE NEED GLOBAL SUPPORT
TO RAISE FUNDS FOR THIS GROUNDBREAKING STUDY

www.glyphosatestudy.org
Protocol for a systematic review and meta-analysis of human exposure to pesticide residues in honey and other bees' products

Introduction

Pesticide residues play a fundamental role in the functioning of existing terrestrial ecosystems; nearly 75% of the most important food crops are protected from pests by pesticides. Although many of these products are toxic to humans, they are also necessary to protect crops from pests that could otherwise affect the health of consumers. Pesticides are used in many different ways, including as insecticides, fungicides, herbicides, and disinfectants.

Methods

Our methodology adheres to the guidelines for accuracy and transparency in health technology assessment (AHTA), such as the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) and the Cochrane Handbook for Systematic Reviews of Interventions.

Data management and selection process

Lists of relevant references will be kept in EndNote, and all references will be evaluated. At least two reviewers will independently evaluate the titles and abstracts. A full text review will be conducted by at least two independent reviewers. Any conflicts will be resolved by a third reviewer.

Data collection

A data extraction template will be developed and piloted. Two reviewers will independently extract data for each included study. The data will include study characteristics, study design, and results. The data will be presented in a structured format.

Results

We will conduct this version of the AHTA post methodology. Risk of bias tools, specific to each prevalence study, will be evaluated. The domains will include:

- selection bias
- exposure assessment bias
- confounding bias
- other biases

Conclusion

The results will be presented in a narrative format and table format. The data will be presented in a structured format. The results will be presented in a narrative format and table format.

Confidence in conclusion evidence

We will conduct this version of the AHTA post methodology. Risk of bias tools, specific to each prevalence study, will be evaluated. The domains will include:

- selection bias
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- confounding bias
- other biases

Notes

The results will be presented in a narrative format and table format. The data will be presented in a structured format. The results will be presented in a narrative format and table format.
Thank you!