Glyphosate: An Updated Meta-Analysis for Non-Hodgkin Lymphoma

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Glyphosate Overview

- Most widely used herbicide in the world
  - Sold commercially as “Round-up” by Monsanto/Bayer
  - “Glyphosate technical” is combined with “inert ingredients” to form glyphosate-based herbicides (GBHs)
    - Adjuvants (e.g., POEA – polyethoxylated tallow amine, a surfactant) may be more toxic alone or combined with glyphosate
    - Seemingly identical Roundup products can have different adjuvants (e.g., the EU has restricted the use of POEA, but this is not evident from the packaging)
  - Also used as desiccant prior to harvest (“green burndown”)

- A current controversy: carcinogenic or not?
  - IARC (2015): Probably carcinogenic to humans (Group 2A)
  - EFSA (2015): glyphosate is unlikely to pose a carcinogenic hazard to humans and the evidence does not support classification with regard to its carcinogenic potential
  - EPA (2016): not likely to be carcinogenic to humans at doses relevant for human health risk assessment
Why Did I Publish on Glyphosate?

• I served on 2016 EPA FIFRA Panel to evaluate the *carcinogenic potential* of glyphosate (i.e., is it carcinogenic?)
  • I replaced an epidemiologist who was removed from the Panel after objections from CropLife
  • One month to prepare:
    • 227 page “Issue Paper” technical report
    • Supporting information:
      • 67 confidential “10g” (trade secret) study reports
      • EPA’s 2005 *Guidelines for Carcinogen Risk Assessment*
      • International Agency for Cancer Research’s (IARC’s) 2015 *Monograph 112* on glyphosate
      • Dozens of papers from the peer-review literature, including statements of concern about previous official assessments
      • Public docket with over 500 submissions

• I was concerned about EPA’s approach to using the evidence and their conclusions
  • Joined two other FIFRA Panel members to address these concerns
My personal motivation:
At that time I believed Roundup was safe to use in my organic garden
My Glyphosate Publications

1. **Letter** to JNCI highlighting error in the Agricultural Health Study 2018 (AHS 2018) multiple imputation/exposure simulation that is known theoretically to bias results towards the null

2. **Review of glyphosate exposure studies** highlighting the limited exposure information available

3. **Updated meta-analysis** of glyphosate and Non-Hodgkin’s lymphoma (NHL)
Review of Meta-Analysis Paper
What We Did

- Asked whether or not glyphosate-based herbicides (GBHs such as Roundup) are associated with an increased risk of non-Hodgkin lymphoma (NHL)

How
- Combined the evidence from six published epidemiologic studies of workers using meta-analysis
  - One large cohort
  - Five case-control
- Focused on the most highly exposed group in each study

What was novel
- Better approach to asking the question: Are GBHs carcinogenic in humans?
- Incorporated new evidence from the Agricultural Health Study (AHS 2018)
  - 11-12 additional years of follow-up
  - 5x as many NHL cases
### Methods (Exposure Group Selection)

**A priori selection of highest exposure groups when available**

- Relationship may be more likely to be detected with higher exposures
- Less concern with confounding
- Prevents dilution of exposure groups; ensures adequate exposure contrast

<table>
<thead>
<tr>
<th>High exposure category</th>
<th>Reason for selection</th>
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| (1) Highest cumulative exposure & longest lag \(^1\) or latency \(^2\) | • Persistence of glyphosate in the environment  
• Chronic disease (ex: cancer) usually result from cumulative long term exposures |
| (2) Highest cumulative exposure | |
| (3) Longest exposure duration and longest lag or latency | • Decades may be needed for cancer to manifest |
| (4) Longest exposure duration | |
| (5) Longest lag or latency | |
| (6) Ever-exposed | • Avoid excluding relevant data, given so few published studies |

\(^1\) Lag = time before NHL onset, excluded from exposure estimates  
\(^2\) Latency = time between first lifetime exposure & NHL diagnosis
Meta-Analysis Results

**Our Result**: The most highly exposed workers have a 41% increased relative risk (95% CI: 13 – 75%)

- Results robust to sensitivity analyses
- Comparison to previous meta-analyses:
  - Our result: 1.41 (1.13-1.75)
  - IARC: 1.30 (1.03-1.65)
  - Chang & Delzell: 1.27 (1.01-1.59)
Meta-Analysis Forest Plot

**with AHS 2018**

A.
- Andreotti 2018
- DeRoos 2003
- Eriksson 2008
- Hardell 2002
- McDuffie 2001
- Orsi 2009

**Overall**

Meta-RR: **1.41 (1.13-1.75)**

(I-squared = 39.4%  p = 0.143)

**with AHS 2005**

B.
- DeRoos 2005
- DeRoos 2003
- Eriksson 2008
- Hardell 2002
- McDuffie 2001
- Orsi 2009

**Overall**

Meta-RR: **1.45 (1.11-1.91)**

(I-squared = 52.8%  p = 0.060)
Meta-Analysis Strengths & Limitations

**Strengths**

- Included updated AHS results
- Focus on high exposure group to maximize ability to detect association

**Limitations**

- Limited studies (n=6) available for inclusion
- Potential for publication bias
- Key differences between studies (ex: reference group) suggests caution in interpretation of numerical estimate
- None of the studies would have incorporated the increasing adoption of “green burndown” practices since mid-2000s
What Does This Evidence Mean?

- Supports IARC’s conclusion that glyphosate is probably carcinogenic
- Findings apply to the most highly exposed workers; unclear how they translate to the general public
  - Note: With a ubiquitous exposure, even a small increase in risk means many more cases of NHL in the general population
- Currently there are no studies of GBHs impact on the public
  - These studies are much harder to do
  - The absence of studies does not imply no risk
There Is Much More to Learn!

- These studies only know about exposures prior to 2005 (AHS 2018) or earlier
- Glyphosate sales have exploded in recent decades:
  - Most intensively used herbicide in the world
    - For weed control AND as a desiccant prior to harvest ("green burndown")
Timeline

Key point: Epidemiologic evidence was assembled prior to the explosion in glyphosate sales; we don’t know the impact of this exposure trend on health.
Experimental Evidence & Context

• **In vivo animal studies**
  • Supporting evidence from malignant lymphoma in mice and 7 other cancer endpoints in mice and rats (Portier 2020)
    • Evidence of dose-response associations in pooled analyses
  • Challenges & limitations
    • Insufficient follow-up time
      • 80% of cancers occur after the age of 60, but a 2-year rat assay approximates age 60-65
    • Pure glyphosate, rather than “real-world” glyphosate-based herbicides (GBHs)
      • GBHs have been shown to be more toxic

• **Potential mechanisms**
  • Immunosuppression & inflammation
  • Endocrine disruption
  • Genetic alterations
  • Oxidative stress
**New Animal Study Evidence**

Table 6: Summary of level of evidence\(^a\) for tumors observed to have a significant trend in 13 rodent carcinogenicity studies in male and female, mice and rats\(^b\)

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<td>CD-1 Mouse</td>
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8 tumors show clear evidence (CE) in at least one species, strain and sex combination

3 additional tumors show some evidence (SE)

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\(^a\) CE Clear evidence, SE Some evidence, EE Equivocal evidence, NE No evidence; \(^b\) a blank space indicates there is no positive finding in any study for this tumor in this sex/species

Portier 2020 *Environmental Health*
Discussion
Broader Context of Unconstrained Herbicide Use

• Herbicide-resistant (HR) crops are 85% of the world’s GM crop acreage
  • Vast majority (~80-90%) are Roundup Ready
• Development of superweeds (herbicide-resistant weeds)
  • 49% of US farmers surveyed reported glyphosate-resistant weeds on their farm (Fraser, 2013)
  • From Heap & Duke 2017:
    • Thirty-eight weed species have now evolved resistance to glyphosate, distributed across 37 countries and in 34 different crops and six non-crop situations
    • Glyphosate-resistant weeds present the greatest threat to sustained weed control in major agronomic crops
• Reduced populations and diversity:
  • Milkweed & monarchs
  • Insects
  • Birds??
• May affect soil health
Glyphosate in Context

- Other herbicides (dicamba, 2,4-D) are more acutely toxic
  - Application requirements are stricter, more regulations that protect workers and off-target effects
- Glyphosate was considered safe for decades
  - Lower worker protection standards
  - Increased tolerances (residues allowed in foods) over time
  - Single most used agricultural chemical in the world (including fertilizers)
- Recently approved: New herbicide-resistant crops for glyphosate AND other herbicides (e.g., 2,4-D, dicamba)
  - “New era” of more pesticide pollution
  - Anticipate no reduction in glyphosate usage
  - Other pesticides (dicamba) are more volatile and drift to neighbors
  - Weeds are developing stacked resistance
My Conclusions

• **Glyphosate is likely to be carcinogenic to humans**
  • Positive evidence in animal studies in multiple species, sex, strain, and tumor site
  • Strengthened by other lines of evidence
    • Suggestive evidence in human studies
    • Genotoxicity evidence

• **We need a new paradigm for scientific review of registrant-funded studies that are used as a basis for policy**
  • Registrants have a vested interest in certain scientific results

• **It is important to reduce pesticide usage and population exposure**
  • We know from air pollution research that a ubiquitous exposure with small adverse effects can harm millions of people
Further Reading & References

1. **My work**

2. **Selected scientific papers**
   Portier, Christopher J., et al. "Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA)." *J Epidemiol Community Health* 70.8 (2016): 741-745.

3. **A very readable book**

4. **Useful website**
   US Right to Know. [Usrtk.org](http://usrtk.org).
   See e.g. their glyphosate fact sheet [usrtk.org/pesticides/glyphosate-health-concerns](http://usrtk.org/pesticides/glyphosate-health-concerns)
Thank you!

Questions?

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Credits:
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Cynthia Curl, Assistant Professor, Boise State University
Bill Freese, Science Policy Analyst, Center for Food Safety
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Rachel Shaffer
Additional Slides
Methods (Study Selection + Analysis)

- Literature search followed *Preferred Reporting Items for Systematic Reviews and Meta-Analysis* (PRISMA) guidelines
  - Updated August 2018
- Eligible studies & participants
  - 1 cohort & 5 case-control studies
  - ~65,000 individuals
  - Locations: US, Canada, Sweden, France
- Statistical methods: Meta-risk estimation
  - Averages study estimates; gives higher weight to studies with more cases
  - Fixed effects inverse variance method (*primary results*)
  - Random effects method (*secondary results*)