Glyphosate Renewal Group

POST-RAC 40 INPUT FOR CLH CONSIDERATION

NO CHANGES WARRANTED FOR HUMAN HEALTH CLASSIFICATION
EYE DAM. 1; H318

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ECHA RAC 60 Meeting
16th March, 2022

New cancer epi. data vs meta-analyses
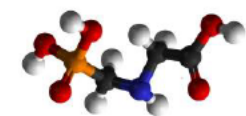
The most recent & reliable epidemiology data today is from the prospective Agricultural Health Study, Andreotti et al. (2018)

→ no clear association between glyphosate use and cancer, including non-Hodgkin's lymphoma (NHL)

Meta-analyses which pool error prone studies, are not more informative than the current high quality AHS data

- **Andreotti (2018)** - new Agricultural Health Study (AHS) data update; large cohort study of US pesticide applicators 54,251 individuals; 44,932 glyphosate users

  - **HIGH quality**

  - No recall bias (prospective study)

  - All participants registered pesticide applicators (accurate reporting of pesticide use)

  - Sophisticated exposure metrics; ever/never/intensity-weighted lifetime days

  - Frequency of glyphosate use exceeds all other studies (median 48 day, IQR 20-166 days)

  - Analyses well described: controlled for many personal factors (smoking, never/former/current; alcohol 0, <6, >7/month), lagged exposures to address latency (5, 10, 15, or 20 years), BMI, co-exposures, etc.

  - Wide range of sensitivity and lagged analyses (up to 20+ years latency-induction)

  - Note: glyphosate registered for > 20 years prior to study start in 1990s

- Meloni (2021) – case-control, potential recall bias, 1,641 individuals, only 36 glyphosate users

  - LOW quality

  - Marked disparity in participation between cases (93%) and controls (62%), suggesting selection bias

  - Did not specify if interviewers were blinded to case or control status during in-hospital or in-residence interviews

  - Multivariate analysis only controlled for age, gender, education and study center… neglecting key confounding factors of other pesticides, other farming exposures, etc.

- Meta-analyses: include mostly low quality case-control studies with glyphosate

  - Averaging the results of questionable reliability as compared with the AHS

    - Reduce random error, but

    - Incorporate systemic error

- Chang & Delzell (2016)

  - Likely confounding and other biases colour the interpretation of meta RR

  - Does not include recent Andreotti (2018) AHS data

- Leon (2019): combines three cohorts (older AHS data up to 2011, AGRICAN, CNAP)

  - AGRICAN and CNAP cohorts

    - Exposure based on crops farmed and equipment used

    - Extremely inaccurate compared to AHS (correlation with AHS ~ 0.1)

    - Widespread misclassification, can't control for potential confounding effects (multiple pesticide exposures)… need to differentiate users from true non-users , calls every pesticide specific RR into question

- Zhang (2019): positive NHL association depends on assumption of long latency period

  - Selectively chose results from case control and other studies

- Pahwa (2019): pooled two old case-control studies with underlying biases

  - McDuffie et al. (2001) & DeRoos (2003)

  - Did not find consistent evidence of a glyphosate/NHL association when considering confounding factors and excluding next-of-kin (surrogate) reporting

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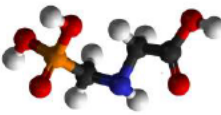# Epidemiology review/statistics publications
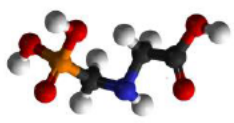
Detailed review (Crump, 2020) highlights shortcomings of specific case-control studies

Statistical review (Kabat et al., 2021) evaluates findings of Zhang (2019) meta-analysis

- Weisenburger (2021; paid expert for plaintiffs in glyphosate litigation): limited literature review
  - incorrectly assumes AHS low lifetime exposure
- **Crump (2020)**: assessed bias in case-control studies
  - case-control studies are contaminated by recall bias, the use of exposure information based on memories for both case and control individuals (or surrogates), and selection bias
  - provides evidence that
    - 4/5 case control studies find associations for the vast majority of pesticides, indicating a biased methodology
  - 4 case-control studies are not reliable in determining whether glyphosate or other pesticides are carcinogenic

- **Kabat et al. (2021)**: sensitivity analysis of Zhang et al. (2019) and meta-analysis
  - results of the AHS provide the most reliable and precise information regarding the risk of NHL following glyphosate exposure
  - combined analyses of the AHS and the case–control studies, rather than enhancing our understanding of the possible association between glyphosate and NHL, may primarily result in diminishing the impact of the very robust prospective AHS
- ████████ (2021): Epidemiologic Studies of Glyphosate and non-Hodgkin's Lymphoma: State of the Science Assessment
 - white paper addressing dRAR public comments for stop the clock submission

NHL = non-Hodgkin's lymphoma; **AHS** = Agricultural Health Study, Andreotti et al. (2018); **dRAR** = Glyphosate draft Renewal Assessment Report

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Animal chronic/carcinogenicity data

- No cancer mechanism/mode of action exists...

  - Lack of consistency across multiple chronic/carcinogenicity studies with the same species for tumor types, and lack of pre-neoplastic histopathology to support a cancer hypothesis

  - No tumorigenic dose-response, and no evidence of tumor progression

- Crump et al. (2020), Accounting for Multiple Comparisons in Statistical Analysis of the Extensive Bioassay Data on Glyphosate. *Toxicological Sciences* 175(2), 156-167

  - analysis provided new statistical evidence that isolated findings of positive trends were due to chance and were mirrored by a similar number of negative trends

  - found no strong or convincing evidence that glyphosate is an animal carcinogen

- US EPA Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential (2017)

  - *"Based on the weight-of-evidence evaluations, the agency has concluded that none of the tumors evaluated in individual rat and mouse carcinogenicity studies are treatment-related due to lack of pairwise statistical significance, lack of a monotonic dose response, absence of preneoplastic or related non-neoplastic lesions, no evidence of tumor progression, and/or historical control information (when available). Tumors seen in individual rat and mouse studies were also not reproduced in other studies, including those conducted in the same animal species and strain at similar or higher doses."*

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Genotoxicity data & publications
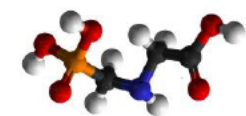
> **Complete genotoxicity data package following current OECD Test Guidelines**
>
> → **all results unequivocal for non-mutagenic, non-clastogenic, and non-aneugenic**
>
> **Weight of evidence across data package and public literature concludes non-genotoxic**

- 13 new/previously unreviewed genotoxicity papers reviewed in current dRAR, Vol.3.B.6.4
  - RMS reviewed all in weight of evidence evaluation and determined
    - 1 reliable with restrictions
    - 9 supportive only
    - 3 unreliable
- OECD test guideline compliant studies conducted since RAC 40
  - Glyphosate
    - Bacterial Reverse mutation (Ames, OECD 471) - **negative**
    - Micronucleus assay (human lymphocytes, OECD 487) - **negative**
  - Aminomethylphosphonic acid (AMPA, main metabolite)
    - Bacterial Reverse mutation (Ames, OECD 471) – **negative**
    - HPRT forward mutation (OECD 476) – **negative**
    - Micronucleus assay (human lymphocytes, OECD 487) - **negative**

Chromosome   DNA

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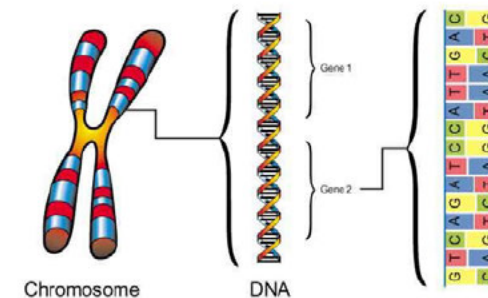
Considerations for RAC 2022 on glyphosate
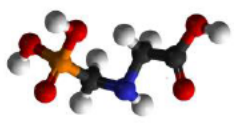
No compelling new toxicology or epidemiology data to change the RAC 40 conclusions

Weight of evidence supports current human health hazard classification of glyphosate

Meta-analyses and Pooled analyses

Chang ET, Delzell E. Systematic review and meta-analysis of glyphosate exposure and risk of lymphohematopoietic cancers. *J Environ Sci Health B* 2016; 51:402–428

Kabat GC, Price WJ, Tarone RE. On recent meta-analyses of exposure to glyphosate and risk of non-Hodgkin's lymphoma in humans. *Cancer Causes & Control*. 2021; 32(4): 409-414

Leon ME, Schinasi LH, Lebailly P, et al. Pesticide use and risk of non-Hodgkin lymphoid malignancies in agricultural cohorts from France, Norway and the USA: a pooled analysis from the AGRICOH consortium. *International Journal of Epidemiology* 2019, 1–17 doi: 10.1093/ije/dyz017

Pahwa M, Beane Freeman LE, Spinelli JJ. Glyphosate use and associations with non-Hodgkin lymphoma major histological sub-types: findings from the North American Pooled Project. *Scand J Work, Environ & Hlth* 2019; 45(6):600–609

Zhang L, Rana L, Shaffer RM, et al. Exposure to Glyphosate-Based Herbicides and Risk for Non-Hodgkin Lymphoma: A Meta-Analysis and Supporting Evidence. *Mutation Res*. 2019; 781, 186-206

Animal Chronic/Carcinogenicity Statistics Reviews

Portier C. A comprehensive analysis of the animal carcinogenicity data for glyphosate from chronic exposure rodent carcinogenicity studies. Environmental Health. 2020; 19:18

Crump K, Crouch E, Zelterman D, Crump C, Haseman J. Accounting for Multiple Comparisons in Statistical Analysis of the Extensive Bioassay Data on Glyphosate,. Toxicological Sciences. 2020; 175(2), 156-167

Primary Epidemiology Data

Andreotti G, Koutros S, Hofmann JN, et al. Glyphosate Use and Cancer Incidence in the Agricultural Health Study. *J Natl Cancer Inst*. 2018; 110(5): 509–516

Meloni F, Satta G, Padoan M, Montagna P, Pilia I, Alessandra Argiolas A, Sara Piro S, Magnani C, Gambelunghe A, Muzi G, Ferri GM, Vimercati L, Zanotti R, Scarpa A, Zucca M, De Matteis S, Campagna M, Miligi L, & Cocco P. Occupational exposure to glyphosate and risk of lymphoma: results of an Italian multicenter case-control study. *Environmental Health* 2021; 20:49

Epidemiology Review/Analyses

Weisenburger DD. A Review and Update with Perspective of Evidence that the Herbicide Glyphosate (Roundup) is a Cause of Non-Hodgkin Lymphoma. *Clinical Lymphoma, Myeloma and Leukemia*. 2021; 21(9), 621-630

Crump K. The Potential Effects of Recall Bias and Selection Bias on the Epidemiological Evidence for the Carcinogenicity of Glyphosate. Risk Analysis 2020; 40 (4), 669-704.

███████ Epidemiologic Studies of Glyphosate and non-Hodgkin's Lymphoma: State of the Science Assessment (2021, white paper)

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