

Key issues of the CLH proposal on Glyphosate

- Carcinogenicity
 - Animal studies (tumour incidence)
 - Epidemiological studies
 - Underlying mechanism of action (oxidative stress)
- Genotoxicity
 - Missing studies
 - Analysis of the studies submitted by the companies
- Reproduction
 - Evidence from the studies submitted by the companies
 - Evidence from the scientific peer-reviewed literature

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Animal Carcinogenicity Data

- There is no “strategy for the assessment”¹
- One-sided statistical tests should be used
- Historical controls used inappropriately
 - Selective use of historical control data without a-priori strategy
 - Only used to remove positive findings, never used to support observed tumours
- Reliance on “*no increasing dose-response*” and “*lack of significant pair-wise tests*” seriously reduces statistical power
- Semi-quantitative comparisons across studies
 - Duration of study not considered, no adjustment for years between studies
 - Adjustment needed: Apply pooled analysis to all studies
 - Should be applied uniformly across all tumour endpoints
 - Should control for differences in control response by study
- Inconsistent inclusion/exclusion of tumours: Every decision to accept or refute a positive finding ends in exclusion of the positive finding (systematic bias)

¹ <https://www.efsa.europa.eu/en/efsajournal/pub/4121>

Tumours showing sufficient evidence of carcinogenicity in animals

- Mice
 - Malignant lymphomas (males and possibly females)
 - Kidney tumours (males – rare tumour at 18 and 24 months)
 - Hemangiosarcomas (males – very rare tumour at 18 months)
 - Hemangiomas (females)
- Rats
 - Skin kertoacanthomas (males)
 - Skin basal cell tumours (males – rare tumour)
 - Hepatocellular adenomas (males)

Presumed Carcinogen (Cat 1B): presumed to have carcinogenic potential to humans, largely based on **sufficient evidence** from animals- a causal relationship has been established between a chemical and an increased incidence of malignant neoplasm or a combination of malignant and benign in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols.

Epidemiology- Andreotti et al. (2018)

- Imputation is poor
 - Overall Accuracy 55.7% (random would be 50%)
 - Under-predicts exposed (52.73% exposed in hold out, 45.42% predicted)
 - Likely differential misclassification below null
- Use of glyphosate rapidly increased during questionnaire period
 - 12.5 million kilos in 1995 to 71.1 million kilos in 2005
 - Leads to non-differential exposure misclassification to the null
- Intensity of exposure misclassified because of weighting by PPE use
 - PPE use not required for glyphosate, question is not pesticide specific
- Overall, study would be expected to trend toward null with little power to detect an effect

Other Epidemiology

- Pahwa et al. (2019) used different study populations than DeRoos et al. (2003) and McDuffie et al. (2001)
 - Additional participants are mostly women from Nebraska
 - Overly simplistic imputation methods applied with no discussion of the impact
 - All three studies must carry weight in the evaluation
- Leon et al. (2019)
 - Not a study of glyphosate use, a study of crop tillage
- Additional epidemiology studies and meta-analyses
- Overall, an association exists that could be credibly causal, but chance, bias and confounding cannot be excluded (*Limited Evidence*)

Presumed Carcinogen (Cat 1B): In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing **limited evidence of carcinogenicity in humans** together with **limited evidence of carcinogenicity in experimental animals**.