HEAL's response to the public consultations on the EU's initial assessment of glyphosate

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In November 2021, the Health and Environment Alliance (HEAL) commented on the EU assessment report of the toxicity of the popular pesticide glyphosate, which was published in the framework of the two public consultations launched by the EU Chemicals Agency (ECHA) and the EU Food Safety Authority (EFSA) [1]. The EU market license of glyphosate expires on 15 December 2022.

Regrettably, HEAL's review of the EU assessment report confirms that the evaluation is still mostly based on studies and arguments provided by industry and fails to endorse the scientific evidence from published literature reporting that glyphosate causes adverse effects on health.

This briefing outlines HEAL's main response to the two public consultations, which focused on providing comments on certain sections that assess the toxicity of glyphosate (as an active substance) with relevance to human health.

Key concerns about the EU assessment report on glyphosate

1. THE ASSESSMENT REPORT CONCLUSION SHOWING GLYPHOSATE IS NOT CARCINOGENIC IS NOT SUPPORTED BY AVAILABLE SCIENTIFIC EVIDENCE

HEAL expresses concerns on the conclusion reached in the EU assessment report that glyphosate is not carcinogenic. This conclusion is not supported by the available scientific evidence, whether it is from the animal studies on cancer provided by industry, or from studies available in peer-reviewed scientific literature.

The WHO's International Agency for Research on Cancer (IARC) classified glyphosate as "probably carcinogenic to humans" in 2015. IARC concluded that the evidence of cancer in humans and animals or of DNA damage was limited, sufficient and strong, respectively. The EU assessment concluded however that there was insufficient evidence of cancer in humans or experimental animals. It also concluded that there was insufficient evidence that glyphosate can cause damage to DNA (genotoxicity) [2].

Cancer incidents from animal studies are largely dismissed

The assessment report does not reflect those health impacts detected in animal studies provided by industry in preparation for the 2022 market renewal process of glyphosate. The five mice carcinogenicity studies submitted by industry and considered acceptable for the assessment actually found evidence of malignant tumours in the exposed animals [3]. Nevertheless, this evidence was repeatedly dismissed from the assessment for scientifically unfounded reasons.

According to the EU Regulation on the classification, labelling and packaging of substances of mixtures (CLP Regulation, No 1272/2008), an increased incidence of malignant neoplasms in two studies is enough to consider the evidence of carcinogenicity sufficient and classify a substance as a category 1B carcinogen. Glyphosate was found to induce malignant tumours in five different mice studies, meaning there is sufficient evidence to classify it as a category 1B carcinogen under the CLP Regulation.

Oxidative stress is not considered as a mechanism of action for carcinogenicity

Oxidative stress may cause genotoxicity (DNA damage) and is a recognized mechanism of carcinogenicity. Yet, the EU assessment report does not take into consideration the available evidence from published literature on the potential of glyphosate to cause oxidative stress as a possible mechanism of action through which glyphosate causes cancer.

- Out of the ten studies published since 2015 and available at the time of the assessment, only eight are mentioned in the assessment report. It should however be noted that none of these studies were actually used in the report's carcinogenicity section to discuss oxidative stress as a possible mechanism through which glyphosate causes cancer, despite evidence from the abovementioned mice studies.

- This is especially concerning considering that the WHO's International Agency for Research on Cancer (IARC), the gold standard on cancer research, also concludes that glyphosate has the potential to cause oxidative stress and that the evidence that glyphosate can cause genotoxicity (DNA damage) is therefore "strong".

Deficits found in interpreting the evidence from epidemiology studies

The assessment report gives emphasis to the Agricultural Health Study (AHS) from the United States, which is referred to as the largest prospective study on agriculture and cancer risk performed to date: more than 89,000 farmers, commercial applicators and their spouses in Iowa and North Carolina have been involved in the AHS since 1993. So far, the two evaluations, one carried out in 2005 and the other in 2012, show no clear association of glyphosate use and risk of non-Hodgkin lymphoma (NHL). However, the AHS has important shortcomings that the EU assessment report neglects to mention [4]:

- For the first evaluation in 2005, the median time period following the exposure was too short (6,7 years) to detect any meaningful increase in NHL. The average latency period for the development of NHL due to long-term exposure to carcinogenic chemicals, such as organic solvents, is approximately 20 years (with a range of 10 to 30 years or more).

- Only 44% of about 58,000 farmers enrolled in the study replied to a supplementary questionnaire following initial enrolment of the AHS. This supplementary questionnaire included more detailed questions on habits, diet, diseases and family history, the absence of which can lead to a distorted image of reality. While 63% out of 57,310 eligible farmers that participated in the original survey (1993-1997) responded to the follow-up questionnaire regarding their exposure to pesticides approximately five years after enrolment (1999-2005), they provided data only for the last year of farming prior to the survey. This leaves a data gap of 6 to 12 years on pesticide use.

To make up for missing data of those participants who didn't respond to the follow-up survey (37%), researchers behind the AHS used a complicated imputation method based on limited data from a previous year, instead of analysing the whole study period. This could lead to misclassification and underestimation of glyphosate use among the study's participants. The EU assessment report also dismisses all evidence gathered from the retrospective case-control studies - studies that are looking back in time based on questionnaires - on the potential of glyphosate to cause non-Hodgkin lymphoma, without providing any scientific justification. Here, however, five out of the six studies performed have found a significant link. HEAL highlights that assumptions about retrospective studies being based on speculations, without providing any actual evidence for this, are unfounded underestimations of the work carried out by experienced epidemiologists that use widely accepted study designs and methods.

In a similar vein, the EU assessment report also dismisses all meta-analysis studies that have included those case-studies in their assessment, many of which have unsurprisingly found a significant relation between glyphosate exposure and the incidence risk of non-Hodgkin lymphoma.

2. GENOTOXICITY ASSESSMENT: SHORTCOMINGS IN INDUSTRY-SPONSORED STUDIES

HEAL's review of the EU's renewal assessment report uncovered several shortcomings in relation to its use – or lack thereof – of genotoxicity studies on glyphosate:

- In their contributions to the EU assessment report, industry failed to include two protocol studies based on OECD test guidelines (transgenic rodent mutation and comet assay) to examine further the genotoxic potential of glyphosate in various organs [5]. Evidence from peer-reviewed scientific literature suggests that these assays reveal the potential of glyphosate to cause DNA damage and therefore are key for the assessment.

- Based on a previous assessment by independent genetic toxicology experts, HEAL calculated that out of all industry studies provided by the companies and taken into consideration for the current genotoxicity assessment of glyphosate (about 38 in total), only two can be considered reliable from a methodological point of view [6].

- The assessment report considers almost all peer-reviewed scientific studies on genotoxicity to be mostly unreliable because they deviate from OECD test protocols and, the evidence they provide is completely excluded from the assessment. These studies were not designed to follow OECD protocols and therefore it is unacceptable to exclude them from the overall assessment for this reason.

3. REPRODUCTION: CONCLUSION THAT GLYPHOSATE CAUSES NO TOXICITY TO REPRODUCTION LEAVES OUT AVAILABLE EVIDENCE

According to HEAL's own review on the available peer-reviewed scientific literature on the impact of the active substance glyphosate on male and female reproduction [7], the conclusions of the EU's assessment report that glyphosate does not cause any toxicity to reproduction is not supported by the available scientific evidence.

The summaries of the multi-generational studies submitted by industry mention certain cases where relevant adverse health effects (reduced number of implantations, effects on ovaries or sperm counts, organ weights) were found. However, these were either not reported or were considered unrelated to exposure without adequate scientific justification.

This is a point of concern for HEAL because exposure to glyphosate has been linked to impaired sperm quality in males, a shortened gestational length among spontaneous deliveries in pregnant women, birth of female infants with higher anogenital distance and increased risk of late abortions. Furthermore, scientific literature provides evidence on the underlying mechanisms through which these effects may occur.

4. ENDOCRINE DISRUPTION: INCOMPLETE DATA USED IN ASSESSMENT

Our review of the EU's renewal assessment report uncovered several shortcomings in relation to its use – or lack thereof – of studies on potential endocrine disrupting properties of glyphosate:

- None of the multigenerational studies provided by industry in preparation for the EU assessment report are based on the most up to date sensitive methods available to assess the endocrine disruption (ED) potential of glyphosate. The most recent industry study is a two-generations one

based on a protocol from 2001, which includes only certain ED-relevant endpoints. Some of these seem to be affected by glyphosate (low sperm count in males and larger ovary follicles in females).

- Other animal studies provided by industry are not specifically designed to examine adverse effects following exposures during the sensitive periods of development in life, which are crucial to assessing a substance's ED potential.

- While some of the industry studies observe some ED-related adverse effects, these effects have been repeatedly dismissed in the EU assessment because they do not follow a dose response and because they are not consistent across different generations or across genders. It should be noted that according to the European Chemicals Agency (ECHA) and the Food Safety Authority (EFSA)'s guidance document on the identification of endocrine disruptors, these would not be reasons to dismiss such adverse effects [8].

- Furthermore, public scientific literature indicates that glyphosate may cause adverse effects on male and female reproduction and evidence suggests that these are caused via endocrine-related mechanisms [7]. This type of evidence is not fully taken into consideration in the assessment report and is always dismissed from the conclusions as "inconsistent".

Conclusion

Following our evaluation of the assessment report, HEAL calls upon all EU institutions and Member States in charge of the next steps of the European assessment of the toxicity of glyphosate to scrutinize objectively all the available scientific evidence and endorse the independent literature findings in the assessment, as the latter clearly shows the potential of glyphosate to cause cancer and that it is dangerous for human health [9].

NOTES:

HEAL submitted the following files to the public consultation:

1. [GLY_Reproduction_HEAL] https://www.env-health.org/wp-content/uploads/2022/02/GLY_Reproduction_HEAL.pdf
2. [GLY_Genotoxicity_HEAL] https://www.env-health.org/wp-content/uploads/2022/02/GLY_Genotoxicity_HEAL.pdf
3. [GLY_Epidemiology_HEAL] https://www.env-health.org/wp-content/uploads/2022/02/GLY_Epidemiology_HEAL.pdf
4. [GLY_Endocrine Disruption_HEAL] https://www.env-health.org/wp-content/uploads/2022/02/GLY_Endocrine-Disruption_HEAL.pdf
5. [GLY_Carc Oxic Stress_HEAL] https://www.env-health.org/wp-content/uploads/2022/02/GLY_Carc-Oxid-Stress_HEAL.pdf
6. [Annex R] https://www.env-health.org/wp-content/uploads/2022/02/Annex-R.pdf

REFERENCES:

1. https://www.iarc.who.int/featured-news/media-centre-iarc-news-glyphosate/
2. https://www.iarc.who.int/featured-news/media-centre-iarc-news-glyphosate/
3. See for example: Portier, C.J. A comprehensive analysis of the animal carcinogenicity data for glyphosate from chronic exposure rodent carcinogenicity studies. Environ Health 19, 18 (2020). https://doi.org/10.1186/s12940-020-00574-1 ; Clausing P, Robinson C, Burtscher-Schaden H. Pesticides and public health: an analysis of the regulatory approach to assessing the carcinogenicity of glyphosate in the European Union. J Epidemiol Community Health. 2018;72(8):668-672. doi:10.1136/jech-2017-209776 ; Weisenburger DD. A Review and Update with Perspective of Evidence that the Herbicide Glyphosate (Roundup) is a Cause of Non-Hodgkin Lymphoma. Clin Lymphoma Myeloma Leuk. 2021 Sep;21(9):621-630. doi:10.1016/j.clml.2021.04.009.

4. Weisenburger DD. A Review and Update with Perspective of Evidence that the Herbicide Glyphosate (Roundup) is a Cause of Non-Hodgkin Lymphoma. Clin Lymphoma Myeloma Leuk. 2021 Sep;21(9):621-630. doi:10.1016/j.clml.2021.04.009.
5. The Organisation for Economic Co-operation and Development (OECD) Guidelines for the testing of chemicals are a collection of internationally agreed testing methods used by governments, industry and laboratories to assess the safety of chemicals. They are primarily used in regulatory safety testing and subsequent chemical notification and registration. They form part of the data requirements for the pesticide active substances.
6. https://www.env-health.org/revealed-eu-glyphosate-assessment-was-based-on-flawed-science/
7. See "Annex R": https://www.env-health.org/wp-content/uploads/2022/02/Annex-R.pdf
8. https://www.efsa.europa.eu/en/efsajournal/pub/5311
9. For an overview of HEAL's reports, briefings, letters and contributions to public consultations on glyphosate, visit https://www.env-health.org/campaigns/glyphosate-why-the-eu-needs-to-protect-health-ban-the-popular-weedkiller/

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The Health and Environment Alliance (HEAL) is the leading not-for-profit organisation addressing how the environment affects human health in the European Union (EU) and beyond. HEAL works to shape laws and policies that promote planetary and human health and protect those most affected by pollution, and raise awareness on the benefits of environmental action for health.

HEAL's over 90 member organisations include international, European, national and local groups of health professionals, not-for-profit health insurers, patients, citizens, women, youth, and environmental experts representing over 200 million people across the 53 countries of the WHO European Region.

As an alliance, HEAL brings independent and expert evidence from the health community to EU and global decision-making processes to inspire disease prevention and to promote a toxic-free, low-carbon, fair and healthy future.

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