Committee for Risk Assessment

RAC

Annex 3

Records

of the targeted consultation following the identification of additional documents potentially relevant to the classification of

glyphosate (ISO); *N*-(phosphonomethyl)glycine

EC Number: 213-997-4
CAS Number: 1071-83-6

CLH-O-0000007122-85-01/F

Adopted

30 May 2022

ANNEX 3 – RECORDS OF THE TARGETED CONSULTATION FOLLOWING THE IDENTIFICATION OF ADDITIONAL DOCUMENTS POTENTIALLY RELEVANT TO THE CLASSIFICATION OF GLYPHOSATE (ISO); *N*-(PHOSPHONOMETHYL)GLYCINE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

The proposal for the harmonised classification and labelling (CLH) of Glyphosate (EC 213-997-4; CAS 1071-83-6) was submitted by Sweden and was subject to a consultation, which ended on 22/11/2021.

During opinion development some published articles which are potentially relevant to classification of the substance for Respiratory Sensitisation (opened for comments during this ad hoc consultation), Specific Target Organ Toxicity - Single Exposure (respiratory irritation), Germ Cell Mutagenicity, Carcinogenicity, Reproductive Toxicity and Hazardous to the Aquatic Environment were identified which were not summarised in the CLH report. An ad hoc consultation of these documents was therefore launched. Further documents addressing some of the hazard classes as well as physical hazards were added to the ad hoc consultation.

Comments provided during consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

ECHA accepts no responsibility or liability for the content of this table.

Substance name: glyphosate (ISO); *N*-(phosphonomethyl)glycine
EC number: 213-997-4
CAS number: 1071-83-6
Dossier submitter: Sweden

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
14.04.2022	Belgium	Health and Environment Alliance (HEAL)	International NGO	1
Comment received				
The Health and Environment Alliance welcomes the opportunity to comment on the targeted consultation. We are pleased to see that some of the missing studies we had identified in the first consultation are now included. Below we provide some additional studies that are missing from the assessment, that give further evidence on the potential of glyphosate to cause cancer and reproductive toxicity.				
RAC's response				
Noted.				

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Date	Country	Organisation	Type of Organisation	Comment number
14.04.2022	Poland		Individual	2
Comment received				
I am a chemist and i worked in analytical department where I performed pre-registration studies for plant protect products, active substances and also I analysed pesticide residues in food. I know how difficult is to analyse the content of glyphosate and its metabolites and impurities which are also dangerous. We are not yet aware of the effects of accumulated residues from different products containing the same substance on human health and life. The long-term effects of such exposure are also not well-studied. Due to the significantly different diet of society today compared to that of 20 years ago, great emphasis should be placed on a thorough and factual examination of this substance, and in particular its residues in food, and therefore on reducing the residue limit to a minimum.				
RAC's response				
Comments not related to the hazard classification of glyphosate.				

Date	Country	Organisation	Type of Organisation	Comment number
13.04.2022	Germany		MemberState	3
Comment received				
We noticed that a significant number of references to additional studies of relevance to the human health hazard assessment was made available for ad hoc consultation. However, an adequate assessment of the additional information from 11 epidemiological publications, 2 human biomonitoring reports, 5 papers studying potential effects on the reproductive system, 2 contributions on toxicity to the salivary gland and further publications relevant to animal health or methodological issues, was not possible within the set time limit of two weeks. Notably, a study summary was provided only for Liu et al., 2022b. For most of the studies, only a reference was shared and the full text was not readily available for all of these, partially stored behind a paywall.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.04.2022	France	Générations Futures	National NGO	4
Comment received				
Générations Futures welcomes the opportunity to give comments after the submission of new industrial and public studies. However, the goal of this ad-hoc public consultation is not clear. It is hard to understand the rational for submitting studies in this ad-hoc consultation. Have all new applicant studies been submitted? Indeed, there are still many studies missing in comparison to the list of studies to be generated (p.820/868 of the RAR). Also why the applicant has submitted an assessment of the Liu et al.; 2022 study and not for all other new literature studies? Finally, as for the first public consultation, the delay is very short (too short!) and thus it makes it difficult to answer in a satisfactory way.				

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Ecotoxicity endpoint_Génération Futures.docx
RAC's response
Noted.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
14.04.2022	Belgium	Health and Environment Alliance (HEAL)	International NGO	5

Comment received

In relation to human exposure to glyphosate, the following study should be included in the assessment, which provides further evidence about the underlying problems of the Agricultural Health Study, that lead to the underestimation of the relative risks following exposure to glyphosate. The AHS has several underlying problems and should be excluded from the assessment.

Blair A, Thomas K, Coble J, Sandler DP, Hines CJ, Lynch CF, Knott C, Purdue MP, Zahm SH, Alavanja MC et al: Impact of pesticide exposure misclassification on estimates of relative risks in the Agricultural Health Study. Occupational and environmental medicine 2011, 68(7):537-541.

Further, the carcinogenicity section should consider oxidative stress as the potential underlying mechanism through which glyphosate causes cancer (Gao et al., 2019; Tang et al 2020).
The following study is missing:
Tang, Q. et al. (2020) 'Glyphosate exposure induces inflammatory responses in the small intestine and alters gut microbial composition in rats', Environmental Pollution, 261, p. 114129. doi:10.1016/j.envpol.2020.114129.
For oxidative stress the following study is also relevant and should be included:
Eaton JL, Cathey AL, Fernandez JA, Watkins DJ, Silver MK, Milne GL, Velez-Vega C, Rosario Z, Cordero J, Alshawabkeh A, Meeker JD. The association between urinary glyphosate and aminomethyl phosphonic acid with biomarkers of oxidative stress among pregnant women in the PROTECT birth cohort study. Ecotoxicol Environ Saf. 2022 Mar 15;233:113300. doi: 10.1016/j.ecoenv.2022.113300. Epub 2022 Feb 11.

RAC's response

The study by Eaton et al. (2022) has been included in the RAC opinion under developmental toxicity and under germ cell mutagenicity due to the assessment of an association between oxidative stress biomarkers in the urine of pregnant women and urinary levels of glyphosate and AMPA.
The study by Tang et al. (2020) has been included in the RAC opinion in the sections on STOT RE and germ cell mutagenicity due to the assessment of an association between levels of antioxidative enzymes in different segments of the small intestine in male rats exposed to repeated doses of glyphosate for 35 days.
RAC considers that these two studies do not lead to any changes in the classification proposed by RAC since no adverse effects related to the CLP criteria for a classificaiton for developmental toxicity, STOT RE or germ cell mutagenicity were reported in the studies.

In the study by Blair et al. (2011) the impact of pesticide exposure misclassification on estimates of relative risks in the Agricultural Health Study (AHS) was assessed. RAC

considers that this study is not considered relevant in the RAC opinion for glyphosate. It was noted that the accuracy of reporting of pesticide use by farmers was comparable to that for many other factors commonly assessed by questionnaire for epidemiological studies, so not considered specific for the epidemiological studies for glyphosate. Further, the challenges in the expsoure assessments in epidemiological studies, normally performed by questionnaire or interview, considered related to recall bias and other confounding factors, are disussed in the RAC opinion. In addition, it is noted that even with the reduction in power from exposure misclassification as discussed in the publication, the AHS has identified some statistically significant links between various agricultural exposures and health outcomes.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
14.04.2022	France	Générations Futures	National NGO	6

Comment received

Comments on the publication of Liu J.B et al.; 2022 Glyphosate damages blood-testis barrier via NOX1-triggered oxidative stress in rats: Long-term exposure as a potential risk for male reproductive health and on the document "Literature-Liu_2022_Glyphosatedamagesblood_sum"

The applicant qualified this study as "non relevant". This is totally unacceptable as this study investigates effects of glyphosate on the blood-testis barrier and on sperm quality and quantity in a mammalian test animal. Moreover it gives indications on the possible mode of action. How can it be qualified as non-relevant? It is obviously the way chosen by the applicant to discard a disturbing study to their eyes.
This study must be considered by authorities as relevant and reliable with restrictions. This is not the first study showing such effects on the quality and quantity of sperm resulting from an oxidative stress effect (cf. Abarikwu et al (2015). Even if this study has several limitations, it can't be ignored and must be taken into account in the weight of evidence assessment. A classification in category 2 (at least) should be considered.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Ecotoxicity endpoint_Génération Futures.docx

RAC's response

The study by Liu et al. (2022) is included in the RAC Opinion and is discussed together with the other studies assessing reproductve toxicity following exposure to glyphosate. RAC notes that the results were not reported quantitatively in the Liu et al. (2022) study, and in addition a low number of animals was used in the studies.

Date	Country	Organisation	Type of Organisation	Comment number
14.04.2022	Belgium	Health and Environment Alliance (HEAL)	International NGO	7

Comment received

In relation to the potential of glyphosate to cause oxidative stress and reproduction toxicity, the following study should be included in the assessment:
Eaton JL, Cathey AL, Fernandez JA, Watkins DJ, Silver MK, Milne GL, Velez-Vega C, Rosario Z, Cordero J, Alshawabkeh A, Meeker JD. The association between urinary glyphosate and aminomethyl phosphonic acid with biomarkers of oxidative stress among

pregnant women in the PROTECT birth cohort study. Ecotoxicol Environ Saf. 2022 Mar 15;233:113300. doi: 10.1016/j.ecoenv.2022.113300. Epub 2022 Feb 11.
RAC's response
A short summary of the study has been included in the RAC Opinion together with the other test guideline compliant animal studies on developmental toxicity. RAC considers that the study does not lead to any changes in the proposed classification for developmental toxicity.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
08.04.2022	United Kingdom	Health and Safety Executive	National Authority	8
Comment received				
Please see our comments on the original CLH proposal (PC end: 22/11/2021) regarding the proposed key chronic fish study, the formulation study with Myriophyllum aquaticum, the amphibian data and the surrogate approach with acute oyster toxicity data - which still apply. The new GLP, OECD TG 239 Myriophyllum spicatum study completed in 2022 appears reliable and relevant for hazard classification, filling a data gap for higher aquatic plants with the glyphosate active substance. All 14-day endpoints from this study are above 1 mg/L and would normally therefore lead to no Aquatic Acute or Chronic classification for the substance itself. An academic thesis from 1997 including a study on the toxicity of the glyphosate active substance to Myriophyllum sibiricum has been submitted as additional literature. This non-GLP study was conducted according to an in-house method which was submitted to the American Society for Testing and Materials (ASTM) for inclusion in their Annual Book of ASTM Standards. Existing standard ecotoxicity test guidelines were considered during the development of the test method. Reported 14-day NOEC values based on different 'growth parameters' and the EC50 based on root length for this study with glyphosate were within the 0.1 – 1 mg/L range and would therefore lead to an Aquatic Acute 1 (M=1) and Aquatic Chronic 2 classification if these are considered reliable and relevant. However, these endpoints do not appear to be based on growth rate which is the preferred endpoint for hazard classification. Also, ErC10 endpoints are preferred to NOErCs. We additionally note that test concentrations were not analytically verified. This is important to understand relevant test item concentrations over the 14-day study period with no renewal. Noting the test species was not a standard Myriophyllum species, it is important to consider the performance of the study controls to understand if the study is reliable and relevant for hazard classification. It is currently unclear if the following OECD TG 239 validity criteria (OECD, 2014) were met: "For the test results to be valid, the mean total shoot length and mean total shoot fresh weight in control plants at least double during the exposure phase of the test. In addition, control plants must not show any visual symptoms of chlorosis and should be visibly free from contamination by other organisms such as algae and/or bacterial films on the plants, at the surface of the sediment and in the test medium. The mean coefficient of variation for yield based on measurements of shoot fresh weight (i.e. from test initiation to test termination) in the control cultures does not exceed 35% between replicates."				

While raw control and treatment data to calculate preferred ErCx endpoints and confirm validity of the controls do not seem to be included in the document provided, please can the dossier submitter consider if additional information is available to inform the overall reliability and relevance of the study for hazard classification.

The other newly submitted documents relating to the environmental hazards of glyphosate do not impact the aquatic hazard classification as endpoints are above 1 mg/L.

References:

OECD (2014). OECD Guidelines for the testing of chemicals: TG 239, Water-sediment Myriophyllum spicatum toxicity test. Paris: OECD.

RAC's response

The study by Findeiß M. & Witte A. (2022) was conducted according to OECD TG 239 and in GLP. RAC considers the study reliable, and it has considered together with all other reliable studies to conclude on classification.

The study by Roshon R.D. (1997) is a PhD thesis following the ASTM E1913-97 guideline, currently dismissed, resembling OECD TG 238. The lowest acute value was a EC50 of 0.844 mg/L for root length based on percent reduction in yield. This value cannot be used for the purpose of acute classification, as the endpoint is considered only an additional determination to the main shoot length, according to OECD TG 238. A NOEC of 0.332 mg/L based on growth rate for increase in shoot length has been derived by RAC observing the growth curve graph. In fact, although the raw data were missing, the changes in the logarithms of the mean shoot length divided by the test duration can be calculated. Regarding the analytical control, although monitoring is not performed, glyphosate is proven to be sufficiently stable in water, therefore it is not expected to decrease during the 14-days long test. The validity criteria for OECD TG 238 were fulfilled (the mean total shoot length in control plants doubled before the end of the exposure period; the mean coefficient of variation for total fresh weight in control plants did not exceed 35%). It was proven by results shown in a table reporting the mean measured concentrations and relative standard deviations of all the detected endpoints of the controls.
Despite the shortcomings of the study, RAC has concluded that the study is scientifically robust and reliable and can be used as key information to support the proposed classification.

Date	Country	Organisation	Type of Organisation	Comment number
14.04.2022	Hungary	Pesticide Action Network Europe	International NGO	9

Comment received

Comments in the attached document

ECHA note – An attachment was submitted with the comment above. Refer to public attachment PANEU_ECHA_RAC_Glyphosate.pdf

RAC's response

Noted

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Date	Country	Organisation	Type of Organisation	Comment number
14.04.2022	France	Générations Futures	National NGO	10
Comment received				
The study "MON 77973: A Study on the Toxicity to the Sediment Dweller Chironomus riparius Using Spiked Water according to OECD Guidelines for Testing of Chemicals, Guideline 219 "Sediment-Water Chironomid Toxicity Test Using Spiked Water" is not acceptable. Indeed, the analytical measures performed during the range finding test can't be used for the main test and the concentration of the test substance in the range finding test was not maintained above 80% of the nominal concentration throughout the test. The NOEC based on the nominal concentration (1000 mg a.s/L) is therefore clearly overestimated and must be revised. Please see attached document for more details. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Ecotoxicity endpoint_Génération Futures.docx				
RAC's response				
RAC agrees that analytical measurements from range finding tests cannot be used for the main test, moreover, notes the decline of test item concentration recorded over the exposure period. In fact, after 14 and 28 days at the highest nominal concentration of 1000 mg/L, the glyphosate concentration measured in overlying water dropped to 63% and 54.5% of nominal values, respectively. No analytical determination was performed for pore water and sediments. Further deviations from the test guideline contribute to weaken the reliability of this study including the absence of measurements at concentrations lower than the highest tested treatment (1000 mg/L). Based on the above considerations, the NOEC of 1000 mg/L for emergence ratio and development rate based on nominal glyphosate concentrations is not considered acceptable; thus, the RAC considers the study as not reliable and not relevant for classification purpose.				

PUBLIC ATTACHMENTS
1. Ecotoxicity endpoint_Génération Futures.docx [Please refer to comment No. 4, 6, 10]
2. PANEU_ECHA_RAC_Glyphosate.pdf [Please refer to comment No. 9]