Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level 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 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON GLYPHOSATE (ISO); *N*-(PHOSPHONOMETHYL)GLYCINE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

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.

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Substance name: glyphosate (ISO); *N*-(phosphonomethyl)glycine
EC number: 213-997-4
CAS number: 1071-83-6
Dossier submitter: Sweden on behalf of the Assessment Group on Glyphosate (France, Hungary, Netherlands and Sweden)

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2021	Spain		MemberState	1
Comment received				
Spanish comments on the Renewal Assessment Report (RAR) of glyphosate (AIR V) - EFSA-Q-2020-00140				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2021	Belgium		Individual	2
Comment received				
Not so long ago all experts of the EU and agencies concluded on the basis of an unprecedented toxicological dataset (over 10 chronic/carcinogenicity studies?) that this substances should not be classified as a carcinogen. We welcomed that decision. How is it that this question is again on the table? Is Science never enough? Are there significant new evidence to spend tax payer money to spend time again on this? There is too much politics behind this, and now as a consumer glyphosate is no more available to consumers. All remaining herbicides are based on the same active substance: pelargonic acid, and we are missing effective herbicide. We see public workers handling a gaz cylinder to burn the weeds between pavements, how much CO2 emissions have we generated by banning glyphosate? What about being CO2 neutral by 2050 according to the Green Deal? And we are increasingly dependent on gaz import for energy and heating because we close nuclear power plants. All this doesn't make sense. Could we have politicians taking a holistic approach to this instead of looking in silos and hoping to blur				

EU citizens? Who is financing all these NGOs who never stop shooting at things? Is this money coming from outside Europe? An EU Citizen having children and wanting a better future for Europe and in an intelligent way.
Dossier Submitter's Response
Noted. Not within the scope of the scientific assessment in relation to the proposal for classification.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
24.09.2021	France		Individual	3
Comment received				
From a chemical/eco-toxicology perspective: The demonstrated effect on freshwater ecosystems is a sufficient reason to ban glyphosate. Potential cocktail effects are understudied and could prove more harmful than the current proven toxicity of glyphosate alone. From a socio-economic perspective: Removing glyphosate might require more labour intensive solutions against weeds, which could prove beneficial to the local job market.				
Dossier Submitter's Response				
Noted. Not within the scope of the scientific assessment in relation to the proposal for classification.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Germany	Bund für Umwelt und Naturschutz Deutschland e.V.	National NGO	4
Comment received				
Proposed decision (Vol. 1, Level 2, (No. 1) on pages 862/63) The proposed decision is only readable for authorities. In view of FoE Germany (BUND), due to the multitude of direct and indirect negative effects on biodiversity, no further approval of glyphosate must be granted. Some of these negative impacts might perhaps partly be managed by complex risk mitigation measures, but in practice they would not be respected as past experience has shown. FoE Germany (BUND) contradicts to the conclusions of the assessment report that glyphosate can be applied in agriculture and for other purposes in a safe manner. In the following comment we concentrate on indirect effects and impacts on microbiota. Regarding carcinogenity and genotoxic effects we refer to the comments of Pesticide Action Network Germany. 1. Indirect effects on biodiversity (here: mammals and birds): In Vol.3, B.9 (No.29) on page 395 it is stated by the RMS with regard to indirect effects on birds and mammals that 11 of 21 studies give specific information on glyphosate. A large fraction shows negative effects. The RMS concludes "that evidence for negative effects prevails" and sees that glyphosate may pose a risk for indirect effects on biodiversity. However, other methods of weed control may also cause negative effects.				

But the ease of using Glyphosate, its low price and its particular broad activity on both mono- and dicotyledonous plants made it the most used herbicide globally. Glyphosate like other herbicides does more than just eliminate weeds on agricultural areas farmers want to control. They also cause many wild herbs in the agricultural landscape to disappear. Air-borne transport of glyphosate beyond farmland has been shown to occur; in a recent German study, the substance was found at all sampling sites, even at sites such as national parks and forests far away from agricultural areas (Kruse-Plaß et al. 2021, Pesticides and pesticide-related products in ambient air in Germany. Env Sci Eur, https://enveurope.springeropen.com/articles/10.1186/s12302-021-00553-4). By depletion of the food sources many mammals, birds as well as insects, including pollinators and parasitoids, are eliminated. According to the German Federal Agency for Nature Conservation, the intensive use of highly effective broad-spectrum herbicides such as glyphosate inevitably leads to the impoverishment of plant life and massive impacts on the food web and higher trophic levels (BfN 2018, Auswirkungen von Glyphosat auf die Biodiversität). Many bird species, such as skylarks, yellow buntings, or partridges, but also mammals and other animal species in the agricultural landscape, are significantly deprived of their basic source of nutrition. They often loose both food and shelter. Data on European birds show a continued decline of European farmland birds, in contrast to common forest birds, over the last decades (EBCC 2020, European Indicators. https://pecbms.info/trends-and-indicators/indicators/). From the perspective of FoE Germany (BUND) these severe indirect effects are underestimated in the assessment report and should be given more weight in the overall conclusion.

2. Indirect effects on biodiversity (here: bees and other arthropods)
In Vol. 1, Level 2, (No. 1) on page 718 the RMS discusses the indirect effects on bees: "However; indirect effects following reduction of floral resources that could follow application of herbicides such as glyphosate are not taken into account. RMS considered that reduction of floral resources and its impact on bees is difficult to handle in a risk assessment approach based on local scale (field). It requires tools that allow assessment on landscape level…". Acknowledging the problem we firmly contradict this conclusion. Application of glyphosate strongly affects the biodiversity in agricultural landscapes. Wild bees which are equally important pollinators (FiBL 2016, Wild bees and pollination. https://www.fibl.org/fileadmin/documents/shop/1645-wild-bees.pdf Sutter et al. 2021, Bestäubung von Kulturpflanzen durch Wild- und Honigbienen in der Schweiz. https://www.agrarforschungschweiz.ch/2021/09/mit-optimaler-bestaeubung-zu-mehr-kirschen-und-groesseren-aepfeln/#download) are endangered at least to the same extent as honey bees, as they are not cared for by beekeepers or moved away to other places. We do not see effective risk mitigation measures. Therefore, phasing out glyphosate application will be the only solution to save biodiversity.
The effects on arthropods other than bees is intensively discussed on pages 719-722. It is difficult to differentiate between direct and indirect effects of glyphosate and effects of the agricultural practice which is associated with the application of glyphosate. In any case, as there is ample evidence that insect biomass, abundance and diversity has been reduced significantly within the last decades (Hallmann et al. 2017, More than 75 percent decline over 27 years in total flying insect biomass in protected areas. PLOS ONE https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0185809. EEA 2019, Common birds and butterflies – Briefing. https://www.eea.europa.eu/airs/2018/natural-capital/common-birds-and-butterflies) and as glyphosate is the most used herbicide, the evidence that glyphosate may play a negative role is sufficiently robust aiming at a strong restriction of glyphosate applications as a matter of precaution.

3. Direct impacts on non-target organisms
- Direct effects on non-target organisms such as insects have also to be taken into

account. Bees, for instance, will take up glyphosate and carry it into the hive, as shown by glyphosate residues in honey. The high residue levels found for honey (page 550 - 2.7.8.1 Effect on the residue level in pollen and bee products) lead the RMS to the conclusion that the existing MRL of 0.05 mg/kg honey needs to be raised more than tenfold to at least 0.6 mg/kg, if not to 20 mg/kg – to accommodate the intended uses.
- From this it can be derived that insects are exposed to glyphosate to a considerable extent and toxic effects on them are expected. For instance, melanin production can be inhibited which could, as melanin is important in pathogen tolerance, render insects more susceptible to microbial pathogens (Smith et al. 2021, Glyphosate inhibits melanization and increases susceptibility to infection in insects. PLOS Biology https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.3001182).

4. Impacts on microbiota
- The mode of action of glyphosate is to block 5-enolpyrovylshikimate-3-phosphate-synthase (EPSPS) which plays a central role in the synthesis of aromatic amino acids and other important substances via a metabolic pathway known as the shikimate pathway. Also, microorganisms exhibit EPSPS and the shikimate pathway. However, microorganisms have two different forms of the EPSPS enzyme, one sensitive to glyphosate and one that is tolerant to it. Therefore, depending on which form they possess, microorganisms react insensitively or sensitively to glyphosate. Thus, the application of glyphosate alters the activity and composition of microbial communities. The assessment report concedes that glyphosate is not readily degraded in soil (pages 560-564 – 2.8.1 Fate and behaviour in soil). For this reason, soil organisms including microorganisms will be exposed to the substance for several months. In fact, glyphosate may persist in soil for even more than a year after application (Laitinen et al. 2009, Glyphosate and phosphorus leaching and residues in boreal sandy soil. Plant Soil 323:267–283. https://doi.org/10.1007/s11104-009-9935-y). In European soils, glyphosate was among the most frequently found pesticide compounds and compounds at the highest concentrations and glyphosate and its metabolite AMPA contributed the most to the total pesticide content in soils (Silva et al. 2019, Pesticide residues in European agricultural soils – A hidden reality unfolded. Sci Total Env 653 1532–1545, https://www.sciencedirect.com/science/article/pii/S0048969718343420?via%3Dihub).
- There is overwhelming literature on the fact that glyphosate is affecting the composition of microbiomes not only in the soil microflora but also in the intestines of mammals and insects such as bees. The biodiversity not only of the microorganisms but also of higher organisms living in the agricultural landscape is therefore endangered. The assessment report of the RMS mostly neglects this detrimental effect. As far as we could see only the publication of Motta et al. (2018) (Motta et al. 2018, Glyphosate perturbs the gut microbiota of honey bees; PNAS https://www.pnas.org/content/115/41/10305) is reviewed. (Vol. 3, B.9 (No. 30) page 68). The authors conclude: "Since bee gut symbionts affect bee development, nutrition and defence against natural enemies, perturbation of these gut communities may be a factor making bees more susceptible to environmental stressors including poor nutrition and pathogens." However it is finally concluded that "suitable scientific approaches to assess (these) effects are not specified, thus relevance of the effects remained unclear. … The findings are not relatable to the EU level risk assessment …".
- New data collected under laboratory and field conditions show that glyphosate affected the abundance of beneficial bacteria in the bee gut in a dose-dependent way and that bees from exposed hives exhibited increased mortality compared with bees from control hives (Motta et al. 2020:Impact of Glyphosate on the Honey Bee Gut Microbiota: Effects of Intensity, Duration and Timing of Exposure, mSystems.00268-20.pdf (nih.gov)).
- With respect to the publications mentioned below we urgently demand an assessment of the effects of glyphosate on microbiomes and their consequences for animal and plant

health and biodiversity:
a) Gut microbiome of mammals and birds:
- Mesnage R. et al. (2019): Shotgun metagenomics and metabolomics reveal glyphosate alters the gut microbiome of Sprague-Dawley rats by inhibiting the shikimate pathway, bioRxiv, 1-36, https://www.biorxiv.org/content/10.1101/870105v1
- Mesnage R. et al. (2021): Use of Shotgun Metagenomics and Metabolomics to Evaluate the Impact of Glyphosate or Roundup MON 52276 on the Gut Microbiota and Serum Metabolome of Sprague-Dawley Rats, Environ. Health Persp., 1-27, https://www.x-mol.com/paper/1354521735587045376
- Syromiatnikov M.Y. et al. (2020): The Effect of Pesticides on the Microbiome of Animals, Agriculture, 10, 79; https://www.mdpi.com/2077-0472/10/3/79
- Ruuskanen et al. 2020, Glyphosate-based herbicides influence antioxidants, reproductive hormones and gut microbiome but not reproduction: A long-term experiment in an avian model. Env Poll https://www.sciencedirect.com/science/article/pii/S026974912032537 9?via%3Dihub
b) Gut microbiome of invertebrates:
- Owagboriaje et al. (2021): Impacts of a glyphosate-based herbicide on the gut microbiome of three earthworm species (Alma millsoni, Eudrilus eugeniae and Libyodrilus violaceus): a pilot study. Toxicol Rep https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8027525/
- Motta et al. 2020: Oral or topical exposure to glyphosate in herbicide formulation impacts the gut microbiota and survival rates of honey bees. Appl Env Microbiol 86/18, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7480383/pdf/AEM.01150-20.pdf .
c) Impacts on soil microbiota including shifts in community composition:
- Meena R.S. et.al. (2020): Impact of Agrochemicals on Soil Microbiota and Management: A Review, Land, 9, 34; https://www.mdpi.com/2073-445X/9/2/34
- Van Bruggen et al. (2020): Impacts of Genetically Engineered Crops on the Soil Microbiome, Biological Processes, and Ecosystem Services, https://www.researchgate.net/publication/348159632_Impacts_of_Genetically_Engineered_Crops_on_the_Soil_Microbiome_Biological_Processes_and_Ecosystem_Services.
- Van Bruggen et al. (2018), "Environmental and health effects of the herbicide glyphosate", Sci Total Env https://pubmed.ncbi.nlm.nih.gov/29117584/
d) Root mycorrhization, fungal diseases and other effects:
- Zaller et al. (2018)., Herbicides in vineyards reduce grapevine root mycorrhization and alter soil microorganisms and the nutrient composition in grapevine roots, leaves, xylem sap and grape juice, Env Sci Poll Res, 2018, https://doi.org/10.1007/s11356-018-2422-3
- Martinez et al. (2018), Impacts of glyphosate-based herbicides on disease resistance and health of crops: a review, https://link.springer.com/article/10.1186/s12302-018-0131-7
- Kremer & Means (2009): Glyphosate and glyphosate-resistant crop interactions with rhizosphere microorganisms, https://pubag.nal.usda.gov/download/35795/PDF

ECHA note – An attachment was submitted with the comment above. Refer to public attachment FoE Background on Glyphosate.pdf

Dossier Submitter's Response

Noted.
The information provided on biodiversity, bees, insects and other terrestrial organisms and effects on microbiota are not in the scope of the scientific assessment related to the criteria for classification.
Regarding persistence in the environment, this is covered by the proposal for classification 'Aquatic Chronic 2'.

The comment will also be considered in EFSA's process (comment 5(18) of EFSA Reporting Table comment from public), which has a wider scope.
RAC's response
Noted. RAC agrees with the DS response.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	United Kingdom		Individual	5

Comment received

There has been a failure to recognize that ingested glyphosate is incorporated into proteins, demonstrated by Sleight and Macek's 1973 study " Exposure of fish to 14C-Roundup (1), accumulation, distribution, and elimination of 14C residues. This study made for Monsanto was apparently not made available to EU regulators who were provided with two substitute studies by Monsanto namely Macek & Sleight 1989 and Ridley and Chott 1989 which were examined together in 2017 relicensing at Glyphosate B.9.2.1.3. Unlike EU regulators the USA EPA chemist concluded in regard to these two studies "A significant portion of total sample radioactivity was found to be incorporated into proteins" (USA EPA data evaluation record study7 Chem 103501 - this is avail in pdf format at ECHA .
I have made the point to EFSA, unanswered at this time that ingested glyphosate residues could be expected to adversely affect the human immune system and could therefore be a major factor as to why so many people die from COVID-19. ECDC data for week 42 showed for example that Germany having had 4,463,052 cases of COVID-19 and 94,627 deaths, i,e, one death in 47.2 cases: whilst Bhutan, a country that has eschewed glyphosate, 2617 cases, and 3 deaths, i.e. one death in 872.3. Is this just a coincidence, or an indication of the terrible harm that ingested glyphosate residues is largely responsible for?

Dossier Submitter's Response

Thanks for the comment. Regarding the point on bioaccumulation, the study of Sleight and Macek's 1973 study " Exposure of fish to 14C-Roundup (1), accumulation, distribution, and elimination of 14C residues" was indeed not available to RMS/Dossier Submitter. In the previous assessment report (2015), other studies were considered in the assessment by former RMS who stated : "*several studies (Ridley et al., Rep. MSL9309, 1989, Purdum et al., Rep. MSL 2952, 1983; McAllister et al., Rep. MSL 5019, 1985, Purdum et al., Rep. MSL 2937, 1983) on different aquatic organisms, a bioconcentration factors of max. 10 was determined*". Thus in view of the data already available on bioaccumulation in fish and as Glyphosate acid has a log P lower than < -3.2, the potential for bioconcentration is considered to be negligible.
We do not expect that the study of Sleight and Macek's 1973 will change the conclusion that glyphosate is not expected to bioaccumulate in fish. However the study was requested from the applicant (EFSA reporting table 06, comment 5(189)).

With respect to the comment regarding the immune system, please note that classification and labelling is based on a comparison of effects clearly observed in studies with high reliability and the criteria stated in the legislation. The methodology used and results obtained must be clearly documented and a relation to treatment with the substance must be clearly demonstrated. The potential effects of glyphosate on the immune system has been investigated in mice (section 2.6.8.2) and some parameters and organs of the immune system are routinely investigated in the studies discussed in the sections for hazard classes STOT-RE and carcinogenicity. In the absence of any robust data demonstrating an effect of glyphosate on the immune system, and any link between

exposure to glyphosate and COVID-19 infection, this cannot be considered for classification and labelling.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Belgium	Health and Environment Alliance (HEAL)	International NGO	6
Comment received				
Health and Environment Alliance disagrees with the proposed classification of glyphosate and considered that glyphosate should be classified as Carcinogen Category 1B and Reprotoxic (at least Category 2). Comments are provided in parts ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment HEAL_Public consultation Glyphosate ECHA.zip				
Dossier Submitter's Response				
See response to HEAL's specific comments no 24, 27, 56 and 90.				
RAC's response				
Noted. See response to comments no 24, 27, 56 and 90.				

Date	Country	Organisation	Type of Organisation	Comment number
05.11.2021	Norway		Individual	7
Comment received				
It is well known that glyphosate may cause cancer in humans and should be banned from the market completely. It is also documented to cause harm to bees and other pollinators and the natural ecosystem. In these times it is important to protect life. Speaking for tens of thousands of health customers in Norway we all agree that glyphosate must be banned.				
Dossier Submitter's Response				
Noted. Not within the scope of the scientific assessment in relation to the proposal for classification. No scientific data provided to support the statement regarding carcinogenicity.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	France	Générations Futures	National NGO	8
Comment received				
Générations Futures maked the count of the percentage of the public literature studies taken into account in the RAR/CLH report of glyphosate. The results, detailed in a report (https://www.generations-futures.fr/wp-content/uploads/2021/11/evaluation-du-glyphosate-un-rapport-biaise-v4.pdf) are the followings: For the toxicity endpoints, on the 1550 public studies found in the search: - 76.9% (1192) are considered as non relevant - 5% (79) are considered as relevant and providing data for establishing or refining risk assessment parameters (category A)				

- 4% (63) are considered as relevant, classified in category A and reliable with restrictions
- 0.7% (11) are considered as relevant, classified in category A and reliable without restriction

In other words, about 95% of the public toxicity studies on glyphosate are deemed non relevant, not useful for the assessment or not reliable.

If we consider the whole toxicity and ecotoxicity studies and the studies used for the ED assessment, only 0.4% (30) of the total number of studies found in the literature search (7188) are considered as relevant and reliable without restriction.

In consequence, the public literature had no weight in the whole studies weight of evidence assessment.

These numbers are facts and raise many questions. Is it normal that the differences between academic science and regulatory science being so huge? What is the purpose of the academic science and knowledge if it can't be applied? Are the OECD compliant studies the only ones who can be used for regulatory purpose?

Beyond these figures, Générations Futures also have specific comments and questions regarding the document "Glyphosate_RAR_14_Volume_3CA_B6.7 - B6.10_2021-08-10", section B.6.10.1 Literature search. These comments are detailed in the attached document named "Comments of Générations Futures on the literature search and genotoxicity endpoint". In this document, many flaws regarding the rapid and detailed assessment and the reliability assessment are described in details and using references to EFSA and ECHA guidelines.

Considering all the flaws described in the attached document regarding the selection of relevant studies and the lack of transparency of the reliability assessment of the studies, Générations Futures considers that the legal requirements regarding the literature search (article 8.5 of the Regulation 1107/2009) are not met.
No decision regarding the classification of glyphosate and its renewal can be made without taking into account all the actual relevant available studies.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments of Générations Futures on the litterature search and genotoxicity endpoint.pdf

Dossier Submitter's Response

The concern is noted.
The DS made a thorough evaluation of the submitted literature search. For >300 published articles, either a study summary or a study summary and the full-text article was requested at an early stage of the evaluation. It should also be noted that such requests have been made for additional ca 200 studies in Volume 1 of the draft RAR/CLH report, at the final stage of the evaluation. Several data requirements on literature data following comments received have also been proposed. The outcome of the analysis of the literature data may therefore change.

Please also note that criteria for relevance in the EFSA GD (2011) are related to the specific data requirements for active substances and plant protection products. Hence, that a study has been categorised as "not relevant" does not mean that the study is not relevant *per se*, but that it may not be relevant in the specific context of hazard and risk assessment under the Regulation (EC) No 1107/2009 and Regulation (EC) No 1272/2008.

Many scientific experiments published in the peer-reviewed literature are designed to address specific questions of academic interest, and thus may not necessarily be performed nor reported with the aim of being used for the assessments under these regulations. The DS (RMS) intends to clarify the assessment of relevance and reliability of literature data. Studies on formulations presents a specific problem. The decision on classification and labelling is based on whether or not available data indicate that the intrinsic properties of a substance fulfils criteria for classification in Regulation (EC) No 1272/2008. Such assessment is primarily based on relevant and reliable information on the substance since any impact of co-formulants in a formulation must be unequivocally excluded if data on formulations are used. Finally, it is noted that for this specific substance extensively more studies are available in the public literature compared to any other pesticidal active substance. Therefore, it is difficult to make a comparison regarding the amount of studies from the public domain compared to the studies submitted by the applicant. All studies, public literature and studies submitted by the applicant, were assessed for their relevance and reliability, using EU agreed assessment points for this. As public literature studies often miss essential information, the reliability and quality of these studies tends to be lower compared to those implementing international standards guaranteed by Good Laboratory Practices and OECD Test Guidelines, and to which applicants are required to comply with according to EU regulation. For specific comments regarding the attachment on genotox, see comment 57.
RAC's response
Noted. See also response to comment no 57.

Date	Country	Organisation	Type of Organisation	Comment number
01.11.2021	Germany	Reckert Landwirtschaft	Company-Manufacturer	9
Comment received				
Der Einsatz von Glyphosat bewirkt in derLandwirtschaft eine Verringerung der Bodenerosion, da durch den Wirkstoff Mulchsaatverfahren ermöglicht werden. Die CO2 Emissionen verringern sich durch eine verringerte Bodenbearbeitung.Dadurch wird auch die Umwandlung zu Nitrat verlangsamt und Bodenlebewesen werden geschont.Die Pflanzenschutzbehörden von Frankreich ,Niederlande, Schweden und Ungarn bewerten die gesundheitlichen Gefahren durch Glyphosat als gering.				
Dossier Submitter's Response				
Noted. Not within the scope of the scientific assessment in relation to the proposal for classification.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
24.09.2021	France		Individual	10
Comment received				

The use of hazardous substances must be prohibited everywhere and forever. We mustn't put in danger our safety and the one of futures generations.
Dossier Submitter's Response
Noted. Not within the scope of the scientific assessment in relation to the proposal for classification.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Belgium	EFFAT - European Federation of Food, Agriculture and Tourism Trade Unions	Industry or trade association	11

Comment received

EFFAT is the European Federation of Trade Unions in the Food, Agriculture, and Tourism sectors and allied branches. EFFAT represents the interests of 25 million workers in the Food, Agriculture, Tourism, and Domestic Work sectors as well as other related sectors, services, and activities in Europe. EFFAT is glad to contribute the ECHA's consultation on glyphosate. EFFAT's top priority is the protection of farm workers' health and safety, as well as job security.
EFFAT calls for the immediate ban on glyphosate as an active substance in herbicide products in the renewal process which is expected to end in 2022.
EFFAT's demand for a ban is driven by the existing evidence of the carcinogenicity of glyphosate in animal studies and the compelling link between exposure to glyphosate-based herbicides and increased risk for non-Hodgkin lymphoma in human epidemiological studies.
EFFAT is therefore of the opinion that glyphosate (CAS 1071-83-6) meets at the minimum the criteria for classification as a carcinogen category 1B according to the CLP regulation (EC) No 1272/2008.
The US litigations on glyphosate and the Monsanto papers(*) have brought to light how Monsanto manipulated the scientific debate and misled the public over glyphosate's dangers. In the views of EFFAT, RAC/ECHA assessment of the harmonised classification of glyphosate should give priority to published, peer-reviewed and independent studies and disregard all the data provided by this manufacturer that are known to be biased.
(*)https://www.baumhedlundlaw.com/toxic-tort-law/monsanto-roundup-lawsuit/monsanto-secret-documents/

ECHA note – An attachment was submitted with the comment above. Refer to public attachment EFFAT Position Paper - Ending the use of glyphosate and building a more sustainable agriculture EN.pdf

Dossier Submitter's Response

We take note of your expert review. Please note that the hazard and risk assessment for the current dossier on glyphosate was conducted according to the criteria laid down in Regulation (EC) No 1272/2008 and Regulations (EC) No 1107/2009 and (EU) No 283/2013 which are harmonised within the EU. Based on this risk assessment, no unacceptable risks following dietary and non-dietary exposure were identified.

Considering carcinogenicity, see comment number 30 of this RCOM.

On page 3, it is stated that "a recent study has proven glyphosate acts as an endocrine disruptor in the case of exposure" with reference to a publication by Lesseur et al. (2021). This publication presents interesting results indicating a link between glyphosate exposure and anogenital distance in newborns. In female infants, high maternal urinary glyphosate (above the median) was associated with longer AGD-AC but this was not significant after covariate adjustment. Increased AMPA was associated with longer AGD-AF after adjusting for infant size and age at AGD examination. There were no associations detected in male offspring. It should be noted, as also recognized by the study authors as one of the

limitations of the study[1], that it is not possible to exclude that effects could also result from coformulants as the urinary analysis inly included glyphosate and AMPA. Therefore, the relevance for classification and labelling is unclear since classification and labelling is based on a comparison of the data on intrinsic properties of the active substance with the criteria in CLP and any effects of co-formulants must be excluded.

[1] *"Nevertheless, exposure to pure glyphosate is unlikely, since this is applied to crops in GBH formulations that contain other "inert" ingredients not listed on the commercial product. Thus, comprehensive quantification of GBH additives is not possible and we used urinary glyphosate and AMPA as biomarkers of exposure. The effects of formulation of GBHs should also be addressed in future studies."*

Manservisi et al. (2019) performed a pilot study in Sprague-Dawley rats (8/group) for an extended-one generation study (OECD 443). In this study the F0 female breeders received the test item from gestation day (GD) 6 to the end of lactation, while the offspring (F1) continued to be exposed after weaning for an additional 6 or 13 weeks. The test item, glyphosate (G) (> 99.5% pure), was diluted in drinking water to achieve glyphosate dose of 1.75 mg/kg bw/day (the US Acceptable Daily Intake). The endpoints analysed in the study were body weight, water and food consumption, gestational parameters, litter parameters, landmarks of sexual development, estrous cyclicity, gross and histopathology of reproductive and endocrine tissues, sperm parameters and serum and plasma hormone levels. Reproductive parameters remained to be unaffected by glyphosate exposure at 1.75 mg/kg bw/day. The anogenital distance (AGD) on PND 4 was statistically significantly increased in males. Furthermore, increased TSH level in plasma was reported in male animals at this dose level. This publication was considered restricted (low number of test animals and uncertainties with regard to timing of blood sample collection).

RAC's response

Noted. The study by Lessure et al. (2021) is included by RAC in the assessment for the classification of glyphosate for reproductive toxicity taking into account that the exposure was to glyphosate based herbicies.

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2021	Switzerland		Individual	12

Comment received

Some of the analyses presented in this comment were conducted to develop expert opinions for court cases and were supported by funding from attorneys involved in these litigations. Some of the text in this comment are duplicative of written expert testimony by the author for these court cases. These funders had no role in the in developing or presenting this comment.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments.zip

Dossier Submitter's Response

Please see response to comment number 31.

RAC's response

Noted. See response to comment no 31.

Date	Country	Organisation	Type of Organisation	Comment number
21.10.2021	Germany		Individual	13
Comment received				
Der Wirkstoff Glyphosat ist auf EU-Ebene aktuell noch bis 12.12.2022 zugelassen. Im Rahmen der ,,Prüfung der Zulassungsverlängerung`` erhielten die Mitgliedsländer Frankreich, Niederlande, Schweden und Ungarn den Auftrag den Wirkstoff Glyphosat wissenschaftlich zu bewerten. Im Berichtsentwurf (seit 15.06.2021 öffentlich) kommen die Wissenschaftler und Pflanzenschutzbehörden der vier Länder zu folgender Einschätzung: ...siehe Antworten auf untenstehende Fragen! Damit erfüllt Glyphosat alle Voraussetzungen, um auch in der EU weiterhin als Wirkstoff für Pflanzenschutzmittel zugelassen werden zu können. Insgesamt kommen die Bewertungsbehörden der vier Länder einstimmig zu dem Fazit, dass in allen zur erneuten Zulassung beatragten Indikationen (Einsatzgebieten) eine sichere Anwendung glyphosathaltiger Produkte möglich ist!!!				
Dossier Submitter's Response				
Noted. Not within the scope of the scientific assessment in relation to the proposal for classification.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.10.2021	Germany		Individual	14
Comment received				
Glyphosate is obviously not improving human health, but if applied correctly and under the conditions, originally foreseen (as pre-emergence total herbicide on non erodible soils with notill and mulch cover) it does not enter into the aquatic bodies or foodchain and is as such probably one of the most ecological herbicide active ingredients. Gyphosate must therefore never be used on a growing crop, neither for weed control on glyphosate resistant crops, nor as desiccant to assist with harvest. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Literatur.7z				
Dossier Submitter's Response				
Noted. The attachments do not provide data within the scope of the scientific assessment in relation to the proposal for classification.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.10.2021	Germany		Individual	15
Comment received				
a				
Dossier Submitter's Response				
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RAC's response				

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Date	Country	Organisation	Type of Organisation	Comment number
18.10.2021	Germany	<confidential>	Company-Downstream user	16

Comment received

Die Pflanzenschutzbehörden der Mitgliedsländer Frankreich, Niederlande, Schweden und Ungarn bewerten den Wirkstoff Glyphosat wissenschaftlich. Diese kommen zu dem Schluss , dass Glyphosat nicht krebserregend, unschädlich für das Erbgut, nicht reproduktionstoxisch, nicht organschädigend und für den Hormonhaushalt nicht gefährlich ist. Außerdem trägt der Wirkstoff Glyphosat dazu bei Klimaziele durch eine Vermeidung von unnötiger Bodenbewegeng durch alternative Verfahren und damit unnötigen CO2-Ausstoß zu erreichen. Zusätzlich wird durch eine Vermeidung von Bodenbewegung das Bodenleben gefördert, Erosionsgefahr gemindert und weniger Nährstoffe ausgewaschen. Daher sind wir der Ansicht, dass Glyphosat alle Voraussetzungen erfüllt, um in der EU weiterhin als Wirkstoff für Pflanzenschutzmittel zugelassen werden zu können. Insgesamt kommen die Behörden der oben genannten vie länder zu dem Fazit, dass in allen zu erneuten Zulassung beantrakten Indikationen eine sichere Anwendung glyphosathaltiger Produkte möglich ist.

Dossier Submitter's Response

Noted. Not within the scope of the scientific assessment in relation to the proposal for classification.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Germany	Glyphosate Renewal Group	Company-Manufacturer	17

Comment received

The applicant, the Glyphosate Renewal Group (GRG), would like to emphasize the necessity of a bidirectional exchange of information between all relevant stakeholders of the active substance / plant protection product (PPP) process and the CLH process, in order to ensure that any evaluation is based on the latest available and most complete data set (see section "Comments on CLH process" of this webform: "If the substance is an active ingredient in a plant protection product (PPP) or biocidal product (BP), comments submitted in this consultation may be used in the PPP/BP processes, and, comments received for the PPP/BP processes may be used in the CLH process.").
The applicant therefore assumes that any comments and supporting information submitted to EFSA in the public consultation phase and thereafter during the stop-of-clock will be made available by EFSA to ECHA and are as well taken into account in the CLH process by ECHA.
The applicant will provide copies of the information referenced above to ECHA in case access will not be provided by EFSA. This relates to all hazard classes open for commenting.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Glyphosate_Supporting documents_public.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Glyphosate_Supporting documents_confidential.zip

Dossier Submitter's Response
Noted. For consideration of ECHA and EFSA.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
18.11.2021	France	Inserm - French National Institute of Health and Medical Research	Academic institution	18

Comment received

In response to a request by five Directorates General of the French government, the French National Institute of Health and Medical Research (Inserm) recently conducted a collective expert review of the open scientific literature on the effects of glyphosate on human health.

Inserm has made available an English translation of the chapter on glyphosate, originally published in June 2021 as part of a broader review examining the effects of pesticides on human health. Comments are provided here only for certain sections where the conclusions of the RAR and the Inserm collective expert review diverge and interested parties are invited to consult the accompanying document and the websites below for further information.

Glyphosate and glyphosate-based herbicides. Extract from "Pesticides and health effects: new data": https://www.inserm.fr/expertise-collective/pesticides-et-sante-nouvelles-donnees-2021/

English executive summary: https://www.inserm.fr/wp-content/uploads/inserm-collective-expert-report-pesticides2021-executive-summary.pdf

Complete report in French (1009 pages): https://www.inserm.fr/wp-content/uploads/2021-07/inserm-expertisecollective-pesticides2021-rapportcomplet-0.pdf

Inserm. Pesticides et effets sur la santé: Nouvelles données. Collection Expertise collective. Montrouge: EDP Sciences, 2021

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Inserm EC pesticides 2021_glyphosate_EN_18112021.pdf

Dossier Submitter's Response

Thank you, we take note of your expert review.
The decision on classification and labelling is based on whether or not available data indicate that the intrinsic properties of a substance fulfills criteria for classification in Regulation (EC) No 1272/2008. Such assessment is primarily based on relevant and reliable information on the substance since any impact of co-formulants in a formulation must be unequivocally excluded if such data is used.
Moreover, since classification and labelling is based on the intrinsic properties of a substance, real exposure situations and exposure levels are less relevant for this type of assessment.

Please also note that the risk assessment for the current dossier on glyphosate was conducted according to the criteria laid down in Regulation (EC) No 1107/2009 and (EU)

No 283/2013 which are harmonised within the EU. Based on this risk assessment, no unacceptable risks following dietary and non-dietary exposure were identified.

For specific comments regarding human toxicity, the DS refers to the response to comment 39, 68, 104, 206 and 229.

The FR public monitoring data for environmental compartments mentioned in the Inserm report were already collected and analysed by the applicant in the reports of Multsch 2020 and Hughes 2020 for a larger period (up to 2019). These reports were assessed by the DS (RMS) in the RAR (Vol. 3 CA B.8.5). For air compartment, the publication mentioned in the Inserm report (Ravier et al. 2019) was also considered in the RAR (Vol. 3 CA B.8.5).

RAC's response

Noted. See response to comment no 39, 68, 104, 206 and 229.

Date	Country	Organisation	Type of Organisation	Comment number
18.11.2021	Germany	Landwirtschaftskammer Nordrhein Westfalen	Regional or local authority	19

Comment received

Das drohende Verbot von Glyphosat betrachten wir mit Sorge. In unserer Region wird Glyphosat z.B. gerne vor der Erneuerung von Dauergrünland zum Abtöten der alten Grasnarbe genutzt. Wenn im Dauergrünland Problemunkräuter vorhanden sind (z.B. Quecke) hat man keine mechanischen Alternativen, um diese Wurzelunkräutern sicher zu beseitigen. Auf Ackerland hingegen ist Glyphosat zurzeit noch zugelassen, wenn dort "perennierende Unkräuter" wie z.B. Quecke in einem bekämpfungswürdigen Umfang auftreten. Wo bleibt hier die Logik? In logischer Konsequenz werden die Grasnarben in Zukunft untergepflügt werden müssen. Gerade bei Dauergrünland setzt aber der Umbruch der Grasnarbe erhebliche Mengen Nitrat frei, die das Grundwasser belasten können. In Zusammenarbeit mit der unteren Naturschutzbehörde (Deutschland) haben wir daher Begrenzungen der Düngermenge in den ersten 4 Jahren nach einem Grünlandumbruch festgesetzt. Wenn nun die Grasnarbe in Zukunft mit dem Pflug gebrochen wird, dann ist die Gefahr der Auswaschung von Nitrat noch größer als bisher.
Durch den Verzicht auf Glyphosat wird es in Zukunft zu einer verstärkten Nutzung anderer, selektiver Herbizide kommen. Ob diese in jedem Fall umweltfreundlicher sind als Glyphosat, wage ich anzuzweifeln.
Bei der Bekämpfung von Problemunkräutern, wie z.B. Ackerfuchsschwanz, wird es in Zukunft zu erheblichen Problemen kommen. Da bereits viele Resistenzen gegenüber selektiven Herbiziden bekannt sind, gab es bisher mit Glyphosat immer noch die Möglichkeit in einer Vorsaatbehandlung (Scheinsaatbett) den Ackerfuchsschwanz in großer Anzahl zu bekämpfen.
Der Wegfall von Glyphosat würde bedeuten, dass auch deutlich weniger Fläche ohne Pflugeinsatz beackert wird. Mulch- und Direktsaat sind auf den Wirkstoff Glyphosat angewiesen und haben erwiesenermaßen sehr viele Vorteile für die Vermeidung von Erosion, für die Förderung des Bodenlebens und für die Speicherung von CO^2. Damit einhergehend wird es auch dazu kommen, dass Humus, der über lange Zeiträume durch Mulchsaat bzw. Direktsaat aufgebaut wurde, wieder durch vermehrte Bodenbearbeitung abgebaut wird.
Das gerne genutzte Argument, dass Glyphosat die Biodiversität schädigt, ist in meinen Augen absolut nicht haltbar. Glyphosat ist ausschließlich für die Nutzung auf landwirtschaftlichen Nutzflächen zugelassen. Darüber hinaus darf es nicht angewendet werden von Landwirten. Glyphosat beseitigt Beikräuter/Gräser nur dort wo es eingesetzt

wurde und nicht irgendwo anders. Ob diese unerwünschten Beikräuter/Gräser nun mit Glyphosat beseitigt werden, ob der Landwirt diese dann nachträglich mit selektiven Herbiziden beseitigt oder ob die Pflanzen mechanisch oder von Hand entfernt werden, hat auf die Biodiversität immer genau denselben Effekt. Das Unkraut ist weg. Auch ökologisch wirtschaftende Betriebe wollen ihre Acker- und Grünlandflächen "sauber" haben und beeinträchtigen die Biodiversität damit in genau demselben Umfang wie es die konventionell wirtschaftenden Kollegen mit den chemisch-synthetischen Pflanzenschutzmitteln tun.
Dossier Submitter's Response
Noted. Not within the scope of the scientific assessment in relation to the proposal for classification.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
18.11.2021	Germany		MemberState	20
Comment received				
The published proposal corresponds to the current harmonised classification. It is transparently described that a previous proposal for additional classification for STOT RE based on maternal toxicity in rabbit developmental studies (DE, 2016) was not considered as justified by RAC. 1.3.8.3, Relevant impurities As in the LoEP and the current legislation, the maximum contents of formaldehyde and N-nitrosoglyphosate should be less than 1 g/kg and 1 mg/kg, respectively.				
Dossier Submitter's Response				
Thank you, noted. 1.3.8.3 Relevant impurities: Agree, the maximum content of formaldehyde is strictly less than 1 g/kg and the maximum content of N-nitrosoglyphosate is strictly less than 1 mg/kg.				
RAC's response				
Noted.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
15.10.2021	United States of America		Individual	21
Comment received				
The conclusions of the CLH report regarding the carcinogenic potential of glyphosate are clearly supported by the scientific evidence. I have concerns, however, about the use of one-sided significance levels (exclusively in the direction of a positive association) to summarize the results of the glyphosate rodent studies. The discussion of one-sided versus two-sided tests on page 257 of the CLH report is reasonable, but it should note that the use of one-sided p-values for positive associations will not only increase statistical power, but will also increase the number of false positive findings. This is particularly problematic for the glyphosate rodent studies; for both the studies relied				

upon by IARC (Tarone, Regul Toxicol Pharmacol 2018;98:A1-A4) and the larger collection of studies evaluated in the AGG glyphosate report (Crump et al., Toxicol Sci 2020;175:156-167) there were more tumor types showing significant decreases in tumor rates with increasing glyphosate levels than there were showing significant increases. Reporting only 1-sided tests for positive associations ignores inverse associations and obscures the inconsistency of results of the glyphosate rodent studies. There is no scientific justification for reporting such 1-sided tests for glyphosate rodent studies.

The exclusive use of one-sided tests for positive associations overstates the evidence of a carcinogenic effect, and the reporting of p-values based on the normal approximation to the Cochran-Armitage test for trend further exaggerates the strength of evidence (the approximate p-values will consistently be smaller than the exact p-values because of the very high glyphosate exposure at the highest levels in the studies). The use of approximate one-sided p-values by <confidential> in order to overstate significance is consistent with his substantial financial conflict of interest, but should be avoided in a regulatory report.

It would be more informative to report exact one-sided p-values in the direction of the observed associations. In Table 2.6.5.1-9b of the CLH report, for example, the p-values would be: 0.065 for the first study (rather than 0.034); 0.042 [N], where [N] indicates an inverse association, for the second study (rather than NS); 0.062 for the third study (rather than 0.0078); and 0.090 for the fifth study (rather than 0.039). Reporting approximate 2-sided test results will not completely remedy the overstatement of significance for positive associations. For the third study the approximate 2-sided p-value is 0.0158, while the exact 2-sided p-value is 0.062.

The summary of epidemiology studies of glyphosate is generally satisfactory. It would seem advisable, however, to provide slightly more information about the Zhang et al. meta-analysis paper than is noted on page 303 of the CLH report. This paper is being strongly promoted by advocates arguing that glyphosate is carcinogenic. Kabat et al. (Cancer Causes Control 2021;32:409-414) note the dependence of the summary estimate reported by Zhang et al. on mechanistic assumptions underlying their choice of estimates from the individual studies included in the meta-analysis, and demonstrate the absence of empirical evidence to support those mechanistic assumptions. Kabat et al. also provide summaries of recent meta-analyses of glyphosate epidemiology studies through the year 2000, including the Leon et al. paper cited on page 303.

<confidential>

I retired in July 2016 after 28 years as mathematical statistician at the <confidential> and 14 years as Biostatistics Director at the <confidential>. I have received no pay for my scientific efforts since my retirement. I coauthored IARC Scientific Monograph No. 79 on the statistical analysis of animal carcinogenicity studies.

Dossier Submitter's Response

Statistics

In reply to the comment above, the DS would like to give the following response. The statistical analyses provided by the DS are based on values reported in the original study reports, the statistical re-assessment of the data given in the previous CLH report (2016) and/or by the DS own statistical analysis. The results from one-sided testing were shown in Volume 1 (section 2.6.5) at the statistical analysis section in the assessment of each tumour type as this represents another view based on the public literature publication by Portier (2020). In the above comment, the use of exact one-sided p-values in the

direction of the observed associations is proposed. This is a third option for the statistical analysis of the tumour incidence data from the carcinogenicity studies. According to the comment above the two-sided method provides less power, but also decreases the number of false positives in the direction of greater incidences tested. However, as explained in Volume 1, both one- or two-sided significance can be calculated, depending on the hypothesis to test. As shown in other comments, in this context some authors prefer one-sided *i.e.,* increased power and as such both options are presented. Nevertheless, it should also be taken into consideration that, as also indicated in OECD GD 116 and in the previous EU evaluation, statistical significance is not the only criteria to decide if an effect observed in a carcinogenicity study is treatment-related. This is extensively being discussed in Volume 1 of the RAR (Section 2.6.5.1.1.3 Overall consideration of tumour incidences). The opinion of the DS is that the interpretation of the tumour incidences observed among the carcinogenicity studies in rats and mice should be made based on weight of evidence which balances between statistical analysis and biological plausibility.
Based on the above, the DS submitter proposes that RAC performs its own statistical analysis of the data according to the most appropriate hypothesis to test, but also to apply a weight of evidence analysis based on animal and human data and considering statistical as well as biological significance of results in the comparison against CLP criteria.

Minor remark: while re-reading, we consider that the text in Volume 1 (CLH report) at Table 2.6.5.1-9b for the second mouse study should not be "No significant increase" but "No significant change" instead as the tumour incidences were 2/50, 2/50, 0/50 and 0/50 when two-sided testing was applied.

Epidemiology

In total, five open literature studies (meta-analyses/review articles) were mentioned in this comment and by other commentors. For three of these five studies a data gap for a full assessment has been set in the PPP process (Chang and Delzell, 2016; Leon et al., 2019 and Zhang et al., 2019) and thus no complete assessment is available at this timepoint. The two others are new open literature publications that were not available at the time of submission of the dossier (Kabat *et al.*, 2021 and Weisenburger, 2021). In addition, a new epidemiological study was identified (Meloni *et al.*, 2021). In the section below, the DS provides some initial reflections on these meta-analyses/review articles and on the additional epidemiological study.

The DS welcomes a full assessment of these 'new' studies by RAC. The DS has evaluated all submitted epidemiological studies for their reliability using the recommendations made in the Scientific Opinion of the PPR Panel on the follow-up of the findings of the External Scientific Report 'Literature review of epidemiological studies linking exposure to pesticides and health effects' (EFSA Journal 2017; 15(10):5007). For each study, an assessment has been made on:
- Study design and conduct: Was the study design appropriate to account for the expected distributions of the exposure and outcome, and population at risk? Was the study conducted primarily in a hypothesis generating or a hypothesis-testing mode?
- Population: Did the study sample the individuals of interest from a well-defined population? Did the study have adequate statistical power and precision to detect meaningful differences for outcomes between exposed and unexposed groups? Was there a potential for selection bias?

- Exposure assessment: Were the methods used for assessing exposure valid, reliable and adequate? Was a wide range of exposures examined? Was exposure assessed at quantitative level or in a categorical or dichotomous (e.g. ever vs never) manner? Was exposure assessed prospectively or retrospectively?
- Outcome assessment: Were the methods used for assessing outcomes valid, reliable and adequate? Was a standardised procedure used for collecting data on health outcomes? Were health outcomes ascertained independently from exposure status to avoid information bias?
- Confounder control: were potential confounding factors appropriately identified and considered? How were they controlled for? Were the methods used to document these factors valid, reliable and adequate?
- Statistical analysis: Did the study estimate quantitatively the independent effect of an exposure on a health outcome of interest? Were confounding factors appropriately controlled in the analyses of the data?
- Reporting: Is reporting adequate and transparent? Are key elements of the material and methods and results section are reported in sufficient details?

In addition to the above considerations for assessing the reliability of the studies, it is important in the overall assessment of the studies to distinguish between an association (an increased relative risk (RR) or odds ratio (OR) for a certain type of tumour) and the causality of the effect (can exposure be confirmed or not, or only in some cases; was there a time-space consistenty found). Also, the possible influence of exposure to other pesticides should be considered, as the possibility to exclude simultaneous exposure may differ between studies. In addition, strengths and limitations of the case control and cohort studies included in the meta-analyses and the consistency between the results among the underlying studies included in meta-analyses may be further discussed. Some positive associations were found, however, a consideration on sample size or sub-group size in which the association was found is also advisable. Lastly, consistency between the results of the available human epidemiological data and the findings from the carcinogenicity studies in mice and rats should be considered.
And finally this 'new' information, previously not considered by RAC, should be included in a weight of evidence analysis based on animal and human data and considering statistical as well as biological significance of results in the comparison against CLP criteria.

1) Chang and Delzell, 2016
Systematic review and meta-analysis of glyphosate exposure and risk of lymphohematopoietic cancers - PubMed (nih.gov)

Initial reflection by the DS on the study:
Systematic review and meta-analysis that examines the relationship between glyphosate exposure and risk of lymphohematopoietic cancer (LHC), including NHL (12 studies), Hodgkin lymphoma (HL, 2 studies), multiple myeloma (MM, 7 studies), and leukaemia (3 studies). Significant associations were found for the risk of NHL (meta-RR 1.3, 95%-CI 1.0-1.6, six studies) and MM (meta-RR 1.4, 95%-CI 1.0-1.9; four studies). In addition, meta estimates for other lymphopoietic cancers were the following: HL (meta-RR = 1.1, 95%-CI = 0.7–1.6; two studies), leukemia (meta-RR = 1.0, 95%-CI = 0.6–1.5; three studies), and NHL subtypes except B-cell lymphoma (two studies each). The study was supported by Monsanto Company.
Recall and selection bias inherent to case-control studies, and confounding of the original studies may impact the observed associations as the meta-analysis could not correct

them. Meta-analysis is constrained by a few studies and a crude exposure metric. The degree of control for confounding varied widely among the reviewed studies, some studies do perform multivariate analysis, while some others do not (for instance Eriksson). The magnitude of the associations is not enough as to exclude modest bias or confounding explanations for the observed results.
This meta-analysis did not consider additional evidence published after June 2015, particularly data from the AHS by Andreotti et al. (2018). The limited number of included studies confines the interpretation of meta-estimates.

2) Leon *et al.*, 2019
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 - PubMed (nih.gov)

Initial reflection by the DS on the study:
A pooled analysis of 3 large agricultural cohorts (AHS in the USA, AGRICAN in France, NCAP in Norway) investigating the association between ever use of 14 pesticide groups and 33 individual active ingredients with NHL overall and for four major NHL subtypes (NHL malignancies, CLL/SLL, DBCL). Cox regression models were used to estimate cohort-specific hazard ratios (HRs) and 95%-confidence intervals (CIs), which were combined using random-effects meta-analysis to calculate meta-HRs.
The strength of the study stems from its large combined sample size: overall, the pooled analysis included > 300 000 participants and 3.5 million person-years of follow-up between January 1993 and December 2011. There is very limited selection bias and the covered period is long enough. In addition, in this cohort, participants are enrolled via national systems of social security or public health, which allows an adequate tracing of the participants and their exposure throughout the cohort, and collected information is more reliable. Lastly, the chosen methodology (Cox model) seems adequate.
The authors acknowledged the study's limitations and included that the frequency of exposure was not considered (e.g. re-entry). Pesticide use was derived from the self-reported history of crops cultivated combined with crop-exposure matrices (AGRICAN and NCAP) or self-reported lifetime use of active ingredients (AHS). An error-prone indirect methodology was used for exposure classification by the AGRICAN and CNAP cohorts with over-attribution of exposure. No specific questions were asked about specific pesticide applications or application practices. Differences in nature and characteristics of the cohorts and agricultural practices may have affected risk estimates/exposure matrices, respectively. This approach failed to control for the confounding effect of other pesticide exposures. The authors noted non-differential misclassification of exposure. This indicates an inadequacy of an ever versus never exposure metric for characterizing cancer risk from pesticide exposure.
No association was observed for glyphosate and NHL overall or for most subtypes, except for diffuse large B-cell Lymphoma (DLBCL) (mRR 1.36, 95%-CI 1.00-1.85). The latter result is inconsistent with Andreotti *et al.* (2018). When considering the studies individually, only the Norwegian CNAP study excluded the null value for the DLBCL subtype with an RR of 1.67 (95%-CI 1.05-2.65) based on 100 cases, whereas the AHS showed an RR of 1.2 (95%-CI: 0.72-1.98) based on 93 exposed cases and the AGRICAN study showed an RR of 1.06 (95%-CI: 0.51-2.19) with 28 cases.
The DS notes that US EPA also made an assessment of this meta-analysis. They concluded that this additional information does not impact their conclusion that glyphosate is "not likely to be carcinogenic in humans". Refer to https://www.epa.gov/sites/production/files/2020-01/documents/glyphosate-epidemiological-review-zhang-leon-proposed-interim-decision.pdf

3) Zhang *et al.*, 2019
Exposure to glyphosate-based herbicides and risk for non-Hodgkin lymphoma: A meta-analysis and supporting evidence - PubMed (nih.gov)

Initial reflection by the DS on the study:
The authors conducted a meta-analysis on studies investigating the relation between non-Hodgkin's Lymphoma (NHL) and exposure to glyphosate-based herbicides. Five case-control studies and the updated cohort study from the AHS (Andreotti *et al.*, 2018) was selected for the final analysis.
The *a priori* hypothesis of the study builds on previous meta-analyses that the longer and greater the exposure, the bigger the risk of developing NHL. Therefore, the authors choose the highest quantiles of glyphosate exposure with the longest lag time reported from the AHS study. Using the highest exposure groups when available in each study, the overall meta-RR for NHL development was 1.41 (95%-CI 1.13-1.75). Random-effect model, which is generally considered the default model, was also performed and yielded RR = 1.56 (95%-CI 1.12–2.16) for high cumulative exposure. The authors performed sensitivity analyses, assessed publication bias, and ranked the included studies according to the Newcastle-Ottawa scale.
The authors discuss the limitations of the included studies, the cohort study's imputation problem, and latency period. The *a priori* hypothesis is partly supported by Andreotti *et al.* (2018) since the glyphosate use quartiles overlap in the 20-year lag time. The authors also acknowledge that exposure may have been misclassified due to recall bias pertinent in case-control studies. A methodological limitation arises from the combination of cohort and case-control studies. For this reason, subgroup analysis was performed for case-control studies with fixed and random effects; both showed an elevated risk of NHL.
The DS notes that US EPA also made an assessment of this meta-analysis. They concluded that this additional information does not impact their conclusion that glyphosate is "not likely to be carcinogenic in humans". Refer to https://www.epa.gov/sites/production/files/2020-01/documents/glyphosate-epidemiological-review-zhang-leon-proposed-interim-decision.pdf

4) Kabat *et al.*, 2021
On recent meta-analyses of exposure to glyphosate and risk of non-Hodgkin's Lymphoma in humans - PubMed (nih.gov)

Initial reflection by the DS on the study:
This brief report examines the outcome of recent meta-analysis (Zhang *et al.*, 2019) on the exposure to glyphosate and risk of non-Hodgkin lymphoma in humans. The authors performed a sensitivity analysis based on the five case-control studies and one cohort that were included in the original meta-analysis. The aim of the sensitivity analysis was to determine how the definition of exposure and choice of latency period (20-year in Zhang *et al.*, 2019) affect the meta RR. Secondly, the authors also conducted a meta-analysis of ever-exposure to glyphosate incorporating the most updated results from the case-control studies. One of the main difference to Zhang *et al.* (2019) is the use of pooled RR from US and Canadian case-control studies (NAPP), which was not published at the time Zhang *et al.* (2019) submitted their manuscript.
Using the highest reported exposure levels, evidence of an association between glyphosate and NHL was strongest when estimates from analyses in the cohort study with

a 20-year lag (RR=1.41 (95%-CI 1.13–1.76) and a 15-year lag (RR=1.25 (95%-CI 1.01–1.25) were included. In their meta-analysis of ever-exposure with no lag period, the summary relative risk with updated estimates was 1.05 (95%-CI 0.87–1.28). Substituting the AHS 20-year lag Q4 RR of 1.12 for 0.87 resulted in a summary RR of 1.16 (95%-CI = 0.96–1.4).
There are some limitations of the article. The authors dispute the assumption of Zhang *et al.* (2019) that NHL has a long latency period. Authors argue that the use of long latency period in the original meta-analysis is unfounded since the original assumption, made by Weisenburger (1992), was based on indirect evidence of the latency period between glyphosate exposure and NHL development. The authors argue that "long latency periods for NHL cannot be ruled out but the Zhang et al. (2019) preference for a 20-year latency period, like their hypothesis that NHL risk increases with increasing glyphosate level, is open to question." However, the authors do not provide supporting evidence for the latter statement. Further, a detailed assessment of bias of the included studies is not presented.

5) Weisenburger, 2021
A Review and Update with Perspective of Evidence that the Herbicide Glyphosate (Roundup) is a Cause of Non-Hodgkin Lymphoma - PubMed (nih.gov)

Initial reflection by the DS on the study:
This review article examines relevant scientific literature linking exposure to glyphosate and glyphosate-based formulations to the development of NHL. The author evaluates the literature in view of the Bradford Hill criteria of causation. The literature search only covered a brief 6-year period between 2015 and 2020. The author states that 7 of the 8 criteria are fully or partly fulfilled. The author acknowledges that the results are not consistent, since cohorts of higher reliability do not confirm the positive associations found in case-control studies. Furthermore, the author argues that negative result of the AHS should not be used to negate the results of case-control studies, since lifetime years of exposure to glyphosate still remains low.

6) Meloni *et al.*, 2021
Occupational exposure to glyphosate and risk of lymphoma:results of an Italian multicenter case-control study - PubMed (nih.gov)

Initial reflection by the DS on the study:
This case-control study was part of the "Gene-environment interactions in lymphoma etiology" (ItGxE) multicentre study that took place between 2011 and 2017 in 6 Italian centres. The study aimed to explore the risk of lymphoma subtypes following occupational exposure to glyphosate. The controls were either hospital controls recruited from other hospital departments (exclusion criteria well defined) or random controls from the general population, depending on the centre. The controls were 2:1 age and gender frequency matched. Overall, 867 cases (500 males and 367 females) and 774 controls (428 males and 346 females) were included.
The questionnaire included questions on socioeconomic data and lifetime occupational history. Duration, frequency and intensity to exposure were calculated as a cumulative summary estimate for each subject with the support of a "crop exposure matrix". The outcome was classified based on the 2008 update of WHO classification of lymphoma and

its subtypes. Multivariate models (unconditional logistic regression) were adjusted by age, gender, education level, and study centre. No association was observed with risk of lymphoma (any subtype), NHL, B-cell lymphoma, or the major lymphoma subtypes. Risk of follicular lymphoma was elevated 7-fold in subjects classified as ever exposed to glyphosate with medium and high confidence (OR = 7.1, 95%-CI 1.57-31.9), a 4.5-fold in association with medium-high cumulative exposure level (OR = 4.5, 95%-CI 0.82-24.1), 12-fold with medium-high exposure intensity (OR = 12.0, 95%-CI 2.95–49.0), and 6-fold with exposure for 5-10 days or more per year (OR = 6.0, 95%-CI 1.40–26.1). It must be taken into account that very few study subjects (2.2%, n=36) were classified as ever exposed to glyphosate. Therefore the study suffered from low statistical power. This increased the probability of chance findings and a very wide CI (1.06–12.79 for follicular lymphoma). Leon *et al.* (2019, B.6.5.18.30) did not find an excess risk of follicular lymphoma in association with ever exposure to glyphosate. Orsi *et al.* (2009, B.6.5.18.26) found a non-significant 40% excess risk of follicular lymphoma in ever exposed subjects, but again the study suffered from a low prevalence of exposure. The trained interviewers conducted in-person interviews at the hospital or at the residence of study subjects. The study could not assess the confounder effect of co-exposure to other pesticides. The refusal rate 7.4% among cases and 38.4% among controls (38.4% among hospital controls and 41.4% in general population), which could indicate another source of bias. Exposure was based on self-reported answers; however, the experts were responsible for organising the exposure replies into exposure metrics, limiting but not eliminating recall bias.
RAC's response
Noted. RAC appreciates the assessment and discussion by the DS regarding the statistical methods used in the animal carcinogenicity studies with glyphosate and have been taken into account in the assessment for classification for carcinogenicity. Further, the assessment and discussion of the epidemiological studies, both the studies already included in the CLH report as well as more recent reviews, meta-analysis and a case-control study are appreciated. These have been taken into account in the assessment in the RAC opinion for the classification for carcinogenicity following exposure to glyphosate based herbicides.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina	Cazenave y Asociados SA	Company-Downstream user	22
Comment received				
Page 316 "Conclusion on classification and labelling for carcinogenicity": Cazenave y Asociados SA agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina	<confidential>	National NGO	23
Comment received				

Page 316 "Conclusion on classification and labelling for carcinogenicity": <confidential> agrees with the assessments and conclusions achieved.
Dossier Submitter's Response
Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Belgium	Health and Environment Alliance (HEAL)	International NGO	24

Comment received

Please refer to the attachment "carcinogenicity" (Section Vol1/2.6.5.1 and Vol 3/B.6.5) for comments in relation to the assessment of the glyphosate epidemiology studies. HEAL supports the conclusion of IARC on the classification of glyphosate as probable carcinogen (equivalent to EU category 1B) based on limited evidence in humans, strong evidence from animal studies and strong evidence on genotoxicity. The comments provide evidence that the epidemiological evidence that support exposure to glyphosate and cancer are at least sufficient.

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment HEAL_Public consultation Glyphosate ECHA.zip

1	Vol. 1/2.6.5.1/ 2.6.5.1.2 Epidemiological studies	p.300. The analysis of the epidemiology data doesn't seem to reflect the evidence. Refer to the revie of Weisenburger, 2021.
2	Vol. 3. B.6.5.18.5. Supporting publications – Crump 2019	p. 205. Crump 2019 Unfortunately, this study is based on speculations and underestimates the work done behind the case-related control studies, these were performed "by experienced epidemiologists using widely accepted study designs and methods, were published in peer-reviewed journals, and are acceptable for review and consideration". Furthermore, none of the arguments raised have been proven and therefore can only be considered as speculations.
3	Vol. 3.B6.5/ B.6.5.18.10. Supporting publications – Andreotti, 2018	p.246 Andreotti, 2018 The AHS should only be considered as interim. In the first AHS report, the median follow up was only 6.7 years, which is a short period to detect meaningful increase in NHL or other cancers. According to Weisenburger's review this period should be approximately 20 years and not less than 10 years. The recent update in 2018, added 11 years of follow up to the cohort and the cases of NHL increased significantly to 575 cases. Still the media lifetime years of glyphosate use was 8.5 years with a median follow up of only 18 years. The study reports no association of glyphosate use and risk of NHL overall or for the major subtypes. However, it has several shortfall, that make the conclusions unreliable (from Weisenburger, 2021): • only 44% of the applicators completed and returned a supplemental questionnaire following initial enrolment • there was a poor response to the first follow-up survey in 1999 to 2005, in which 37% of the applicators failed to respond and for whom no actual recent data on pesticide exposure were available for analysis • For those who responded, pesticide use data were only obtained for the last year of farming prior to the follow-up survey, thus leaving a data gap of 6 to 12 years for actual pesticide use from the time of initial enrolment.

		• Because 37% of the applicators failed to complete the follow-up survey, the AHS researchers decided to use a complicated imputation method to estimate the exposures for the non-responders based on their prior exposures and data obtained from the responders, which could lead to misclassification. Furthermore, the imputation method underestimated glyphosate use by 7% to 8% (Heltcher et al). • Thus, this type of misclassification will reduce the power of a study to detect any genuine cause-effect relationship and thus reduces the validity of the study findings.
4	Vol.3 B.6.5.18. Long-term toxicity – public literature	Study missing: Weisenburger, Dennis D. 2021. "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, April, S2152265021001518. https://doi.org/10.1016/j.clml.2021.04.009. Relevance: This is a review from a medical doctor who works with NHL patients and carries out research on this issue. This very recent review is valuable for the CLH/RAR as it examines closely all the evidence from all available epidemiology studies.

Dossier Submitter's Response

Response to comment 1: Noted. A reflection on the Weisenburger study (new data) is given at comment 21.

Response to comment 2: The study by Crump 2019 (B.6.5.18.5) provides an example of a well-known phenomenon in epidemiological studies that is called 'recall bias'. It is a type of information bias that may occur in case control studies. Information bias is a potential systematic error when there are systematic differences in the way information regarding exposure or the health outcome are obtained from the different study groups that result in incorrect or otherwise erroneous information being obtained or measured with respect to one or more covariates being measured in the study. Information bias results in misclassification which in turn leads to incorrect categorisation with respect to either exposure or disease status and thus the potential for bias in any resulting epidemiological effect size measure such as an OR or RR (EFSA Journal 2017; 15(10):5007). Recall bias may occur when a diseased subject may be more likely to recall an exposure that occurred at an earlier time period than a non-diseased subject.

The purpose of this analysis by Crump was to evaluate the evidence for recall bias in the overall pattern of results in five case control studies and two cohort studies that comprise the main part of the glyphosate-NHL literature.

In evaluating the case control studies, Crump reasoned that the percentage of odds ratios > 1 for **non**-glyphosate exposures should be approximately 50% if recall bias was not operative and those exposures did not cause NHL. Yet, it turned out that the percentages of ORs >1 for **non**-glyphosate exposures were 90% for Hardell et al. (2002), 90% for Erikson et al. (2008), 93% for McDuffie et al. (2001), 76% for Orsi et al. (2009), and 53% for DeRoos et al. (2003). Thus based on the high percentage of ORs above 1 for exposure to other pesticides and NHL, it seems that recall bias may have played a factor in a number of the case-control studies.

Irrespective from the conclusions by Crump (2019), all submitted epidemiological studies have been evaluated by the DS for their reliability using the recommendations made in the Scientific Opinion of the PPR Panel on the follow-up of the findings of the External Scientific Report 'Literature review of epidemiological studies linking exposure to pesticides and health effects' (EFSA Journal 2017; 15(10):5007) (refer to Vol 1

2.6.5.1.2.1). One of the many aspects is to consider if health outcomes were ascertained independently from exposure status to avoid information bias (including recall bias) and if the methods used for assessing exposure were valid, reliable and adequate.

Response to comment 3:
The DS agrees that the report by Andreotti 2018 may be seen as an interim report as the AHS study is still ongoing. And indeed, as for most epidemiogical studies, there are some shortcomings. However, overall no clear association was seen between exposure to glyphosate and cancer in the AHS data that was gathered up to now. Only a weak association can be seen for subjects with a relatively high exposure (third tertile) and acute myeloid leukaemia and Non-Hodgkin Lymphoma after a 20-year lag time. As it only concerns a very small research population of n=15 and n=9 cases, respectively, these findings are considered of questionable value. Further, some weak positive association has been observed in some case-control studies or in meta-analyses of these studies between exposure to glyphosate and cancer-outcomes. However, no causal relationship could be established as chance, bias, and confounding factors could not be ruled out in these studies.

Response to comment 4:
This open literature publication is not included in the dossier as it was published after the submission of the dossier by the applicant. In this publication, the results from the available epidemiological studies on glyphosate and NHL are discussed. All underlying data (epidemiological studies and animal studies) are already included in the current dossier, assessed by the DS and taken into account in an overall weight-of-evidence approach. An initial reflection on this study is provided in comment number 21.

Please note that an identical comment was submitted in the EFSA process (refer to RT 2(74).

RAC's response

Noted. The studies mentioned in the comments, including the recent study by Weisenburger (2021), has been included by RAC in the assessment of the epidemiological data. RAC notes that the study by Weisenburger (2021) includes no new epidemiological studies, but examines the scientific literature linking exposure to glyphosate and glyphosate-based formulations to the development of NHL.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Germany	<confidential>	National NGO	25

Comment received

Reference to assessment report Volume 1, 2.6.5.1.1. Short summary and overall relevance of the provided information on long-term toxicity and carcinogenicity, pages 250-298.

Chapter 2.6.5.1.1 contains a numerous flaws. Some are due to the wrong use of guideline criteria others due to mis-interpretation of the data presented. Details with reference to page number and quote from the text are explained in the attachment.
Furthermore, on page 256 it is stated: "A 'weight of evidence' approach should and may be applied, therefore, as a general principle." However, this approach is not followed. An appropriate weight of evidence needs to integrate findings of the rodent carcinogenicity bioassays (tumour incidences) and mechanistic evidence (mode of action). The latter was completely ignored. Potential mode of action was taken into consideration – although not

in an integrated manner – by RMS Germany during the 2015 assessment. Since then at least 15 papers using analytical grade glyphosate or AMPA have been published addressing oxidative stress (a recognized mechanism of carcinogenicity). Details are explained in the attachment ECHA note – An attachment was submitted with the comment above. Refer to public attachment <confidential>_HEAL_Glyphosate_carcinogenicity_ATTACHMENT.pdf
Dossier Submitter's Response
The DS refers to comment 31 for our response to **Part 1** of the attachment. Considering **Part 2** of the attachment the DS notes the following: RMS has included an overall assessment on oxidative stress in Vol.1 2.6.4.1. The information from the previous RAR (2015) were taken into consideration by RAC during their evaluation and RMS has included this assessment. In addition, the DS has added their considerations on new data found in public literature regarding this subject. Please note that the same comment was also submitted for the EFSA process (Reporting Table TOX comment 2(86))
RAC's response
Noted. RAC has included in the opinion an assessment of the animal carcinogenicity studies (including the assessment by Portier (2020)) as well as the epidemiological studies including the recent studies from the consultation. In arriving at the conclusion for a classification for carcinogenicity, RAC has reviewed the animal and human data according to the CLP criteria including a weight of evidence assessment. Mechanistic evidence/mode of action, e.g. oxidative stress, has been assessed as part of the weight of evidence assessment.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Belgium	<confidential>	National Authority	26
Comment received				
Compared to the former EU-evaluations, several papers from the open scientific literature in epidemiology have been published regarding the possible association between exposure to glyphosate and subtypes of non-hodgkin lymphoma (NHL) in prospective cohorts. Notably, Leon et al (2019), revealed a weak but statistically significant increased incidence of the DLBCL subtype of NHL: N=221, mHR:1.36; 95%CI (1.00-1.85) in the AGRICOH cohort. Further, while NHL was globally unaffected in the AHS Andreotti et al (2018), it was highlighted that also for NHL of T cell subtype (NHL) an elevated risk ratio was found for the 20-year lagged exposure (NHL: RR of 2.97, 95% CI: 1.20-7.31). Although a low number of cases was included in this subgroup (n=9), the RR is statistically significant, and should not be ignored. Further, they found a moderately ↑RR for acute myelogenous leukaemia in the highest exposure Q4 that was statistically significant when a 20-year lag period (to account for tumour latency) was considered (RR = 2.04, 95%-CI = 1.05-3.97, ptrend = 0.04). The impact of the Zhang et al study (2017) where meta-RR were recalculated on case-control studies and a specific subset of the AHS-cohort (Andreotti, 2018) is unclear, and should further be investigated by RAC. In conclusion, we propose that the impact of all new epidemiological data as regards the possible classification of glyphosate (NC <> Carc. Cat.2, H341), not yet considered under				

CLP, should be discussed.
We are in any case of the opinion that neither guideline studies nor published data justify a classification of glyphosate as Carc Cat 1B, as could be inferred from opinions of many authors in the open public literature.

Dossier Submitter's Response

For the meta-analyses by Zhang *et al.* (2019) and Leon *et al.* (2019) a data gap was identified for providing a full assessment of the study including a relevance and reliability assessment. The applicant was asked to submit the missing information during the public consultation period of the EFSA process. For this CLH-process, initial reflections on these studies are provided in RCOM comment 21. The results of the meta-analysis of Andreotti *et al.,* 2018 were already take into consideration (refer to Volume 3 section B.6.5.18.10). Please note that a similar comment was also submitted for the EFSA process (Reporting Table TOX comment 2(339 and 340)).

The RR values reported in the comment by BE are correct, however, the RR for AML data is not for Q4 but for the third tertile of exposure.

The DS agrees that these studies/meta-analyses (Zhang *et al.* (2019) and Leon *et al.* (2019) and Andreotti *et al.* (2018)), which were previously not considered by RAC, should be included in a weight of evidence analysis based on animal and human data and considering statistical as well as biological significance of results in the comparison against CLP criteria. Refer to RCOM comment 21 for a further response by the DS.

RAC's response

Noted. The classification for carcinogencity has been discussed by RAC, including the epidemiological studies described in the CLH report by the AGG as well as the recent epidemiological data from the consultation. RAC concludes that based on the epidemiological data as well as the data from long-term studies in rats and mice, taking a weight of evidence approach, no classification for carcinogenicity is warranted.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Germany	Health and Environment Alliance (HEAL)	International NGO	27

Comment received

Volume 1, 2.6.5.1.1. Short summary and overall relevance of the provided information on long-term toxicity and carcinogenicity, pages 250-298.
Chapter 2.6.5.1.1 contains a numerous flaws. Some are due to the wrong use of guideline criteria others due to mis-interpretation of the data presented. Details with reference to page number and quote from the text are explained in the attachment.
Furthermore, on page 256 it is stated: "A 'weight of evidence' approach should and may be applied, therefore, as a general principle." However, this approach is not followed. An appropriate weight of evidence needs to integrate findings of the rodent carcinogenicity bioassays (tumour incidences) and mechanistic evidence (mode of action). The latter was completely ignored. Potential mode of action was taken into consideration – although not in an integrated manner – by RMS Germany during the 2015 assessment. Since then at least 15 papers using analytical grade glyphosate or AMPA have been published addressing oxidative stress (a recognized mechanism of carcinogenicity). Details are explained in the attachment.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment ATTACHMENT_.pdf
Dossier Submitter's Response
The DS refers to the reply to comment 25 above as it is the same comment.
RAC's response
Noted. See responses to comment no. 25.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina		Individual	28
Comment received				
Page 316 "Conclusion on classification and labelling for carcinogenicity": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Denmark		MemberState	29
Comment received				
2.6.5.3: Agree with the outcome of the current evaluation that no classification for carcinogenicity is warranted based on the available information. Most of the observed tumors are only observed in one or a few studies. Furthermore, most effects are only observed in one species and one sex e.g. pancreatic islet cell tumors and skin basal cell tumors observed in male rats and renal tubule tumors observed in male mice. Some of the observed tumors including renal tumors and malignant lymphomas are observed at very high doses above what is recommended in the OECD TGs. The relevance of these high doses in regard to human exposure is questionable. Only for few effects were dose-response observed within the study and no apparent dose-response between studies were observed for the tumors observed in multiple studies as would have been expected if the effects were related to treatment with glyphosate.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Belgium	EFFAT - European Federation of Food, Agriculture and Tourism Trade Unions	Industry or trade association	30
Comment received				
EFFAT supports a harmonised classification of glyphosate (CAS 1071-83-6) as a minimum as carcinogenic category 1B according to the CLP criteria because of the evidence provided in the following studies: 1) The International Agency of Research on Cancer (IARC) classified glyphosate as "probably carcinogenic to humans" in 2015. 2) Zhang et al, Exposure to glyphosate-based herbicides and risk for non-Hodgkin lymphoma: A meta-analysis and supporting evidence. Mutat Res. 2019 Jul - Sep; 781:186-206. doi: 10.1016/j.mrrev.2019.02.001. 3) Maria E Leon 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. Int J Epidemiol. 2019 Oct 1;48(5):1519-1535. doi: 10.1093/ije/dyz017
4) 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
5) Denis D. Weisenburger. 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,Vol. 21, No. 9, 621–630. https://doi.org/10.1016/j.clml.2021.04.007

ECHA note – An attachment was submitted with the comment above. Refer to public attachment EFFAT Position Paper - Ending the use of glyphosate and building a more sustainable agriculture EN.pdf

Dossier Submitter's Response

The RMS notes that all data that has been used in evaluation by IARC has also been considered in the current evaluation together with more recent data (including the report by Portier (2020)).
The studies 2) Zhang et al (2019), 3) Leon et al (2019) and 5) Weisenburger (2021) are new information and are discussed elsewhere. Please refer to comment 21 for a further response on these studies by the DS.

Please note that the same comment was also submitted for the EFSA process (Reporting Table TOX comment 2(68))

RAC's response

RAC has included in the opinion an assessment of the animal carcinogenicity studies (including the assessment by Portier (2020)) as well as the epidemiological studies including also the recent studies by Zhang *et al*. (2019), Leon *et al.* (2019) and Weisenburger (2021). In arriving at their conclusion for a classification for carcinogenicity, RAC has reviewed the animal and human data according to the CLP criteria, including a weight of evidence assessment.

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2021	Switzerland		Individual	31

Comment received

Attached is a zip file (Comments.zip) containing two separate pdf documents.

The first document (ChronicCarcinogenicityStudies.pdf) contains a series of comments on the evaluation of the animal carcinogenicity data conducted by the Assessment Group on Glyphosate (AGG) of the Rapporteur Member States (RMS). This file contains 14 sections and 2 appendices.
The first 5 sections deal with general issues that are incorrectly used by the AGG to exclude positive findings in the cancer bioassays being reviewed. These include: Section 1 - failure to use one-sided statistical p-values (we are not interested in tumour protection in this risk evaluation); Section 2 – the lack of a consistent analysis plan and how this leads to selective use of different data groupings, different methods of analysis, etc. in the different studies creating bias in the overall evaluation; Section 3 – incorrect use of historical control data to exclude positive findings for multiple tumours in multiple studies; Section 4 – a failure to use an objective, quantitative evaluation of consistency of response across the same tumor in multiple studies except in one case where the analysis

is done incorrectly; and Section 5 – incorrectly excluding findings at top doses in several studies by claiming they exceeded some limit that does not apply to carcinogenicity studies.

The next 8 sections deal with individual tumour types as follows:
- Section 6 – malignant lymphomas in male mice
- Section 7 – kidney tumours in male mice
- Section 8 – haemangiosarcomas in male mice
- Section 9 – hemangiomas in female mice
- Section 10 – skin keratoacanthomas in male rats
- Section 11 – skin basal cell tumors in male rats
- Section 12 – hepatocellular adenomas in male rats
- Section 13 – other tumours

In each section, the data supporting the finding for that specific tumour are summarized, issues with the review by the AGG are identified and an alternative evaluation of the data is provided, in most cases demonstrating there is sufficient evidence for a causal association between exposure to glyphosate and an increased risk of the given tumour.
Section 14 summarizes the overall findings from my review of the AGG draft report. Basically, I find that this evaluation falls short of the rigor required by science on almost all points. I find that, although there are published guidelines and scientific literature describing how to evaluate carcinogenicity studies, for the AGG to reject every single positive cancer finding, the AGG must bend and/or break these guidelines repeatedly. The conclusions of the AGG draft are not supported by the available scientific evidence and should be rejected.
Appendix 1 addresses a serious reduction in the probability of detecting a true positive finding in animal carcinogenicity studies using the review methods applied to these data by the AGG. This is a rather technical point and might require some review by other statisticians. The bottom line is that you could have a 4-5 fold reduction in statistical power (the probability of detecting a real carcinogen) as the result of the multiple steps required by the AGG for a positive finding to be "a real finding".

Appendix 2 is a list of technical corrections to the document.

The second document (Epidemiology.pdf) addresses issues related to the epidemiological studies included in the AGG draft evaluation.
The first section of this document addresses direct evidence (see Appendix 1 of this document) of exposure misclassification in the imputed exposures and indirect evidence of exposure misclassification in the respondents to the most recent update by Andreotti et al. (2018). In my opinion, this exposure misclassification is serious enough to label this study as inadequate.
The second section addresses the differences between the North American Pooled Project (NAPP) study population and the study populations in the original studies. The greatest difference has to do with gender. These differences strongly support using both the NAPP and the original studies when considering the evidence for an association using the epidemiological literature.
The third section briefly describes three publications not mentioned in the original draft review that should be included for completeness. Two of these papers are meta-analyses and one is a new case-control study from Italy.
In the fourth section, I provide my comments on the study by Leon et al. (2019). I argue that because of the exposure misclassification in this study and because this is basically a study of crop tillage and not glyphosate use, this study is unreliable for use in evaluating the linkage between NHL and exposure to glyphosate formulations.

In the last section (five), I argue that the correct category from the CLP Regulations for the epidemiological literature is that glyphosate formulations show limited evidence in humans of a causal association with NHL.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments.zip

Dossier Submitter's Response

Carcinogenicity

Each comment is given in Times new roman fonts (in black) and the response by the DS is given in Verdana fonts (in blue).

Please note that the same comment was submitted in the EFSA process. Refer to RT public TOX 2(67).

Comment section 1: one-sided statistical p-values

Throughout this document, two-sided tests are applied to the tumour findings from the animal carcinogenicity studies rather than one-sided tests. In fact, the RAR states "*In the AGG analysis on the relevance of malignant lymphomas in mice, two-sided testing is applied as this is in-line with how the statistical analysis was established in the study protocols*.", (RAR, p.289).

Common sense, objectivity, ethical neutrality and OECD Guidance 116 call for the use of one-sided tests in carcinogenicity studies. In the OECD Guidance, it states that "*In a carcinogenicity study, the expectation is often that the change will be an increase in tumours in the treated group, so a one-sided test may be considered more appropriate, although this can be controversial. If the treatment could also be protective (i.e., reduce tumour incidence or delay it) then a two-sided comparison may be more appropriate*", (OECD 116, p.133). In the case of pesticides, a therapeutic action is not the focus of the evaluation and is irrelevant for the assessment of glyphosate, therefore a one-sided test is more appropriate.

According OECD TG 451 (p.2), the "*statistical methods most appropriate for the analysis of results, given the experimental design and objectives, should be established before commencing the study*." When a statistical analysis is "established" in the study protocol, it is still unclear, whether the most appropriate statistical method was selected. The authorities should:

- disclose the respective parts of the study protocols, e.g. by quoting them.
- describe their judgment whether the method used in the study report is the "most appropriate"
- apply the most appropriate method themselves (re-calculate), if it was not used in the study report."

Finally, a one-sided error can be applied to any valid statistical method and does not depend on the statistical method.

Dossier submitter's response to comment section 1:

The statistical analyses provided by the DS are based on values reported in the original study reports, the statistical re-assessment of the data given in the previous CLH report (2016) and/or by the DS own statistical analysis (please also refer to the DS response to comment 21 of this RCOM). Besides, the results from one-sided testing were shown in Volume 1 (section 2.6.5) at the statistical analysis section in the assessment of each tumour type as this represents another view from the public literature publication by Portier (2020). However, it should be considered, as also indicated in OECD GD 116 and in the previous EU evaluation, statistical significance is not the only criteria to decide for classification for carcinogenicity. This latter is extensively being discussed in Volume 1 of the RAR (Section 2.6.5.1.1.3 Overall consideration of tumour incidences). The opinion of the DS is that the interpretation of the tumour incidences observed among the carcinogenicity studies in rats and mice should be made based on weight of evidence which balances between statistical analysis and biological plausibility.

Based on the above, the DS submitter proposes that RAC performs its own statistical analysis of the data according to the most appropriate hypothesis to test, but also to apply a weight of evidence analysis based on animal and human data and considering statistical as well as biological significance of results in the comparison against CLP criteria.

Considering the comment on the statistical methods applied, for each study the statistical analysis protocol of each study is summarized in Volume 3 CA B.6.5 and, if needed, could be checked in the original study reports which are disclosed by the applicant.

Comment section 2: the lack of a consistent analysis plan

An objective scientific assessment of any set of data requires that there is a clear analysis plan in place to avoid bias in the final review product. In fact, EFSA's own guidance on "Dealing with Evidence (PROMETHEUS)1", a scientific assessment is based upon a four-step approach as follows:

- • Upfront planning of the assessment strategy, defining the relevant data and the approach for collecting, appraising, and integrating them
- • Conducting the scientific assessment in line with the plan, and independently of prior knowledge of the results of the available studies
- • Verifying the process to ensure alignment with the plan and the guiding principles
- • Documenting and reporting of all steps, including deviations from the original plan.

In the case of this assessment, there is no assessment strategy, no plan on how to use the available data independent of prior knowledge, no verification that any sort of plan has been followed and no documentation of the steps taken to stick with this plan or deal with deviations from a plan.

There is no systematic scientific review of the 23 chronic carcinogenicity/toxicity studies available for glyphosate (see Portier, 2020) or any objective scientific assessment plan established. For the studies that are included, there is no common strategy for what data to use, how to analyze that data and how to present the results of these analyses. For some studies, animals from interim sacrifices not intended for the evaluation of tumour incidence are included in the analyses; for other studies, these data are excluded. An incomplete pathology protocol is used to disqualify some results from one mouse study (1993 study, see volume 3, p.154), but ignored for the five other studies (two mice, three rats) using a similar incomplete pathology protocol. Some analyses use survival-adjusted methods and others do not. Trend tests are applied selectively and pairwise comparisons are used to ignore trends in the tumour incidence when they are found. Studies of different durations and even different strains of animals are compared to each other as though they are replicates. It is assumed tumours seen in one sex must also be seen in the other sex in order to be real. For some studies, observed tumours are grouped (e.g. leukemias and lymphomas) and in others they are not. Positive findings are nullified using criteria that are not defined (e.g. positive dose-response patterns, weight-of-evidence) and little or no explanation is provided as to why these criteria are reasonable. Most of them reduce the ability of the evaluation to identify a positive effect if one truly exists (see Appendix 1). Subjective evaluations are common (e.g. qualitative evaluation of the agreement across studies) that cannot be repeated because the underlying hypothesis tied to the evaluations is unclear.

Dossier submitter's response to comment section 2:

The assessment of the available data has been done according to the many EFSA guidances on the assessment of active substances for PPP, OECD guidelines and the CLP guidances. As already stated by the DS in Volume 1, for overall assessment, it is acknowledged that glyphosate is different from most other active substances in plant protection products because a number of comprehensive and high quality studies are available for nearly all toxicological endpoints. If dose levels are comparable, it would be expected that adverse effects were, at least to a certain extent, reproducible in other studies. A weight of evidence approach should and may be applied, therefore, as a general principle. Depending on the nature of effect and/or the overall pattern e.g. pre-neoplastic changes, findings (including neoplastic) that are not dose-related or cannot be

confirmed at similar or higher dose levels in other studies are generally considered to have occurred by chance.

Considering the interim sacrifices: the study protocols differed between the studies. This makes it impossible the have the same analysis for all studies. Some studies included in interim sacrifice group, whereas others didn't. Further, not all studies with an interim group did study neoplastic effects at interim sacrifice. In addition, the number of animals investigated in the low and mid dose groups differ between studies and also the way they were investigated. Therefore, attention should be made to the number of animals that were investiged in each group, which might be different for each tumour type. This is taken into account by the DS in the overall analysis. However, we agree that this was incorrectly done for the mice 1993 study (see volume 3, p.154). For this study it was noted that not all animals from low and mid dose levels were examined; only the animals that died during the study or that were killed in extremis were investigated in these groups, therefore indeed no comparison can be made for the low and mid dose groups. For malignant lymphoma the reported incidences in males were 4/50, 2/25, 1/21 and 6/50 for the control, low, mid and high dose, respectively. In females, the reported incidences of malignant lymphoma are 14/50, 12/34, 9/24 and 13/50, respectively. For the other tumour types, the total number of animals investigated was given as 50 in the low and mid dose, however this should be 25 (low dose males), 21 (mid dose males), 34 (low dose females) and 24 (high dose females). This does not change the overall picture. For the rest of the comments, none of the statements has been made explicit to which study of which part of the overall assessment these refer. Thus no specific response can be given.

Comment section 3: incorrect use of historical control data

OECD Guidance Document 116 has an entire section (Section 4.22) on how to consider historical controls in evaluating carcinogenicity and toxicity data. At the very beginning of this section emphasis is given that "*In any discussion about historical control data, it should be stressed that the concurrent control group is always the most important consideration in the testing for increased tumour rates.*". This caveat is ignored throughout the evaluation where historical control data is routinely used to override the significant increases seen relative to the concurrent control and ignore a positive finding. They reference a number of publications that provide rigorous methods for applying historical controls to the evaluation of carcinogenicity data, any one of which could have been used by RMS to rigorously determine if findings would change based upon historical controls. **All of these publications and the IARC2 reject the use of the range of historical controls as a proper method for evaluating a cancer bioassay**; the only method used in the evaluation by AGG. When the observed effects in the dosed groups fell within the range of historical controls, the AGG rejected the findings as being not due to glyphosate exposure. Even when the observed tumour incidence was outside of the range of the historical controls, AGG concluded the results were not due to glyphosate exposure. Basically, any set of historical controls was a reason to reject a significant finding creating a bias in the evaluation process.

Dossier submitter's response to comment section 3:

For each tumour type, in the overall assessment of the relevance of the tumour incidences the following is taken into account: the outcome of the statistical analysis, a comparison of the incidence with the appropriate historical control data (where available; within five years, from same strain, from same laboratory), the dose-response of the effect and - in case dose levels are comparable between studies - the reproducibility of the effect.

Comment section 4: Quantitative Comparisons Across Studies

The CLH/RAR relies heavily on "semi quantitative" comparisons across studies to dismiss the augmented incidence of several tumours in the mouse studies. The evaluation compares how many trend tests were

significant, whether pairwise comparisons were significant, discusses differences in control responses across studies and compares ("semi quantitatively") the magnitude of the responses from one study to the next. However, not once do they test hypotheses associated with these evaluations.
As noted in OECD Guidance 116 (p. 135); "It is widely recognized that large differences can result from disparities in factors such as pathology nomenclature, strain, husbandry, pathologists." Thus, it is clear that studies done in different laboratories many years apart and with different substrains of rats and mice are not directly comparable without taking into account differences in the study designs. If AGG and EFSA/ECHA agree with this type of "semi quantitative" analysis, stringent requirements for comparability should be applied, similar to the ones on the use of historical control data (HCD). The recommendations made by OECD Guidance 116 for the use of HCD need to be taken into account. More specifically, comparisons should only be made

- between the same strain
- within a limited window of time (5 years according to OECD Guidance 116)
- at least under similar housing conditions (according to OECD Guidance 116 even in the same laboratory)

For example, following similar stringent guidelines for a semi-quantitative evaluation of the mouse studies results in the following:

- • only two studies (1983, 2009) have been performed in the same strain (Crl:CD-1). It should be noted that the strain used in the 1997 Study (Crj:CD-1) is a different strain according to textbook knowledge / general standards of laboratory animal science and the strain used in the 1993 study does not give a full characterization. The indifferent use of "CD-1" suggesting that all four studies were conducted with the same strain is incorrect,
- • the two studies performed in the same strain (a precondition for comparability) were performed more than 25 years apart,
- • the housing conditions are not same. Stress effects (immunosuppression) induced by some housing conditions (including, but not limited to individual versus group housing) can have a major influence on tumour incidences. Throughout the evaluation across studies for various tumours, the AGG notes there is no clear dose-effect concordance across studies (sometimes stated as some studies showed significant findings and some did not). This sets up a fully quantitative, statistical evaluation where the null hypothesis is that the studies being compared have no increasing tumour incidence with increasing dose versus the alternative that they have the same pattern of dose-response. Quantitative, statistically rigorous comparisons between studies can be made if the methods used in epidemiological pooling are applied to the animal studies. In the description of the pooled analysis by Pahwa et al. (2019) in RAR Volume3-B6.5, the assessment of the study (page 236) states "*The main advantage of this pooled analysis compared with the previously published individual studies was to enable a more comprehensive analysis for glyphosate with regard to confounding factors and proxy respondents.*" In the parlance of epidemiology, different strains, different housing conditions, different diets, etc. are all confounders in the evaluation of the animal studies and any evaluation of a common dose-response trend should adjust for these factors.

This is exactly what Portier (2020) did in his pooled analyses of these data. Since all animals in any one study have the same strain of animal, housing conditions, diet, etc., then by controlling for study, you control for all of these factors simultaneously. Portier (2020) also used the same logistic regression approach used by Pahwa et al. (2019) to analyze the data. Not once is the pooled analysis by Portier (2020) described or discussed in this evaluation; yet it is the only objective, quantitative analysis of the question of whether these studies show clear dose-effect concordance across studies. An analysis similar to that done by Portier (2020) should be included in this evaluation.

Dossier submitter's response to comment section 4:

The DS notes the above comment. Indeed a semi-quantitative analysis has been done, however a clear explanation is given by the DS which factors have been taken into account in the overall weight-of-evidence approach for determination of the relevance of the observed increases in incidences of certain tumours. The pooled statistical analysis of the data by Portier (2020) was not considered, again as statistical significance is not the only factor to consider (refer to the DS response to comment section 1). However, RAC is welcomed to further consider this part of the statistical analysis provided in the publication by Portier (2020). Alternatively, performing a bench-mark dose analysis of all tumour incidence data may also be useful, as this method could then take into account

any differences between the studies and gives an indication on the variability of the data and on the uncertainty of the outcome.
The DS stated the following in section 2.6.5.2 'Comparison with the CLP criteria' in Volume 1 (page 313 of the first version of the draft RAR): *"As was already indicated in the previous CLH report (2016), one important remark is that for the majority of chemical substances evaluated under the CLP Regulation, normally one study addressing each endpoint is required and this is usually considered sufficient for classification and labelling purposes. In the case of glyphosate, a large quantity of animal data is available (as discussed in the previous paragraph). Therefore, the criteria of the CLP Regulation may not be applicable directly to the available information for glyphosate as several studies are available per endpoint. In line with the previous assessment, all available data should be considered together using a weight of evidence approach with consideration of the biological significance, relationship of the applied doses to the maximum tolerated dose and the consistency of the neoplastic findings. And therefore, no conclusions were based only on the statistical significance of an increased tumour incidence identified in a single study. The current assessment is continued in the same line."*

Comment section 5:

The alleged "recommended maximum dose" does not exist for carcinogenicity studies. OECD TG 453 describes this "limit dose" explicitly for chronic toxicity studies. Instead, for carcinogenicity studies, the OECD Guidance 116 (p. 54) recommends *a maximum concentration* of the test substance in dietary studies: 50,000 ppm for rodents. The studies discussed here are below this level. In addition, the top doses used in these studies *do not exceed the maximum tolerated dose (MTD)*, and, thus, *are compliant* with the recommendations of OECD Guidance 116 for selecting the top dose. OECD Guidance 116 (p. 53): "… *the top dose should ideally provide some signs of toxicity such as slight depression of body weight gain (not more than 10%)*". However, the concern with regard to a higher depression of body weight gain is that this may obscure carcinogenic effects (see also next paragraph). According to OECD Guidance 116 (p. 53, emphasis added): "*The MTD is often used in the assessment of a chronic toxicity or a carcinogenicity study to* ***decide whether the top dose tested was adequate to give confidence in a negative result***." The concept of using the MTD to select the top dose is also applied by ECHA (2017, p.385). MTD-considerations are not limited to a decrease in body weight gain. An exceedance of the MTD includes tissue necrosis, metabolic saturation and a reduced life span due to effects other than tumours, (OECD Guidance 116, p. 53). Such effects, however, were not observed in any of the carcinogenicity studies. As for the MTD, the only concern remaining would be that the top doses were **not adequate to give confidence in a negative result**. In fact, the 1983 Study – the study with the strongest depression of body weight gain (28% reduction over all) – is the only study with a negative result concerning malignant lymphoma (ML). In other words, there is reason (recommended by OECD) to disregard this study. Taking this approach there would be four positive studies concerning malignant lymphoma, three of which show statistically significant results.
The concern regarding false negative results, because of a decreased body weight gain of more than 10% is explained in detail in the "ILSI Principles for Dose Selection in Chronic Rodent Bioassays" (OECD Guidance 116, p. 64): "*Historically, scientists have adopted a 10% decreased body-weight gain at the end of pre-chronic studies (typically 90 days duration) as the target that should not be exceeded in chronic (carcinogenicity) studies. It is now recognised that there is a positive correlation between body weight and the occurrence of certain tumours in rodent species and strains used in safety assessment or for hazard identification; i.e., the higher the body weight between 6 and 18 months on test, the higher the probability that the animal will develop some tumours. Moreover, the lower the body weight, the less sensitive the animal may be to agent-induced toxicity, including cancer.* ***A significant decrease in body-weight gain therefore could reduce the animal's ability to respond to compound-induced toxicities***.(emphasis added)"

Dossier submitter's response to comment section 5:

For carcinogenicity studies with active substances, a top dose of max 1000 mg/kg bw/day is generally applied. This is based on OECD TG 453 (2018) in which is it stated that "*a limit of 1000 mg/kg bw/day may apply except when human exposure indicates the need for a higher dose level to be used".* Thus for glyphosate a top dose of 1000 mg/kg bw/day is considered appropriate as the exposure to humans is far below this level. The

estimated systemic exposure to glyphosate is at or below the level of the current AOEL and ADI of 0.1 mg/kg bw/day and 0.5 mg/kg bw/day, respectively. Therefore, testing of higher concentrations than 1000 mg/kg bw/day is not justified according to the DS.

Please note that there are different definitions on the maximum tolerated dose (MTD). In the perspective of setting a top dose in a carcinogenicity study it is defined as the highest dose to produce toxic effects without causing death and to decrease body weight gain by no more than 10% relative to controls (ref. OECD GD 116, 2012 - ENV/JM/MONO(2011)47). As stipulated by the commentor not only a decrease in body weight gain should be taken into account, but also other effects such as includes tissue necrosis, metabolic saturation and a reduced life span due to effects other than tumours. In the CLP regulation, the MTD is defined as follows:

> *"The MTD is* ***the highest dose of the test agent during the bioassay that can be predicted not to alter the animal's normal longevity from effects other than carcinogenicity*** (emphasis added by DS)*. Data obtained from a sub-chronic or other repeated dose toxicity study are used as the basis for determining the MTD.*
>
> ***Excessive toxicity, for instance toxicity at doses exceeding the MTD, can affect the carcinogenic responses in bioassays. Such toxicity can cause effects such as cell death (necrosis) with associated regenerative hyperplasia, which can lead to tumour development as a secondary consequence unrelated to the intrinsic potential of the substance itself to cause tumours at lower less toxic doses****.* (emphasis added by DS)
>
> *Tumours occurring only at excessive doses associated with severe toxicity generally have a more doubtful potential for carcinogenicity in humans. In addition, tumours occurring only at sites of contact and/or only at excessive doses need to be carefully evaluated for human relevance for carcinogenic hazard. For example, as indicated in this Section (a) 'Tumour type and background incidence', forestomach tumours, following administration by gavage of an irritating or corrosive, non-mutagenic chemical, may be of questionable relevance, both due to the lack of a corresponding tissue in humans, but importantly, due to the high dose direct effect on the tissue. However, such determinations must be evaluated carefully in justifying the carcinogenic potential for humans; any occurrence of other tumours at distant sites must also be considered.*
>
> *The proceedings of a WHO/IPCS workshop on the Harmonization of Risk Assessment for Carcinogenicity and Mutagenicity (Germ cells) - A Scoping Meeting (IPCS, 1995; Ashby et al, 1996), points to a number of scientific questions arising for classification of chemicals, e.g. mouse liver tumours, peroxisome proliferation, receptor-mediated reactions, chemicals which are carcinogenic only at toxic doses and which do not demonstrate mutagenicity.*
>
> ***If a test compound is only found to be carcinogenic at the highest dose(s) used in a lifetime bioassay, and the characteristics associated with doses exceeding the MTD as outlined above are present, this could be an indication of a confounding effect of excessive toxicity. This may support a classification of the test compound in Category 2 or no classification.*** *(emphasis added by DS)"*

In the two mice studies, not only a decreased body weight gain of 11 to 15% was seen at the top dose in both studies, but also severe gastrointestinal signs in the 1997 study and hepatocyte necrosis and kidney chronic interstitial necrosis in the 1983 study. Therefore, there might be some evidence that the top dose levels are near or even beyond MTD. However, also the other arguments made by the DS should be considered when assessing the relevance of the observed tumour incidences. Low, but elevated incidences of renal

tumours were reported at the high doses exposures in three of the five mouse carcinogenicity studies. The effects occurred at dose levels above the OECD-recommended limit of 1000 mg/kg bw/day. The increases in renal tumours were not statistically significant in pairwise comparisons (Fisher's exact test), but only for the Cochran-Armitage trend-test. All kidney tumours were observed at termination. Moreover, no clear pre-neoplastic kidney lesions (such as renal tubular hyperplasia or necrosis) were observed. In two of the five studies, no renal tumours were reported at the two highest doses and in two studies, adenomas/carcinomas were reported in the control groups. Furthermore, no increase in renal tumours was reported in female mice. There was a positive trend in male mice, but the findings were not consistent across all studies. Therefore, human relevance of the renal tumours at very high doses is considered to be low and the overall evidence for the increase in renal tumours having been caused by glyphosate is considered insufficient for classification.

The commentor refers to "*the OECD Guidance 116 (p. 54) recommends a maximum concentration of the test substance in dietary studies: 50,000 ppm for rodents*". However, the DS is of opinion that not only a single consideration from the OECD GD 116 should be taken into account for top dose selection, but all considerations that are presented in section 3.1.2.2 of the OECD Guidance 116 (page 53/53). And as already indicated above, based on OECD TG 453 (2018) a top dose of max 1000 mg/kg bw/day is considered appropriate as the exposure to humans is far below this level. Therefore, testing of higher concentrations than 1000 mg/kg bw/day is not justified according to the DS.

In the comment it is referred to 'false negative results' in the 1983 study in mice by stating the following: "*As for the MTD, the only concern remaining would be that the top doses were not adequate to give confidence in a negative result. In fact, the 1983 Study – the study with the strongest depression of body weight gain (28% reduction over all) – is the only study with a negative result concerning malignant lymphoma (ML). In other words, there is reason (recommended by OECD) to disregard this study*." The DS does not see any reason to dismiss this study based on this argument as it is just a speculation.

The next 8 sections deal with individual tumour types as follows:
• Section 6 – malignant lymphomas in male mice (refer to attachment for the comment)
Reply by DS: In this section the view of the person who commented is given. The DS has a different opinion, which is presented in the overall assessment in Volume 1 of the RAR. The most important comments are replied to in Sections 1 to 5 above and Appendix 2 below.
In the comment it is referred to a study by Wang et al (2019). This study has been assessed in Volume 3 (B.6.5.18.9) and summarized in Volume 1 (assessment copied here).
Wang et al. 2019 evaluated the effect of glyphosate on multiple myeloma (MM) in Vk*MYC and wildtype (WT) mice. Glyphosate exposure resulted in reduced survival, increased spleen weight, chance in splenocyte number. Glyphosate induced benign monoclonal gammopathy (mouse equivalent to monoclonal gammopathy of undetermined significance (MGUS) in human) in WT mice and promotes MM progression in Vk*MYC mice. In Vk*MYC mice, glyphosate causes haematological abnormalities like anaemia and multiple organ dysfunction like lytic bone lesions and renal damage, which are hallmarks of human MM. Some limitations were noted for the study, including a low number of animals in the sub-acute study (n=5) and an unclear number of animals for the chronic study although it appeared to be 10 per group based on the individual data points in the result figures. It is also noted that the dose level used in the chronic study of 1 g/L

correlates to 90 mg/kg bw/day based on default values for water consumption. This dose level is very low compared to the guideline toxicity studies so it is surprising that findings such as effects on haematological parameters were observed in WT C57BL/6 mice while the NOAELs in the guideline chronic studies are far higher. Considering the low number of animals and the remarkably low dose levels in which effects are observed there uncertainties regarding the reliability of the study. Therefore the study is not considered to directly impact the overall assessment of glyphosate.

• Section 7 – kidney tumours in male mice (refer to attachment for the comment)
Reply by DS: In this section the view of the person who commented is given. The DS has a different opinion, which is presented in the overall assessment in Volume 1 of the RAR. The most important comments are replied to in Sections 1 to 5 above and Appendix 2 below. The information provided in this comment may be further considered by RAC.

• Section 8 – haemangiosarcomas in male mice (refer to attachment for the comment)
Reply by DS: In this section the view of the person who commented is given. The DS has a different opinion, which is presented in the overall assessment in Volume 1 of the RAR. The most important comments are replied to in Sections 1 to 5 above and Appendix 2 below. The information provided in this comment may be further considered by RAC.

• Section 9 – hemangiomas in female mice (refer to attachment for the comment)
Reply by DS: In this section the view of the person who commented is given. The DS has a different opinion, which is presented in the overall assessment in Volume 1 of the RAR. The most important comments are replied to in Sections 1 to 5 above and Appendix 2 below. The information provided in this comment may be further considered by RAC.

• Section 10 – skin keratoacanthomas in male rats (refer to attachment for the comment)
Reply by DS: In this section the view of the person who commented is given. The DS has a different opinion, which is presented in the overall assessment in Volume 1 of the RAR. The most important comments are replied to in Sections 1 to 5 above and Appendix 2 below. The information provided in this comment may be further considered by RAC.

• Section 11 – skin basal cell tumors in male rats (refer to attachment for the comment)
Reply by DS: In this section the view of the person who commented is given. The DS has a different opinion, which is presented in the overall assessment in Volume 1 of the RAR. The most important comments are replied to in Sections 1 to 5 above and Appendix 2 below. The information provided in this comment may be further considered by RAC.

• Section 12 – hepatocellular adenomas in male rats (refer to attachment for the comment)
Reply by DS: In this section the view of the person who commented is given. The DS has a different opinion, which is presented in the overall assessment in Volume 1 of the RAR. The most important comments are replied to in Sections 1 to 5 above and Appendix 2 below. The information provided in this comment may be further considered by RAC.

• Section 13 – other tumours (refer to attachment for the comment)
Reply by DS: noted. The information provided in this comment may be further considered by RAC.

Appendix 1 – Power and dose-response (refer to attachment for the comment)
Reply by DS: The author provides some additional comments on the statistical analysis of the results in Appendix 1 (please refer to the Appendix for the full comment). The DS

emphasises again that, as also indicated in OECD GD 116 and in the previous EU evaluation, statistical significance is not the only criteria to decide if an effect reported in a study is treatment-related. Also background incidence and variability of the tumor type was taken into account. Further, it was considered whether or not there was a dose-response or that the effect was only seen at the top dose. It was also taken into account whether or not the top dose was at or above the limit dose or the maximum tolerable dose (MTD). As multiple studies for each species are available, the DS looked for dose-effect concordance between studies. Moreover, biological plausibility was considered e.g. were there any precursor effects seen. The DS is of opinion that for multiple testing as the author did in his analysis a correction should be made for chance findings.

Appendix 2 – Technical comments on individual studies

Each comment is given in Times new roman fonts (in black) and the response by the DS is given in Verdana fonts (in blue).

251:5:all – This study should simply be listed as unacceptable and all other detail removed.

Reply by DS: For completeness a short description of the study (rat, study 3, report no 1231) will be given in an updated version of the RAR and why this study is considered as unacceptable.

251:6:4-5 – The added interim sacrifice groups are listed as being included to study non-neoplastic findings yet they are included in the analysis of neoplastic findings. Why? Even if they are evaluated for neoplastic findings, why are they grouped with the 2-year study findings rather than being discussed separately? Do animals at 26 weeks count the same for carcinogenicity evaluation as animals at 104 weeks? Correct and re-assess accordingly.

Reply by DS: all animals, including the interim groups, were investigated on incidence of microscopic lesions (rat, study 4, 1997, report no IET 94-0150). The first skin keratoacanthoma was seen after 78 weeks (control, 1), and after 104 weeks. In this context the total number of neoplastic findings were taken into account and compared to control. Since the number of animals per group is comparable, the total sum of incidences can be compared. This would be different if you want to know at what age tumors appear.

251:7:9-11 – Interim sacrificed animals are used in this analysis but should have been handled separately. The two-sided p-value for skin keratoacanthomas listed in Volume 3-B6.5 (page 50) of 0.21 cannot be replicated; the number we produced is 0.110. The difference between this p-value and that provided by Portier (2020) of p=0.029 is his use of only the core 2-year animals in the analysis (this is true for all of his analyses) and the p-value is one-sided. There is no mention of the increase in kidney adenomas (p=0.004) in this study (Study 4, 1997) identified in Portier (2020). Why? Update and re-assess accordingly.

Reply by DS: This comment also refers to study 4 in rats (1997, report no IET 94-0150).
With regard to the first point made: *Interim sacrificed animals are used in this analysis but should have been handled separately,* see the DS response on 251:6:4-5.
With regard to the kidney adenomas, according to the statistics performed as set in the study protocol, all changes regarding neoplastic lesions were not statistically significant (see also response on Section 1). Considering the skin keratoacanthomas, based on the RMS re-assessment, there appeared to be a slight non-significant increase in skin keratoacanthomas in male rats, the two-sided p-value of 0.21 for skin keratoacanthomas (two-sided for the extended Mantel-Haenszel test (stratified Cochran-Armitage trend).

252:2:all – It is not apparent why it is reasonable to analyze this study by considering interim deaths separately from terminal sacrifice animals. This is not done for any other study. This study also saw an increase in adrenal pheochromocytomas cited in Portier (2020) which is not addressed, and therefore should be included in the evaluation.

Reply by DS: the results of the interim deaths and the terminal sacrifice animals are indeed reported separately (rat, study 5, 1996, Report No. 886.C.C-R). The evaluation

was done based on the sum of the incidences found in the test groups i.e., interim deaths and terminal sacrifice animals.
With regard to your comment on adrenal pheochromocytomas, an increase of adrenal pheochromocytomas was seen only in controls and in the high dose group male rats, not in the low and mid-dose group. In one other rat study (study 2) this tumor type was also seen. In this study no differences was seen between controls and treated rats, in all groups, with the highest incidence in the control group. Pheochromocytoma is a rare, usually noncancerous (benign) tumor that develops in an adrenal gland. The relevance of this tumor in relation to exposure to glyphosate is therefore questionable.

252:3-6:all – This study is not a carcinogenicity study and this should be clearly stated in the second sentence of paragraph 3.
Reply by DS: The study concerns a one year dietary toxicity study in rats (study 6, 1996; report No. CTL/P/5143), i.e., a long term toxicity study. This is clearly stated in the first sentence.

252:7:3-4 – These 35 animals were sacrificed at 12 months (not mentioned).
Reply by DS: agree with this comment. The following sentence should be added (rat, study 7, 1993; Report No. 7867): In addition, five groups of 35 rats/sex, receiving daily dietary doses of, 0, 10, 100, 300 or 1000 mg/kg bw/day, *were included for interim sacrifice at the 12th month for evaluation of chronic toxicity.* The latter will be added to a revised version of the RAR.

253:4:all – Again, we see a discrepancy in how the interim sacrifice animals are used to evaluate carcinogenicity; in this case they are not included in the counts for keratoacanthomas.
Reply by DS: No abnormality was detected in skin of the rats (male and female) exposed to glyphosate via the diet up to 52 week.

253:6:4-7 – Again, there is an inconsistent use of interim sacrifice animals with the 12-month animals being included in the evaluation of pancreas islet-cell tumours in this study. Not mentioned in this summary are the findings in Volume 3 regarding historical controls. The findings in all three exposure groups are outside the range of the historical controls provided with the study. The actual individual historical controls for islet-cell adenomas and carcinomas combined linked to this study from an EPA internal memo are given as 2/68 (2.9%), 5/59 (8.5%), 4/69 (5.8%), 1/57 (1.8%), 5/60 (8.3%), 3/60 (5.0%), and 3/59 (5.1%) which match the range of 1.8% to 8.5% cited in Volume 3. Thus, the 4.2% in controls in this study is clearly in agreement with these controls. It is unclear why these findings can be excluded as not treatment related simply because there is no increasing response with increasing dose.
Reply by DS: This finding in study 8 (rat, 1990; Report No. MSL-10495) was not considered to be treatment-related, based on the following considerations: no dose-related trend for this finding in the male groups, as indicated by the lack of statistical significance in the Peto trend test. There was also no dose-related response seen in pre-neoplastic effect (hyperplasia) and or progression (carcinoma) of this lesion seen. In addition, in the five remaining carcinogenicity studies in the rat with even higher dose levels clearly no effect of pancreatic islet cell adenomas was observed. And such effects were not observed in females.

253:6:7-9 – As shown by Portier (2020), the increase was seen for both hepatocellular adenomas (p=0.015, Cochran-Armitage trend test one-sided exact) and for combined adenomas and carcinomas (p-0.050). Thus, there was no increase in carcinomas, but the combined adenomas and carcinomas were still increased. Note that the interim sacrificed animals were also used in the RAR for these tumours and the thyroid C-cell tumours and keratoacanthomas mentioned in the next sentence.
Reply by DS: Noted. In study 8 (rat, 1990; Report No. MSL-10495) an apparent increase in liver cell adenomas was observed in high dose males (8 versus 3 in controls) although no effect on non-neoplastic changes in the liver nor a progression to carcinomas was observed. The apparent increase in combined incidence (adenomas and carcinomas) was

not reported to be statistically significant (p=0.0752). See also the reply to Section 1. The relevance of the findings in the context of the classification of glyphosate is extensively discussed in Volume 1.
It should be noted that for the other rat studies the incidences of hepatocellular carcinomas were not explicitly reported in Tables 2.6.5.1-4a/b/c. There was no increase compared with the respective control groups in any of these studies thus this information does not influence the outcome of the assessment. However, for clarity the DS will add the incidences of hepatocellular carcinomas in a revised version of the RAR.

253:8:5-8 – It is difficult to understand how a study with a statistically significant increase in testicular cancers can be discarded because the doses used were too small to elicit an increase in tumour incidence. In addition, the study report is 2,950 pages long, describes clinical chemistry done at 4,8,12, 18 and 24 months, has detailed survival and body weight data, and full histopathological examinations with detailed reports on each animal. In what manner is this particular study report of poor quality? This study should be taken into consideration in the evaluation and the positive findings should be included in the evidence analysis.
Reply by DS: The study is considered not acceptable: dose levels were too low compared to other chronic studies, and there was a lack of general systemic toxicity. More importantly, when considering all acceptable and guideline-compliant studies in rats, it is noted that no effect on interstitial cell tumours of the testis were observed in any of the other six carcinogenicity studies in the rat even though they were dosed at much higher dose levels. In addition, the study report is of poor quality and at times unreadable.

253:9:1-3 – In addition to the tumours mentioned here, this study saw a significant increase in **thyroid C-cell carcinomas** (p=0.003, Cochran-Armitage trend test, one-sided exact) and a marginal increase in C-cell adenomas and carcinomas combined (p=0.072) in females. Historical control data were provided for **the interstitial-cell tumours** in males for 5 control groups in the same laboratory (4/116, 5/75, 4/113, 6/113, 5/118, page 14 of the study report), all of which are below the level reported in the high dose of 6/50. Peto's historical control test for trend using these data yields a p-value of 0.013. Why is this finding so easily excluded?
Reply by DS: As mentioned above this study is considered not acceptable. However, since the study was subject to debate with regard to certain tumour types, it was taken here into consideration, along with the six guideline-compliant studies for the evaluation of the interstitial-cell tumours of the testes and Pancreatic islet cell adenomas (and carcinomas).

254:4:6-7 – Portier (2020) noted a significant increase in lung alveolar-bronchiolar carcinomas in male mice (p=0.028, Cochran-Armitage trend test, one-sided exact), which should be added.
Reply by DS: See reply on Section 1 - The statistical analyses provided by the DS are based on values reported in the original study reports, the statistical re-assessment of the data given in the previous CLH report (2016) and/or by the DS own statistical analysis. It should be taken into consideration that, as also indicated in OECD GD 116 and in the previous EU evaluation, statistical significance is not the only criteria to decide if an effect observed in a carcinogenicity study is treatment-related. This type of tumour was not seen in any of the other studies in CD-1 male mice, neither an increase in lung alveolar-bronchiolar adenomas was seen.

254:7:4-5 – Incident counts for combined male and female data do not match with the individual counts by sex for bone femur hepatopoiesis, subcapsular hyperplasia and kidney nephropathy. Correct accordingly.
Reply by DS: agree, table B.6.5.13-8 in Volume 3 (mouse, study 3) should be adapted accordingly. Not critical for classification and labelling.

255:1:2 – There were also significant increases in hemangiomas (p=0.002, Cochran-Armitage trend test, one-sided exact) and Harderian gland tumours (p=0.040) in females and almost significant increases in hemangiosarcomas (p=0.062), kidney tumours (p=0.062) in males. Portier (2020) saw very significant increases in these tumours when they are compared to the historical controls from a literature database used in the previous review. This information should be included.
Reply by DS:

See reply on Section 1 - The statistical analyses provided by the DS are based on values reported in the original study reports, the statistical re-assessment of the data given in the previous CLH report (2016) and/or by the DS own statistical analysis. It should be taken into consideration that, as also indicated in OECD GD 116 and in the previous EU evaluation, statistical significance is not the only criteria to decide if an effect observed in a carcinogenicity study is treatment-related. For the heamangiomas in females and the haemangiosarcomas in males it is referred to the overall assessment in Volume 1 at Section 2.6.5.1-10. For the kidney tumours it is referred to Volume 1 Table 2.6.5.1-9. The Harderian gland tumours in females were not seen in any of the other studies in CD-1 mice.

255:3:3-4 – The change in hemangiosarcomas in males in the 1993 study was statistically significant (p=0.004, Cochran-Armitage trend test, one-sided exact) and this is an extremely rare tumour based on historical controls used in your previous evaluation (see Portier, (2020)). Malignant lymphomas in males showed a marginal increase (p=0.087) and lung tumours were significantly increased in females (p=0.048) (see Portier, (2020)). In Volume 3 (p.154), the AGG writes "It should be noted that not all animals from low and mid dose levels were examined; only the animals that died during the study or that were killed in extremis were investigated in these groups, therefore no comparison can be made for these dose groups.". This 1993 study is the only study where this issue was mentioned as a problem although the same pathology approach was also used in mouse studies 1(2009) and 2 (2001) and in rat studies 1 (2009), 5 (1996) and 7 (1993). In all cases, the study protocol included histopathological examination on all tissues collected from control and high dose animals, all animals that died or were killed in extremis during the study, all gross and palpable lesions, and select organs including livers, lungs, and kidneys. Thus, tumours that were significant enough to be observed grossly or palpated were also evaluated and it is not clear that "no comparison can be made for these dose groups". If these tumours develop rapidly (such as malignant lymphomas), it is likely all tumours were identified and examined in the interim groups.
Reply by DS: noted. Refer to our comment on section 2 above.

255:8:8 – The patholoy presented here for kidney adenomas is the original pathology from the laboratory and ignores the re-evaluation of the pathology which saw an increase in kidney carcinomas. There were historical controls provided for this study which are available from the USEPA that were used in the analysis by Portier (2020) to show a p-value for trend of 0.008 for the second pathology evaluation using Peto's test. For this one study in mice, Volume 3 combines granulocytic leukemias (which are not lymphomas) with the malignant lymphomas resulting in a non-significant finding in females whereas for malignant lymphomas alone, there was a marginal trend of p=0.070 (Cochran-Armitage trend test, one-sided exact). In addition, Portier noted a significant increase in composite lymphosarcomas of the spleen in females (p=0.016) that is not discussed here. Update accordingly with these fidnings and re-evaluate.
Reply by DS (mouse, study 6, 1983, report no 77-2061):
Kidney adenomas: the DS used the tumor frequencies from the re-evaluation of the pathology findings for study 6 in mice (1983, report no 77-2061). Please refer to Volume 1 section 2.6.5.1.1.3 at point 9 (page 293 of the first draft version of the RAR) were an assessment of these findings is given. Open point for DS to add these tumour frequencies to Volume 1 page 255 and to Volume 3 (Table B.6.5.16-8). The applicant provided a statement that historical control data for this study are not available anymore.
Malignant lymphomas:
The remark is noted. In the overall assessment it was already indicated that in the low dose group there were three cases of cases of granulocytic leukaemia, which are not lymphomas. This does not change the overall picture in the weight of evidence approach for this tumour type.
Composite lymphosarcomas of the spleen: This type of tumour is a systemic tumor. Therefore, the incidence should not be analysed by organ in which it was found, but the overall incidence of composite lymphosarcomas should be considered. This has been done by the DS. In this study, the overall incidences of composite lymphosarcomas in females were 4/49, 1/49, 1/49 and 6/49 for the control group, low, mid and high dose groups, respectively. So, there is no dose-related increase in tumour incidence when all systemic composite lymphosarcomas are considered simultaneously.

255:11:4-5 – The Joint Meeting on Pesticide Residues (2017) that reviewed glyphosate noted another two carcinogenicity study they listed as Takashi (1999), one in CD-1 mice and the other in rats. According to JMPR, the mouse studies showed increases in kidney tumours in male mice and malignant lymphomas in female mice. Why have these studies have not been provided?
Reply by DS: both RMS and applicant had no access to these studies.

292:last paragraph:1 – 1993 is incorrect, this is the 1983 study.
Reply by DS: agree, 1993 should be 1983. This will be amended in a revised version of the RAR.

293:Table 2.6.5.1-9a - 1993 is incorrect, this is the 1983 study.
Reply by DS: agree, 1993 should be 1983. This will be amended in a revised version of the RAR.

293:4:2 - It is stated: "In the study by (1983), nonneoplastic kidney pathology in the form of chronic interstitial nephritis was reported to be increased, but is not considered to be a precursor for renal tubular cell adenoma". However, on 295:3:11 - citing from the CLH report (2016) it says: "There was a positive trend for chronic interstitial necrosis …". However, this second statement is wrong. According to the original study report (Pathology Annex, Table 19C) it is interstitial nephritis. This clarification is important in the context of the "excessive" dose discussion, because "necrosis" could indeed be an indication that the MTD was exceeded. However, interstitial nephritis isn't and therefore the conclusion of exceeding the MTD is not supported by the evidence. Correct accordingly.
Reply by DS: Arguments are mentioned to be an indication that the MTD was exceeded are '*Mean **terminal body weight** of top dose males in the study by (1983) was by **11% lower** than in the controls'.* In addition *there were gastrointestinal signs and lesions in the first and a significant increase in central lobular hepatocyte hypertrophy and central lobular hepatocyte **necrosis** suggesting some liver toxicity in the second study.* In this CLH report was also referred to the chronic interstitial necrosis, but indeed this is not correct. Nevertheless the other observations point in the direction that the MTD was exceeded.

293:5:5-7 - According to the RAR referring to the 2001 Study (p. 293, last paragraph) "The increase at the mid (3.8%; 1/26) and high dose (4.0%; 2/50) was above HCD mean, but within HCD range (mean 2.0%; range 0-6%, based on 8 studies using the same strain of mice, from the same lab, years 1996-2002)." These numbers are very strange. In Volume three, for the 2001 study, the historical control data for malignant lymphomas is described as 7 studies conducted between 1996 and 2002 instead of 8. In the original study report (Annex 8) , historical control data are provided for 5 studies only from 1996 and 1997 with incidences of only kidney adenomas (no carcinomas) with rates of 0/50, 0/50, 0/50, 2/50 and 3/50 for an average of 5/250 or 2%. Because kidney tumours are rare, a spontaneous incidence of 6% appears very high. The control group incidences of all 8 studies should be disclosed– it could be possible that the upper limit of 6% is due to an outlier, and therefore should be excluded.
Reply by DS: The HCD mean and range used for the overall assessment is correctly given in Volume 1. The HCD mean was 2.0% with a range 0 of 6%. This was based on 8 other studies using the same strain of mice, from the same lab, run over the years 1996-2002 (start year 1996 to 1999). The reported incidences for the eight studies are 0% (0/50), 0% (0/50), 0% (0/50), 2% (1/50), 2% (1/50), 2% (1/50), 4% (2/50), and 6% (3/50) (data presented in numerical order, not in chronological order). These data show that incidences of 0 to 3 per study may be considered a background incidence.

Epidemiology

Each comment is given in Times new roman fonts (in black) and the response by the DS is given in Verdana fonts (in blue).

Please note that the same comment was submitted in the EFSA process. Refer to Reporting table public TOX 2(67) for the response by the applicant on the epidemiology studies.

1. Exposure Assessment in the Andreotti et al. (2018) study
Several factors related to exposure that are not discussed in the RAR make the Andreotti et al. (2018) study unreliable regarding findings on NHL.
1.1 The imputation of exposures for participants that did not respond is unreliable and biased.
Heltshe et al. (2012) [3] discuss the reliability of the imputation methods used in the Andreotti et al. (2018) study. In the Andreotti et al. (2018) study, 37% of the study population (20,968 applicators) did not respond to the questionnaire. Using multiple imputation, Heltshe et al. (2012) imputed the exposure for the non-respondents. Heltshe et al. (2012) withheld a random sample of 20% (7,269 applicators) to assess the imputation methods. A simple set of calculations from that manuscript (see Addendum 1) show that the accuracy (defined as (true positives + true negatives)/7269) for estimation of use/non-use of glyphosate was 55.7% in the withheld applicators. This is not very different from 50% which is what would be expected for a random assignment of people to exposed or non-exposed groups. The sensitivity (probability of finding a true positive amongst all true positives) was only 51.1% (effectively random) and the specificity (probability of finding a true negative amongst all true negatives was 60.9%. Blair et al. (2011) [4] estimate that with a sensitivity of 51%, the ability to identify a true relative risk of as high as 3 (see their Figure 1) is greatly diminished with a substantial bias toward a null result. Thus, for the 37% of the study population where imputation was used, the best estimate is there would be almost no power to detect a positive outcome. Add to this the fact that they observed 52.73% as exposed and estimated only 45.42% as exposed could easily result in differential exposure misclassification forcing any true positive relative risk to 1 or below 1. Thus, using their own data on the accuracy of the imputation, there is substantial misclassification of exposure in those who failed to respond.

Reply DS to point 1.1: this comment concerns new information for which no DS response can be given at this timepoint. Please also refer to Reporting table public TOX 2(67) for the response by the applicant to this comment. RAC is welcomed to take this information into further consideration.

1.2 Those who did respond are also likely to have substantial misclassification of exposure
Agricultural use of glyphosate in the United States has increased dramatically over the course of the AHS. Using USDA and EPA data, agricultural use in the US was 12,474, 35,720, 71,144 and 106,963 thousand kilograms in 1995, 2000, 2005 and 2010 respectively [5]. Thus, during the critical windows during which exposure histories were being obtained for the most recent questionnaire (1999-2005), agricultural use of glyphosate doubled in the U.S. and from 1999 to 2010, when case-status was being obtained) agricultural use tripled, mostly due to the introduction of genetically modified crops that are resistant to glyphosate. Farmers interviewed at the beginning of this time period (1999-2002) are likely to have fewer and much smaller exposures than those interviewed toward the end of this period (2003-2005). Using the information over this period as indicative for the entire period will clearly underestimate exposure for the entire period with the underestimation being worse for the early interviewees than for the late interviewees. The only evaluation which is likely to have little exposure misclassification is the evaluation using a 20-year lag time since this evaluation uses neither the imputed exposures nor is biased by the rapidly changing exposure patterns in the US. Using a meta-analysis to combine the results from the analysis using a 20-year lag results in a meta risk ratio of 1.21 with a 95% confidence bound of (0.963, 1.304), a marginally significant finding.

Reply DS to point 1.2: the increased exposure is just a speculation and not supported by any data. Indeed, the use of glyphosate has in general has increased over the years, but this does not say anything for the use pattern of a specific farmer or applicator.

1.3 The intensity of exposure is improperly weighted for glyphosate

The lifetime intensity-weighted days of pesticide use are the product of the frequency of use, days of use and an intensity score. Coble et al. (2011) [6] provide the specifics for this calculation. The intensity score is determined by the formula (MIX+APPL+REPAIR)*PPE where MIX has a score of 0 (never mixed chemicals), 20 (mixed <50% of the time) or 50 (mixed ≥50% of the time), APPL refers to a score between 0 and 150 for herbicides and depends on how the herbicide was applied (0 for never applied herbicide to 150 for air blast spraying), repair was 0 (never repair spraying equipment) or 20 (repaired equipment) and PPE ranged from 0% reduction to up 60% reduction depending on equipment used. For MIX, APPL and REPAIR, specific questions were asked for each pesticide. However, for PPE, the question was general across all pesticides. Thus, applicators who sprayed a variety of controlled pesticides requiring serious protective equipment (Tyvek, gas masks, etc.) and glyphosate (which has no formal requirement for serious protective equipment) would get lower scores than those who did not use pesticides requiring this gear and also applied glyphosate. This is most applicable to professional applicators and would create an exposure misclassification for glyphosate.

Reply DS to point 1.3: this comment concerns new information for which no DS response can be given at this timepoint. The intensity score to assess the exposure seems rather crude and it should be noted that this is based on self-reporting instead of measurement of the actual exposure of an operator/applicator.

1.4 Conclusion for Andreotti et al. (2018)
Overall, this study is of low reliability. The study is likely to be suffering from serious exposure misclassification which will force the relative risks toward the null or even below the null. Thus, the power to detect an effect in this study was likely greatly reduced and the observed low relative risks are expected and unreliable. The only case where this may not be true is for the evaluation using a 20-year lag, which shows a marginally significant positive finding.

Reply DS to point 1.4: the DS considers this study of high reliability (refer to the assessment in Volume 3 and Volume 1). Despite this high reliability, it should be noted that the assessment of exposure (self-reported using questionnaires) may still be affected by recall bias. Non-differential misclassification bias may occur. Also, statistical significant findings may have occurred by chance because of the high number of cancer sites assessed.

2.0 Females in Pahwa et al. (2019)
In Volume 3 (page 238), it is noted that "Compared to the DeRoos et al. 2003 study it is noted that more cases and controls were included in the analysis from Pahwa, 2019 as subjects with missing pesticide data were not excluded from analysis. This may be one of the explanation between the difference in the outcome of the De Roos, 2003 study which found an association between ever use of glyphosate and NHL and this Pahwa, 2019 study." However, the biggest difference between the two studies is the inclusion of females. Both the McDuffie et al. (2001) study and the DeRoos et al. (2003) study included only men. The difference between McDuffie et al. (2001) and the Canadian data in the Pahwa et al. (2019) study is the loss of 4 cases which Pahwa et al. (2019) point out were misclassified cases of NHL. The difference between the DeRoos et al. (2003) study and the American data in Pahwa et al. (2019) constitutes 307 additional cases and 1056 additional controls. Of these, 184 (60%) of the cases and 707 (67%) of the controls are female thus roughly 2/3 of the additional study participants are women. Most of these additional cases and controls came from the Nebraska study.
There are other reasons this study has a greater overall study population including the imputation of age for some study subjects who had failed to answer that question (175 additional study participants). In the analyses, there are clear differences between the studies that could have impacted the results. Some of these differences could explain the results. For example, missing data on duration and frequency of use was excluded in DeRoos et al. (2003) whereas Pahwa et al. (2019) used median values from controls to impute values (simple imputation) in the exposed. This could bias results toward the null because of misclassification. But any differences you might attribute to different methods of analysis could also be attributed to the possibility that females have a different response and/or exposure pattern to glyphosate when compared to males. For a direct comparison, it is useful to conduct a meta-analysis of the most-adjusted values from DeRoos et al. (logistic model) and McDuffiie et al. (no pesticide adjustment). Using the DerSimonianLaird method in Stata to get a combined ever/never odds ratio

yields a value of 1.49 (0.87-2.54). This compares to the result in Pahwa (2019) of 1.13 (0.84-1.51); roughly a 73% reduction in effect between using the results from the original studies and the result of the pooled analysis. Since these two studies are clearly not from the same populations, you cannot just ignore DeRoos et al. (2003) and replace those findings with Pahwa et al. (2019); the studies must be considered independently.

Reply DS to point 2: Please refer to Reporting table public TOX 2(67) for the response by the applicant to this comment. It is agreed with the applicant that "*The commenter argued that imputation of missing values could have exerted a null bias. That is speculation unsupported by evidence. The commenter also speculated that women could have a different response to glyphosate than men, again unsupported by evidence. The commenter's argument that the results from Pahwa et al. (2019) with more comprehensive control of confounding should not supplant the original analyses by De Roos et al. and McDuffie et al. is not supported by evidence.*" Further, the general comment on case-control studies by the DS is repeated here again (Volume 1 page 313): "*As already reported in the previous evaluation (CLH 2016, RAC 2017) some of the case-control studies reported slightly increased ORs for certain tumours. However, most of these studies had limitations such as a lack of adjustment for confounders such as other pesticide exposure or lifestyle factors, were based on a very low number of exposed cases and/or had a high proportion of proxy responders. Adjusting for confounding factors such as exposure to other pesticides was shown to lower the ORs in most of the studies where such an exercise was conducted. Proxy responders were also found to lead to higher ORs than self-responders (e.g. Lee et al. 2005). Besides these limitations there is a concern for recall bias for the case-control studies and it is worth noting that the observed effects were not replicated in the prospective study. Further, considering NHL as an outcome parameter, it should be noted that this is not a specific disease but a broad spectrum of disorders more correctly referred to as lymphocytic lymphomas, each with possible different aetiologies. They are all classified as not being Hodgkin lymphoma, and the terminology has changed over the years - some lymphomas are described differently today compared to previously. This complicates the evaluation of the studies.*"

3.0 Publications Missed In The Evaluation
Donato et al. (2020) [9] conducted a systematic review and then a meta-analysis of studies of glyphosate exposure with NHL and multiple myeloma (MM). Their primary meta-analysis uses 7 studies. This evaluation uses weights in the meta-analysis which cannot be replicated and as such, this study is unacceptable.
Kabat et al. (2021) [10] conducted a sensitivity analysis of the meta-analysis conducted by [11] to determine how the choice of exposure definition and latency period affect the summary estimate from the meta-analysis. They conducted an ever/never analysis for 5 studies [1, 2, 12-14] getting an mRR=1.05 (0.87-1.28) (confirmed by reanalysis by myself). They then show that the Andreotti et al. (2018) [1] study has the biggest impact on their mRR. They then substituted the 20-year lag Q4 value from Andreotti et al. (2018) and got an mRR=1.16 (0.96-1.40) (confirmed by reanalysis). They also examined the exposures and lags used by Zhang et al. (2019) and identified when shorter lags lost statistical significance and what different measures changed statistical significance; all of these sensitivity analyses made changes only in which RRs were used from Andreotti et al. (2018). They confirmed that long-term and high exposures support an association between NHL and glyphosate usage. They also criticize the Leon et al. (2020) [15] study and conclude "Because crop-exposure matrices do not provide specific pesticide exposure information, however, the resulting pesticide use data is of questionable value for epidemiologic studies …".
Meloni et al. (2021) [16] conducted a case-control study of 867 incident lymphoma cases and 774 controls as part of the Italian Gene-Environment Interactions in Lymphoma Etiology study. 2.4% of the cases and 1.9% of the controls were ever exposed to glyphosate. The OR for the association between glyphosate and NHL was 1.4 with a 95% confidence bound of 0.62 to 2.94 based on a total of 14 exposed cases and 15 exposed controls. A full evaluation of this study should be included.

Reply DS to point 3: these studies are new studies that were published after submission of the dossier and were not yet taken into account in the assessment. For Kabat *et al.*

(2021) and for Meloni *et al.* (2021) refer to RCOM comment 21. For Donato *et al.* (2020) no assessment is available at this timepoint.

4.0 Comments on Leon et al. (2019)

Leon et al. (2019) [15] formed the AGRICOH Consortium to evaluate the relationship of 33 pesticides (including glyphosate) with NHL in a pooled analysis of three large agricultural worker cohorts. The three cohorts were the AHS (described above for Andreotti et al. 2017), the AGRGICAN cohort [17] and the CNAP cohort [18]. While they used the AHS cohort, they excluded 4619 commercial applicators (non-farmers) used in the Andreotti et al. (2017) study and included 1620 farmers with no information on frequency of exposure that were excluded from Andreotti et al. (2017). The Agriculture and Cancer (AGRICAN) cohort consists of 181,747 farm owners and farm workers (male and female) over 18 years of age who were affiliated with the French national health insurance system for farm workers for at least 3 years and who resided in one of the 11 departments in France covered by population cancer registries. They were enrolled between 2005 and 2007 and cancer and mortality were assessed up to the end of 2009. Participants completed self-administered questionnaires regarding cultivation of 13 crops and 5 animal species and on the performance of various pesticide treatment tasks. Exposure to the various pesticides was assessed using crop-exposure matrices (CEM1) specific to France that were derived based upon what chemicals were authorized and recommended for what crops in what years. The Cancer in the Norwegian Agriculture Population (CNAP) cohort consists of 147,134 farm-holders (owners and non-owners using a farm, male and female) who had participated in at least one of five national agricultural and horticultural censuses conducted in 1969, 1974, 1979, 1985 and 1989. The census included information on crops and livestock produced, acreage, technology, pesticide expenses and pesticide spraying equipment. Exposure to the various pesticides was assessed using crop-exposure matrices (CEM2) specific to Norway that were derived based upon what chemicals were sold and registered for use in specific years. Cancers were assessed using the Norwegian National Cancer Registry up to the end of 2011. AGRICAN had more females (44%) than the other two cohorts (16% CNAP and 3% AHS) while CNAP contributed the bulk of the person-years of follow-up with 2,396,595 person-years compared to 751,880 for AHS and 426,340 for AGRICAN. The largest crop plantings reported differed also among the three cohorts with 70% of AGRICAN members reporting cultivating hay, meadows and grasslands, 32% in CNAP reporting potatoes and 74% of AHS reporting corn. The majority of the NHL cases were from CNAP (1498) with AHS (493) and AGRICAN (439) contributing many fewer cases.

Leon et al. (2019) reported results for ever/never use of glyphosate only and did not consider lag times or any type of exposure-response analysis. Over 80% of the participants from the AHS reported ever using glyphosate whereas less than 40% used glyphosate in the other two cohorts according to the two CEMs. Minimally- and fully-adjusted (including other pesticides) analyses were run for each cohort and then combined using random effects meta-analysis. The fully-adjusted meta hazard ratio (mHR) for glyphosate and NHL was 0.95 (0.77-1.18) and the crudely-adjusted mHR was 0.98 (0.76-1.25). Separate analyses were also done for various subtypes of NHL. For chronic lymphocytic leukemia and small lymphocytic lymphoma (CLL) the mHRs were 0.92 (0.69-1.24) fully adjusted and 1.09 (0.70-1.70) crude. For diffuse large B-cell lymphoma (DLBCL) the mHRs were 1.36 (1.00-1.85) fully adjusted and 1.12 (0.86-1.45) crude. For follicular lymphoma (FL) the mHRs were 0.79 (0.52-1.21) fully adjusted and 0.95 (0.70-1.45) crude. For multiple myeloma and plasma-cell leukemia (MM) the mHRs were 0.87 (0.66-1.15) fully adjusted and 1.00 (0.83-1.21) crude. There was evidence of heterogeneity among the three cohorts for NHL (I2=57%) but no heterogeneity among the cohorts for the various subtypes of NHL.

The biggest strengths of this study are the sample sizes and the cohort design. The greatest limitation of this study is that AGRICAN and CNAP are studies of crop and livestock production with no self-reported use of glyphosate exposure. Registration of glyphosate and recommendations for use on a specific crop do not guarantee it will be used on that crop which would lead to overestimation of exposure. In addition, off-label use or use for weed control around fields could have occurred which would lead to an underestimate of exposure. It is likely that this exposure misclassification is non-differential reducing statistical power and lowering mHRs towards the null (1.0). They also did not account for re-entry tasks in the questionnaires, only spraying tasks. This could also lead to exposure misclassification in the two European cohorts.

To evaluate the quality of their CEMs with respect to self-reported exposure, Brouwer et al. (2016) [19] applied both CEM1 and CEM2 (modified for US registration and recommendations) to members of the AHS cohort who completed the phase II questionnaires. Agreement between self-reported use and the assigned exposure was poor with CEM1 showing only 65.7% agreement for glyphosate and CEM2 showing 57.8% agreement. In a letter to the editors of the journal, Tomenson (2017) [20] argued that the exposure misclassification introduced by these

CEMs could be differential and in either direction making the pooling project difficult to interpret and utilize. The authors disagreed [21] about the overall value of the pooling effort, but acknowledged the limitations noted by Tomenson (2017). Because of the exposure misclassification also likely in the AHS and because this is basically a study of crop tillage and not glyphosate use, this study is unreliable for use in evaluating the linkage between NHL and exposure to glyphosate formulations.

Reply DS to point 4: the above comment is noted by the DS and it is referred to RCOM comment 21.

5.0 Conclusions From The Epidemiological Literature
The definition of limited evidence of carcinogenicity in humans in the Guidance on the Application of the CLP Criteria [22] (page 373) is "a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence."
This category fits this literature perfectly. The Assessment Group on Glyphosate of the Rapporteur Member States places too much weight on the faulty 2019 AHS study and inappropriately dismisses the remaining studies as having recall bias. These studies have the potential for recall bias, but this cannot be established definitively. All meta-analyses that exclude Andreotti et al. (2019) have shown a positive association and when you use the longest lag time from the Andreotti et al. (2019) study, you have a weak association. Thus, a positive association has been established. Based on the animal carcinogenicity data and the associated mechanistic data, this association is credibly causal. Finally, chance, bias and confounding cannot be ruled out.
The conclusion provided for the epidemiology literature page 316 should read "When all available epidemiological data is taken into consideration, it is concluded that there is Limited Evidence of Carcinogenicity in humans.

Reply DS to point 5: In the studies evaluated by the DS, some weak associations were observed, however, as clearly explained in the assessment in Volume 1 all epidemiological studies (case-control studies, cohort studies and the meta-analyses) had its limitations and therefore chance, bias and confounding could not be excluded. In addition to reliability and robustness with respect to the analyses made in these studies, the relevance for the hazard assessment and classification and labelling of the substance should also be considered. Refer also to RCOM comment 21.

RAC's response

RAC acknowledges the assessment of comments performed by the DS. RAC has included in the opinion an assessment of the animal carcinogenicity studies (including the assessment by Portier (2020)) taking into account the different statistical methods used, as well as the epidemiological studies including also the recent studies mentioned during the consultation. In arriving at their conclusion for a classification for carcinogenicity RAC has reviewed the animal and human data according to the CLP criteria. RAC concludes that based on the epidemiological data as well as the data from long-term studies in rats and mice, taking a weight of evidence approach, no classification for carcinogenicity is warranted.

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2021	Germany	Umweltinstitut München e. V.	National NGO	32

Comment received

The International Agency for Research on Cancer (IARC) of the World Health Organization (WHO), tested the active ingredient glyphosate based on what was available to it (only publicly available studies) in 2015 and came to the conclusion that

- Glyphosate is "probably carcinogenic in humans" (carcinogen group 2A) - there is sufficient evidence available that glyphosate is carcinogenic in laboratory animals Furthermore, the IARC found a positive relationship between glyphosate and the occurrence of non-Hodgkin lymphoma (malignant lymph gland cancer that occurs in all Organs of the human body). The WHO classification is still valid and must urgentlybe taken into account. Source: IARC: Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. Lancet Oncology, March 20, 2015, http://monographs.iarc.fr/ENG/Monographs/vol112/mono112-09.pdf
Dossier Submitter's Response
Noted. The DS reply is that all data that has been used in the evaluation by IARC has also been considered in the current evaluation together with more recent data. As extensively discussed in the CLH report, both the epidemiological data as well as data from long-term studies in rats and mice were taken into account a weight of evidence approach. Any new data should be further considered by RAC in their overall weight of evidence approach. Please note that the same comment was submitted in the EFSA process (refer to RT 2(84)).
RAC's response
RAC has included in the opinion an assessment of the animal carcinogenicity studies (including the assessment by Portier (2020)) as well as the epidemiological studies including also the recent studies mentioned during the consultation. In arriving at their conclusion for a classification for carcinogenicity RAC has reviewed the animal and human data according to the CLP criteria including a weight of evidence assessment.

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2021	Argentina	Asociación Argentina de Consorcios Regionales de Experimentación Agrícola (AACREA)	National NGO	33
Comment received				
Page 316 "Conclusion on classification and labelling for carcinogenicity": AACREA agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2021	Argentina		Individual	34
Comment received				

Page 316 "Conclusion on classification and labelling for carcinogenicity": Ing. Agr. <confidential> agrees with the assessments and conclusions achieved.
Dossier Submitter's Response
Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	<confidential>	National Authority	35
Comment received				
Page 316 "Conclusion on classification and labelling for carcinogenicity": <confidential> agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	Asociación Argentina de Trigo	National NGO	36
Comment received				
Page 316 "Conclusion on classification and labelling for carcinogenicity": Argentrigo agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Germany	Glyphosate Renewal Group	Company-Manufacturer	37
Comment received				
The applicant agrees with the proposal by the RMS (Glyphosate_RAR_01_Volume_1_2021-08-10, "Based on the epidemiological data as well as on data from long-term studies in rats and mice, taking a weight of evidence approach, no hazard classification for carcinogenicity is warranted for glyphosate according to the CLP criteria"), that is consistent with the conclusion of the ECHA Committee for Risk Assessment (RAC 40, March 2017, "RAC concludes that based on the epidemiological data as well as the data from long term studies in rats and mice, taking a weight of evidence approach, no classification for carcinogenicity is warranted"). There are no new animal data presented at this review cycle and the proposal "no need for classification of Glyphosate as carcinogenic" is consistent with previous conclusions by EFSA (List of Endpoints, EFSA Conclusion 2015, EFSA Journal 2015;13(11):4302), ECHA RAC 40, EFSA, and multiple other regulatory agencies from various parts of the world since AIR2, which also included expert reviews of epidemiological data.				

Greim et al. (2015, "Supporting document 1") describes an unprecedented measure of data transparency at that point in time, which "presents the robust glyphosate carcinogenicity data generated by industry. Study summaries will focus on carcinogenicity evaluation, to allow third parties the opportunity to independently evaluate the carcinogenicity data presented alongside other relevant data on carcinogenicity, i.e. genotoxicity testing and epidemiology, and facilitate a multidisciplinary carcinogenicity assessment". All available carcinogenicity studies were assessed in the current proposed AIR5 classification document by the competent authorities of France, Netherlands, Hungary and Sweden, jointly forming the Assessment Group on Glyphosate (AGG), previously during AIR2 by the BfR and EFSA, and were also previously considered by ECHA for RAC 39 and RAC 40, which resulted in the conclusion that no classification for carcinogenicity for glyphosate is warranted. As far as the task force is aware, no new rodent carcinogenicity studies, OECD test guideline or otherwise, have since been undertaken with glyphosate.

The current CLH proposal document systematically addresses all matters subsequently raised in select industry carcinogenicity rodent studies discussed by Portier (2020, "Supporting document 2"), wherein the author declares a conflict of interest as an expert to plaintiff attorneys in Roundup (glyphosate a.i.) litigation. It is important to point out, however, <confidential> also attended the December 2016 ECHA RAC 39 meeting as a stakeholder for "HEAL representing civil society" regarding glyphosate cancer classification, presenting novel statistical approaches to assess specific data from select industry studies, yet did not disclose his financial conflicts of interest at the time to the RAC. On March 29, 2015, the same month as he attended the IARC 112 meeting on glyphosate as an invited expert, <confidential> signed a lucrative contract as an expert witness in Roundup litigation with Plaintiff attorneys (see attached extract from <confidential> personal testimony in the transcript of August 10, 2021 California court proceedings; page 5/14 in extracted transcript, "Supporting document 3").

The only new prospective epidemiology data on glyphosate available since the 2017 ECHA conclusion of no classification for carcinogenicity, is from the Agricultural Health Study (Andreotti et al., 2018, "Supporting document 4"), arguably the most robust pesticide epidemiology investigation ever undertaken. This updated data set and evaluation reaffirms the previous ECHA RAC conclusion, that no classification for this hazard class is justified for glyphosate. Several recent epidemiology meta-analyses have been published on glyphosate since the previous AIR2 and ECHA RAC 40 conclusions (Chang et al., 2016, "Supporting document 5"; Leon et al., 2019, "Supporting document 6"; Zhang et al., 2019, "Supporting document 7"), which in themselves are not primary data. These assessments incorporate mostly low quality data and use this to average out the better quality data. Whilst this technique reduces random error, it introduces systemic error and generates non-interpretable meta-risk ratios. These meta-analyses do not add insight to the available high quality primary epidemiology data presented in Andreotti et al., (2018, "Supporting document 4"). These studies are mentioned in the attached white paper, "Epidemiologic Studies of Glyphosate and non-Hodgkin's Lymphoma: State of the Science Assessment" (Acquavella, 2021, "RMS request dRAR 15").
In the dRAR prepared by the RMS, in the table 3.1.4 "List of studies to be generated, still ongoing or available but not peer reviewed", point 3.1.4.6, the RMS provided the following request:

"1) Volume 1, section 2.6.1.1 short summary on toxicokinetic information.
A public literature study is available in which 13 poisoning incidents with glyphosate-based herbicides in France (Zouaoui et al., 2012) were analysed. This publication was

evaluated during the previous assessment of glyphosate by RMS DE. However, it is not re-submitted by the applicant. The applicant is requested to submit this publication together with a summary and a relevance and reliability assessment of this publication."
This information is provided in the supporting documents "RMS request dRAR 1_113898-001" and Zouaoui et al., 2012, "Supporting document 8", in the public and confidential attachments.

"3) Volume 1, Section 2.6.2.10.1
During the previous assessment, it was noted that for formulations, Burger et al. (2009, refer to Volume 1 2.6.9) reported cases from Germany that might indicate respiratory irritation but these findings were considered to be likely due to POEA surfactants (tallowamines) present in the formulation. The RMS notes that this study was not re-submitted for the present evaluation. The applicant is requested to submit this publication together with a summary and a relevance and reliability assessment of this publication."
This information is provided in the supporting documents "RMS request dRAR 3_113898-003" and Burger et al. 2009, "Supporting document 9", in the public and confidential attachments.

"12) Volume 3 CA B.6.5.5 (CA 5.5/005)
The applicant is asked to provide historical control data for the effect on mandibular lymph node lymphoma, if available."
This information is provided in the supporting document "RMS request dRAR 12_113898-005" and "Supporting document 10" in the public and confidential attachments.

"15) Volume 1, section 2.6.5.1.2.2. summary of epidemiological studies
The applicant is requested to submit a full assessment including a relevance and reliability assessment of the following studies:
Chang and Dellzell (2016)
Zhang et al. (2019)
Leon et al. (2019)"
This information is provided in the supporting documents "RMS request dRAR 15" and as "Supporting document 5", "Supporting document 6" and "Supporting document 7" in the public and confidential attachments.

"30) Volume 1, section 2.6.5.1
The applicant is requested to provide the 2-year study in rats and the 2-year study in mice, if possible, and an assessment of the studies."
This information is provided in the supporting document "RMS request dRAR 30_113898-006" in the public and confidential attachments.

Any cited reference can be found as a supporting document in the public and confidential attachments, which will be uploaded separately via the large file upload link due to size ("Glyphosate_Supporting documents_public.zip" and "Glyphosate_Supporting documents_confidential.zip").

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Glyphosate_Supporting documents_public.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Glyphosate_Supporting documents_confidential.zip

Dossier Submitter's Response

It is noted that the applicant agrees with the proposal by the DS, the applicant further confirms that no new animal data presented at this review cycle and that the overall

conclusion is in line with the previous conclusions by EFSA. The public literature study Greim et al. (2015, "Supporting document 1") does not provide any new information that was not already taken into account by the DS and it not further considered at this stage of the process. The remarks by the applicant considering the conflict of interest of an expert are noted.

The applicant mentions three new epidemiology meta-analyses (Chang et al., 2016; Leon et al., 2019 and Zhang et al., 2019). These not primary data in themselves, however, the DS is of opinion that these studies should be considered in the overall assessment. Any methodology has its limitations and this is not a sufficient reason to not consider the results. All data should be considered and weighed based on their limitations. Please refer to comment 21 in this RCOM table for further considerations by the DS. The applicant refers to an attached paper "Epidemiologic Studies of Glyphosate and non-Hodgkin's Lymphoma: State of the Science Assessment" (Acquavella, 2021)" in which these studies are also evaluated. Noted.

Reply DS on comment "1) Volume 1, section 2.6.1.1 short summary on toxicokinetic information: It is referred to the DS reply to comment 123 (which is the same comment).

Reply DS on comment "3) Volume 1, Section 2.6.2.10.1 (respiratory tract irritation): According to the RMS, based on the publication by Burger et al. (2009), it cannot be concluded that glyphosate should be classified for respiratory tract irritation. Based on the available information in the publication (which is only an abstract of one case) the effects observed cannot be (solely) attributed to glyphosate. Examples of shortcomings are:
- Composition of the formulation: 600 mL of a pesticide containing glyphosate (no details as if other a.i. is present);
- No information on previous health status of the person involved.

Reply DS on comment "12) Volume 3 CA B.6.5.5 (CA 5.5/005):
The applicant was asked to provide historical control data for the effect on mandibular lymph node lymphoma, if available.
The applicant stated in their supporting document that: "*circulating neoplasms like lymphosarcoma are independent of body location and that the important assessment is the* ***number of rats with the neoplasm found anywhere in the body****. Therefore, the assessment of such systemic neoplasms should be independent of the organ(s) in which they are found, rather the relevant information is number of rats with one or more of the same systemic type of neoplasm found in any or multiple locations. Lymphoma are systemic neoplasms, the point being, is it doesn't matter which part of the body or organ it is found, it is still a case of lymphosarcoma.*
In the historical control data provided by the laboratory, please refer to pdf page # 105/116, which shows one lymphosarcoma in the mandibular lymph nodes of one female (study 903). On the same page, in the first column of data, (study 868, male rats) there is one lymphosarcoma found in each of the mesenteric lymph nodes, mediastinal lymph nodes, lymph nodes (others), and kidney, but we have no idea if this is all in the same rat or different rats. What is important regarding this type of systemic neoplasm is the total number of animals with lymphosarcoma found anywhere in the animals within a dose group.
If all the lymphosarcoma in HCD study 868 males are all in one rat, that is a very different story than if they were in different rats. The most important and most relevant piece of information missing in this compilation of HCD are total number of rats with any lymphosarcoma in each study."
The DS agrees with the argumentation provided by the applicant. Mandibular lymph node lymphomas are systemic neoplasms and these may be found at multiple locations in the

body. Therefore, the total number of animals with lymphosarcomas should indeed be considered when comparing with HCD. However, as clearly indicated by the applicant, due to the way the HCD data is presented in the report it is not possible to retrieve this information.

Reply DS to comment "15) summary of epidemiological studies Chang and Dellzell (2016), Zhang et al. (2019) and Leon et al. (2019):
An initial reflection by the DS is provided in comment 21 of this RCOM table.

Reply DS to comment "30) two-year feeding studies in mice and rats.
The applicant replied in the supporting document that the 2-year feeding studies in mice and rats were performed with glyphosate trimesium as test substance. They stated the following: "*Glyphosate trimesium, or sulfosate was originally a Stauffer chemical product. The product was initially launched in 1986. In 1996 and 2000 Zeneca/ICI and later Syngenta moved to the two new salts formulations, ammonium and potassium. Syngenta has not manufactured glyphosate trimesium since 2003 and has not sold the product since 2004. To the best of the knowledge of the Glyphosate Taskforce, glyphosate trimesium is no longer manufactured and sold anywhere in the world. Glyphosate trimesium has always been regulated as a separate active ingredient to glyphosate acid itself. This was due to significant differences in the human safety profile of glyphosate trimesium compared to glyphosate acid. Other international authorities have also changed their evaluation and endpoint selection based only on glyphosate data, as ANVISA did recently, with changing the ADI form the previous endpoint based on trimesium, to a new endpoint based on glyphosate data (Consulta Pública n° 698, de 23 de agosto de 2019 D.O.U de 28/08/2019). Therefore, the data provided on glyphosate trimesium is for information and not deemed relevant when assessing an appropriate risk assessment endpoint for glyphosate acid*."
The DS agrees with this statement and agrees that these two studies should not be further considered for classification and labelling of glyphosate as acid.

RAC's response

Noted. RAC has included in the opinion an assessment of the animal carcinogenicity studies (including the assessment by Portier (2020)) as well as the epidemiological studies including the recent studies from the consultation. In arriving at their conclusion for a classification for carcinogenicity RAC has reviewed the animal and human data according to the CLP criteria including a weight of evidence assessment.

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	CIAFA (Chamber of the Argentine Industry of Fertilizers and Agrochemicals)	Industry or trade association	38

Comment received

Page 316 "Conclusion on classification and labelling for carcinogenicity": CIAFA (Chamber of the Argentine Industry of Fertilizers and Agrochemicals) agrees with the assessments and conclusions achieved.

Dossier Submitter's Response

Noted.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
18.11.2021	France	Inserm - French National Institute of Health and Medical Research	Academic institution	39

Comment received

This comment refers to RAR § 2.6.5.1.2 and § 2.6.5.1.2.2 Summary of the epidemiological studies on glyphosate ; pages 300-306 and 311-312

Conclusion RAR (page 312) :
"Overall, it is concluded that the results reported in the epidemiological studies do not warrant classification and labelling of glyphosate."

Comment by the Inserm expert panel:
(see also the Inserm report, pages 22-26 ; https://www.inserm.fr/expertise-collective/pesticides-et-sante-nouvelles-donnees-2021/) :

The Inserm collective expert review concluded on a medium presumption of a link (for definition, see Annex 2 of the Inserm report) between occupational exposure to glyphosate and increased risk of non-Hodgkin lymphoma (NHL) for farmers or other employment categories. This conclusion is based on :
• the meta-analysis recently published by the consortium of agricultural cohort studies AGRICOH (Leon et al., 2019) which, combining the AHS cohort with two other agricultural worker cohorts (AGRICAN in France and CNAP in Norway) includes over 300,000 subjects and 2,430 cases of NHL, found a statistically significant association between exposure to glyphosate and an increased risk of developing diffuse large B-cell lymphoma. This statistically significant increased risk was primarily based on data from the Norwegian cohort (CNAP), while the risks were slightly elevated but not significant in the US (AHS) and French (AGRICAN) cohorts.
• three recent pooled- or meta-analyses of earlier studies that systematically show an increased risk (Chang and Delzell, 2016; Pahwa et al., 2019; Zhang et al., 2019), particularly among the most exposed farmers.

In the RAR, three of these studies were considered as 'supplementary information' or were not considered ('considered unreliable') (Chang and Delzell, 2016; Leon et al. 2019; and Zhang et al., 2019) while the oldest study by Schinasi and Leon, 2014 was considered 'to be outdated' (Appendix B.6.5.18.28-31, pages 342-358).

As suggested by the RMS, we consider that these studies, i.e. all available meta-analyses published in international peer-reviewed journals, should be taken into account in the report. Furthermore, the methodology of an updated meta-analysis calculation, performed by the applicants and presented in an annex to the RAR, is not described and the reference is missing (Table 1. Updated glyphosate NHL meta-analysis calculation, Annex B.6.5.18.28-31, pages 345 and 349). This information should be provided. It should be noted that this updated meta-analysis does not take into account the latest studies, specifically those on the French and Norwegian cohorts. Furthermore, our conclusion based on epidemiological studies is supported by experimental toxicology studies as glyphosate shows pro-oxidant and genotoxic effects.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Inserm EC pesticides 2021_glyphosate_EN_18112021.pdf

Dossier Submitter's Response

In the above comment reference is made to the following public literature studies:

- Zhang *et al.*, 2019
- Leon *et al.*, 2019
- Chang and Delzell, 2016
- Schinasi and Leon, 2014
- Pahwa *et al.*, 2019;

For the meta-analyses by Zhang *et al.* (2019), Leon *et al.* (2019) and Chang and Delzell (2016) a data gap was identified for providing a full assessment of the study including a relevance and reliability assessment. For the EFSA process, the applicant is asked to submit the missing information during the public consultation period for the EFSA process. For this CLH-process, initial considerations on these studies by the DS are provided in comment 21 of this RCOM table. Please refer to the DS response of comment 21 for further information.

In the publication by Schinasi and Leon (2014, Vol 3 B.6.5.18.28) is considered supportive by the DS. The authors reported on the results of a meta-analysis of six epidemiological studies on the relationship between non-Hodgkin lymphoma (NHL) and occupational exposure to pesticides (based on McDuffie *et al.*, 2001, Hardell *et al*., 2002, DeRoos *et al*., 2003, Eriksson *et al.*, 2008 and Orsi *et al.*, 2009). Phenoxy herbicides, carbamate insecticides, organophosphorus insecticides and lindane were positively associated with NHL. For glyphosate, they calculated an increased meta relative risk (mRR) of 1.5 (95%-CI 1.1-2.0) for one day or more of use in a lifetime. However, there were data extraction errors by Schinasi & Leon that were identified in a subsequent meta-analysis by IARC working groups and by Chang and Delzell (2016). When the calculations were replicated after considering the adjusted estimates of two Swedish studies (Hardell *et al.*, 2002 and Eriksson *et al.*, 2008) in the meta-analysis, a meta-RR of 1.3 (1.03-1.65) was identified. This meta-RR - the result of the meta-analysis - appears to show a very moderate effect. However, a possible causal relationship was not discussed by the study authors. In addition, there is a more recent meta-analysis available using AHS data with extending cancer incidence follow-up through 2012 in North Carolina and 2013 in Iowa and incorporating additional exposure information from a follow-up questionnaire (Andreotti *et al.*, 2018 (refer to B.6.5.18.10)). In addition, the DS has also noted the following shortcomings: the meta-analysis mixes different study designs, biases cannot be controlled through the meta-analysis because those biases are of different natures and weight amongst the studies that constitute the meta-analysis and the authors did not make an effort to include studies published in languages other than English. As the information from this study is limited, together with extended data from a follow-up was evaluated by Andreotti (2018), the study by Andreotti is considered further in the risk assessment and this study by Schinasi and Leon (2014) is considered to be supportive by the DS. The updated meta-analysis calculation performed by the applicant (as presented in Vol 3 section B.6.5.18.28-31, pages 345 and 349) was not taken into account by the DS as details on the calculation are missing.

The study by Pahwa *et al.* (2019, Vol 3 B.6.5.18.8 and Volume 1 2.6.5.1.2.2) is considered reliable with restrictions and the results from the study were taken into account in the overall weight of evidence by the DS.

Please note that the same comment was submitted in the EFSA process (RT public comment 2(75)).
RAC's response
Noted. RAC has included in the opinion an assessment the epidemiological studies including the recent studies from the consultation as well as the animal carcinogenicity studies (including the assessment by Portier (2020)). In arriving at their conclusion for a classification for carcinogenicity RAC has reviewed the human and animal data according to the CLP criteria including a weight of evidence assessment.

Date	Country	Organisation	Type of Organisation	Comment number
18.11.2021	Germany		MemberState	40
Comment received				
There was new experimental data on carcinogenicity in animals. However, as decribed by the DS, different conclusions were drawn by third parties depending on the assessment methodology. In particular, the publication by Portier (2020) was referred to. A RAC discussion (and statement) on the acceptability of the methodology used by Portier (2020) would be appreciated, giving particular considerations to the issues that were criticised such as compensation for multiple testing and one-sided statistical testing.				
Dossier Submitter's Response				
Noted. RAC to be requested to hold a discussion.				
RAC's response				
Noted. RAC has included in the opinion an assessment of the animal carcinogenicity studies (including the assessment by Portier (2020)). In arriving at their conclusion for a classification for carcinogenicity RAC has reviewed the animal according to the CLP criteria including a weight of evidence assessment.				

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina		Individual	41
Comment received				
Page 316 "Conclusion on classification and labelling for carcinogenicity": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina	Bolsa de Cereales de Buenos Aires	Industry or trade association	42
Comment received				
Bolsa de Cereales de Buenos Aires agrees with the assessments and conclusions achieved. Page 316 "Conclusion on classification and labelling for carcinogenicity"				
Dossier Submitter's Response				
Noted.				

RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina	Fundación INAI	National NGO	43
Comment received				
Fundación INAI Agrees with the assessments and conclusions achieved. Page 316 "Conclusion on classification and labelling for carcinogenicity"				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2021	Spain		MemberState	44
Comment received				
Opinion on the posible classification for carcinogenicity of glyphosate After a thorough assessment, based on the epidemiological data as well as on data from long-term studies in rats and mice, taking a weight of evidence approach and comparison with the classification criteria acording to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, Spanish Authorities opinion is that glyphosate does not meet the criteria for classification as carcinogenic Cat 2. We consider that the tumors observed in individual rat and mouse carcinogenicity studies are not treatment-related due to, among others, the lack of statistical significance by pairwise, the lack of a monotonic dose-response, the absence of preneoplastic lesions or of non-neoplastic related lesions, with no evidence of tumor progression, and/or the historical control comparison (when available). These tumors were not observed in all carcinogenicity studies, not even in those carried out in the same species and strain at similar or higher doses. Neither, epidemiological studies revealed an association between glyphosate and specific cancer types.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	<confidential>	National NGO	45
Comment received				
Page 316 "Conclusion on classification and labelling for carcinogenicity": <confidential> agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				
Noted.				
RAC's response				

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	ACSOJA	National NGO	46
Comment received				
ACSOJA agrees with the assessments and conclusions achieved in the Page 316 "Conclusion on classification and labelling for carcinogenicity" (CLH report)				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	<confidential>	Industry or trade association	47
Comment received				
<confidential> agrees with Page 316 "Conclusion on classification and labelling for carcinogenicity"				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Germany	Bund für Umwelt und Naturschutz Deutschland e.V.	National NGO	48
Comment received				
BUND refers to the comments of Pesticide Action Network Germany. ECHA note – An attachment was submitted with the comment above. Refer to public attachment FoE Background on Glyphosate.pdf				
Dossier Submitter's Response				
Noted. The submitted document in the attachment does not contain any specific comments or questions on the carcinogenicity section of the CLH report.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.11.2021	Argentina		Individual	49
Comment received				
Page 316 "Conclusion on classification and labelling for carcinogenicity": <confidential> agrees with the assessments and conclusions achieved.				

Dossier Submitter's Response
Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2021	Argentina	CASAFE	Industry or trade association	50
Comment received				
Page 316 "Conclusion on classification and labelling for carcinogenicity": CASAFE agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2021	Argentina	<confidential>	International NGO	51
Comment received				
Page 316 "Conclusion on classification and labelling for carcinogenicity". <confidential> agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
21.10.2021	Germany		Individual	52
Comment received				
nicht krebserregend!				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.10.2021	Germany		Individual	53
Comment received				
According to the latest report of the pesticide authorities from France, The Netherlands, Sweden and Hungary, it is not carcinogen; contradicting reports were based on exposure rates which are not relevant in case of good agricultural practice for application.				

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Literatur.7z
Dossier Submitter's Response
Noted. The attachments do not provide data within the scope of the scientific assessment in relation to the proposal for classification.
RAC's response
Noted.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina	Cazenave y Asociados SA	Company-Downstream user	54
Comment received				
Page 228 "Conclusion on classification and labelling for genotoxicity/germ cell mutagenicity": Cazenave y ASociados SA agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina	<confidential>	National NGO	55
Comment received				
Page 228 "Conclusion on classification and labelling for genotoxicity/germ cell mutagenicity": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Belgium	Health and Environment Alliance (HEAL)	International NGO	56
Comment received				
Please refer to the attachment "genotoxicity" (Section Vol 3 B.6.4) for comments on the genotoxicity assessment of glyphosate. We disagree with the conclusion that glyphosate does not have a genotoxic potential. According to a recent analysis (Annex G, separate attachment) only two of the studies submitted by the industry can be considered reliable. Further, key studies such as Comet assay or Transgenic rodent (TGR) somatic and germ cell gene mutation assay, or studies carried out in other tissues than the bone marrow are missing. Furthermore, the assessment dismisses almost all the evidence on the				

genotoxic potential of glyphosate from peer-reviewed literature as unreliable. Therefore the conclusion that glyphosate in not carcinogenic is equivocal and is not supported by the evidence.

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment HEAL_Public consultation Glyphosate ECHA.zip

Dossier Submitter's Response

We took note of both attachments that were submitted.
It is argued that no transgenic rodent or Comet assay was submitted by the applicants, whereas public literature gives some indications for the need of these studies. The references included regarding the in vitro Comet assays found in public literature are all included in the RAR and were evaluated by the DS. Four out of the 5 articles mentioned were considered to be supportive, whereas one was considered to be not reliable based on Klimisch scoring. The studies describe in vitro Comet assays (for which there is no specific OECD guideline) performed at non-GLP labs with several deviations noted (incl. limited information on methodology or test substance used, low number of cells scored, no HCD (no lab proficiency information), no metabolic activation included, very high and unrealistic test concentrations).
In the attachments a re-evaluation of the reliability of the studies was conducted by the two authors and this was compared to the outcome as described in the RAR. DS acknowledges that public literature studies are not designed to specifically follow OECD guidelines. However, OECD guidelines make sure there are internationally agreed testing guidelines which ensure mutual recognition of data. Following these guidelines helps to obtain reliable studies that are acceptable in all OECD countries. One of the methods used to assess the reliability of a public literature study is by making a comparison to the OECD guideline and assessing how deviations might impact the reliability of the study.

DS conducted an overall Weight of Evidence assessment on all data available on genotoxicity, including studies submitted by the applicants and found in public literature and considering their reliability. Based on this assessment DS is of the opinion that glyphosate should not be classified for mutagenicity.

RAC's response

Noted. RAC assessed the genotoxicity studies included in the CLH report in a weight of evidence assessment conducted according to the CLP regulation and concluded that when taking all data into account and based on the overall negative responses in the existing gene mutation and oral mutagenicity tests, RAC concludes that no classification of glyphosate for germ cell mutagenicity is justified based on the data available.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	France	Générations Futures	National NGO	57

Comment received

Générations makes comments regarding the genotoxicity assessment of glyphosate in the attached document "Comments of Générations Futures on the literature search and the genotoxicity endpoint". These comments are made in a very detailed way and using EFSA and ECHA guidelines as references. We thank in advance ECHA and EFSA for reading this document and respond to the questions we have.

The conclusion of our analysis is the following:
Générations Futures asks for not taking any decision regarding the genotoxicity assessment and the renewal of glyphosate without taking into account all the followings:

1/ All actual relevant studies must be included in the literature search (see the document "Comments of Générations Futures on the literature search"
2/ All available data obtained in fishes should be taken into account in the genotoxicity assessment
3/ Applicant data and public literature studies must be assessed for their reliability in a transparent and equitable way. A clear method for the reliability assessment of both industry and public studies and a clear method of the weight of evidence assessment must be provided.
4/ The reliability of applicant studies, especially clastogenicity studies, must be re-considered, taking into account their major deviations (not meting the acceptability criteria of OECD guideline). The relevance of the in vivo micronucleus without any convincing demonstration of bone marrow exposure must be questioned.
5/ An in vivo comet assay must be conducted on target organs such as kidney or liver.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments of Générations Futures on the litterature search and genotoxicity endpoint.pdf

Dossier Submitter's Response

In response of the submitted attachment:
Regarding the literature search, it is noted that for this specific substance extensively more studies are available in the public literature compared to any other pesticidal active substance. Therefore, it is difficult to make a comparison regarding the amount of studies from the public domain compared to the studies submitted by the applicant.
All studies, public literature and studies submitted by the applicant, were assessed for their relevance and reliability, using EU agreed assessment points for this. As public literature studies often miss essential information, the reliability and quality of these studies tends to be lower compared to those implementing international standards guaranteed by Good Laboratory Practices and OECD Test Guidelines, and to which applicants are required to comply with according to EU regulation.

Regarding data from non-standard test systems (e.g. fishes): these data could present an interesting approach, provided that the data are generated according to a recognised and validated scientific design. So far there are no scientific robust guidances on this available.

Furthermore, the submitted attachment describes three specific points:

1. A literature search in line with the EFSA guidance document (2011) was conducted by the applicants and was assessed by the DS. As already indicated above, all studies were assessed for their relevance and reliability and taken into account into a weight of evidence approach.
    1-1. References were not just excluded when these concerned a conference contribution, only when the conference abstract did not contain sufficient data.
    1-2. For the evaluation of glyphosate, Regulation 1107/2009 and data requirements 283/2013 apply, which specifically describe which studies should be conducted. In addition, EFSA guidance documents on genotoxicity were applied (2011, 2017). None of these describe the use of tests on aquatic species to address genotoxicity. Also, currently in the CLP regulation no specific guidance is given on this point, which might change following the currently ongoing revision of the CLP regulation. DS considers the substance is sufficiently investigated according to the

current regulations/guidances and a conclusion on mutagenicity can be reached based on these data.

1-3. See response to point 2.

1-4. In the detailed assessment of articles found in the literature search, several criteria were applied to determine the relevance. It is noted that studies on cellular and molecular levels were only excluded in case these data could not be related to the risk assessment.

2. Publications with a non-representative formulation: DS notes that the aim of the hazard assessment is to elucidate the intrinsic properties of a substance. If studies performed with a formulation should be included in the hazard assessment, we consider it necessary to demonstrate that it is unlikely that co-formulants influence the result, either by having a toxic effect or by influencing the toxicity of the active substance e.g., by mechanisms increasing bioavailability, stabilisation, activation etc. This can hardly ever be excluded and considering that a large amount of data from GLP/guideline studies performed with the active substance is available to reliably assess the toxicological endpoints, we question the need to include this in the human health hazard assessment of the active substance. Nevertheless, the representative product is assessed in accordance to data requirements in Regulation 1107/2009 and data available providing useful information for the toxicological assessment of this particular formulation is included and presented in the MCP document of the RAR.
   In addition, one co-formulant which is known to strengthen the toxicity of glyphosate (POEA, tallowamine) is no longer allowed in formulations in the EU, studies conducted with a formulation containing this co-formulant are therefore excluded as they are not considered relevant for the EU evaluation.
3. Reliability assessment for the studies submitted by the applicant were done in a similar matter as the public literature studies, even though the results are not given in a tabular format for each study. A comparison to OECD testing guidelines was made, information given on the test substance, description in the report of study method used, etc. Based on these findings the reliability of the study is indicated by the DS and concluded to be either reliable, reliable with restrictions, or not reliable.

It is noted that the actual renewal report (RAR) will be further adjusted following the EFSA commenting round and data requirements that will be set for the applicant to provide further information.

Please note that the same comment was also submitted for the EFSA process (Reporting Table TOX comment 2(180))

RAC's response

Noted. RAC assesses the studies included in the CLH report as well as relevant infomation submitted during the consultation for the decission on classification for germ cell mutagenicity according to the CLP criteria, including also a weight of evidence assessment.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina		Individual	58

Comment received

Page 228 "Conclusion on classification and labelling for genotoxicity/germ cell mutagenicity": <confidential> with the assessments and conclusions achieved.

Dossier Submitter's Response
Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Netherlands	SumOfUs	International NGO	59
Comment received				
Please see attached reports which raise serious concerns about the scientific quality, and therefore reliability, of all but a few of the genotoxicity and mutagenicity studies submitted to the EU by glyphosate manufacturers. "Evaluation_scientific_quality_studies_genotoxic_glyphosate.pdf" and "Evaluation_scientific_quality_2021_glyphosate_re-evaluation.pdf" were authored by Prof. <confidential> and Dr. <confidential>. "Evaluation_statistical_procedures.pdf" was authored by Prof. <confidential>. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment sumofus-archive.zip				
Dossier Submitter's Response				
In the report 'Evaluation_scientific_quality_studies_genotoxicity_glyphosate.pdf' the different available studies are described with an evaluation comparing the methods used to current testing methods. The authors' conclusions are compared to the previous evaluation report for glyphosate (2015) and not the current assessment. The current conclusions differ somewhat from the conclusions taken in the previous renewal evaluation (2015). We have evaluated all studies and compared them to recent testing guidelines and have indicated the deviations and whether or not they are expected to influence the reliability of the study. In the report 'Evaluation_scientific_quality 2021_glyphosate_re-evaluation.pdf' 11 studies are discussed that are included in the current renewal assessment of glyphosate and which were not included into the previous evaluation (2015). However, this concerns genotoxicity studies on either metabolites or formulations, not on the active substance glyphosate. Therefore, they are not relevant for the classification and labelling of the active substance. The report further argues that metabolic competent cells (such as HepG2 or HepRG) should have been used. However, standard OECD studies are included in the dossier which included a metabolic competent system (e.g. S9 mix), therefore testing both without and with metabolic activation. In the report 'Evaluation_statistical_procedures.pdf' the different genotoxicity assay methods are discussed and what statistical test should be used to analyse the study result. In addition, a table is included with an overview of available studies, what (if any) statistical method was used and if this was considered appropriate by the author of this report. No details on studies are given (e.g. specific references to the renewal report) which would allow ease of reference. However, in the renewal report on glyphosate, DS evaluated all genotoxicity studies and compared the methods used to current OECD guidelines. Deviations were listed and it was indicated whether or not it was expected that deviation might influence study reliability. In this assessment, statistical methods were also considered, in case this was described in the respective OECD guideline.				

Overall, DS submitted considers that these three reports submitted do not influence the overall assessment of the mutagenicity of glyphosate, as included into the current renewal report. DS remains of the opinion that glyphosate was sufficiently investigated in line with Reg. 1107/2009 and data requirements 283/2013 and current scientific opinions (EFSA 2011, 2017). Glyphosate should not be classified for mutagenicity.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Denmark		MemberState	60
Comment received				
2.6.4.3: Agree. Based on the available data, a classification for mutagenicity is not warranted for glyphosate.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2021	Germany	Umweltinstitut München e. V.	National NGO	61
Comment received				
1. The experts on genotoxicity (DNA damage) at the Institute for Cancer Research at the Medical University of Vienna Prof. Dr. <confidential> and Dr. <confidential> examined 53 studies of glyphosate DNA damage that were submitted by manufacturers as part of the previous approval process. Based on these studies, the European Food Safety Authority (EFSA) came to the conclusion that glyphosate is not genotoxic and with this classification contradicted the Cancer Research Agency of the World Health Organization (IARC), which classified glyphosate as genotoxic. In reviewing these studies, the professors also came to a different conclusion. Only 2 of the 53 studies that were used for the current EU approval of glyphosate can be classified as "reliable" according to their analysis. The majority (34 of 53 studies) rated them as "not reliable" and the remaining 17 as only "partially reliable". It should not be repeated that studies have classified glyphosate as Non-DNA Damaging. The report of the Viennese experts must absolutely be taken into account and the studies submitted by the industry should be critically examined when in the last detail. Inadequate studies should not be accepted as reliable. https://www.global2000.at/sites/global/files/Analyse-Glyphosat-Studien.pdf 2. The International Agency for Research on Cancer (IARC) of the World Health Organization (WHO), tested the active ingredient glyphosate on the basis of that available to the organization (only publicly available studies) and came to the conclusion that - Strong evidence of genotoxic effects from exposure to glyphosate - Strong evidence of oxidative stress induction from exposure to Glyphosate, AMPA and based on glyphosate formulations are present.				

The genotoxic effect causes damage to the genetic make-up can trigger carcinogenic processes. Oxidative stress disrupts repair and detoxification function of the cells, which among other things can lead to DNA damage.

IARC (2015a): Carcinogenicity of Tetrachlorvinphos, Parathion, Malathion, Diazinon, and glyphosate. Lancet Oncology, March 20, 2015, http://dx.doi.org/10.1016/S1470- 2045 (15) 70134-8
http://monographs.iarc.fr/ENG/Monographs/vol112/mono112-09.pdf

Dossier Submitter's Response

1. This report describes the studies that were available during the previous renewal evaluation of glyphosate (2015). A comparison was made between the evaluation included in the renewal report at that time and the evaluation performed by the two authors from the University of Vienna. For the current evaluation of glyphosate, DS has re-evaluated all available studies (applicant studies and studies from public literature) and reaching different conclusions for several of the studies compared to the 2015 evaluation. Relevance and reliability of the studies was checked. Methods used in the studies were compared to recent testing guidelines, deviations were indicated and whether or not these deviations are expected to influence the study reliability.
2. In the evaluation performed by DS, both applicant studies and studies from public literature were evaluated, including studies that came available after the previous evaluation. Therefore, the evaluation contains more data than that was available to IARC in 2015. All data were evaluated for their relevance and reliability and all available information was taken into account into a weight of evidence approach to determine the mutagenic potential of glyphosate.

DS remains of the opinion that glyphosate should not be classified for mutagenicity.

RAC's response

Noted. RAC assesses the studies included in the CLH report as well as relevant infomation submitted during the consultation for the decision on classification for germ cell mutagenicity according to the CLP criteria. When taking all data into account and based on the overall negative responses in the existing gene mutation and oral mutagenicity tests, RAC concludes that no classification of glyphosate for germ cell mutagenicity is justified based on the data available.

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2021	Argentina	Asociación Argentina de Consorcios Regionales de Experimentación Agrícola (AACREA)	National NGO	62

Comment received

Page 228 "Conclusion on classification and labelling for genotoxicity/germ cell mutagenicity": AACREA agrees with the assessments and conclusions achieved.

Dossier Submitter's Response

Noted.

RAC's response

Noted.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON GLYPHOSATE (ISO); *N*-(PHOSPHONOMETHYL)GLYCINE

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2021	Argentina		Individual	63
Comment received				
Page 228 "Conclusion on classification and labelling for genotoxicity/germ cell mutagenicity": Ing. Agr. <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	<confidential>	National Authority	64
Comment received				
Page 228 "Conclusion on classification and labelling for genotoxicity/germ cell mutagenicity": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	Asociación Argentina de Trigo	National NGO	65
Comment received				
Page 228 "Conclusion on classification and labelling for genotoxicity/germ cell mutagenicity": Argentrigo agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Germany	Glyphosate Renewal Group	Company-Manufacturer	66
Comment received				
The applicant is in agreement with the proposal by the RMS (Glyphosate_RAR_01_Volume_1_2021-08-10, "No classification for germ cell mutagenicity"), that is consistent with the conclusion of the ECHA Committee for Risk Assessment (RAC 40, March 2017, "no classification of glyphosate for germ cell mutagenicity"). In the frame of the current renewal evaluation, a thorough review of the extensive genotoxicity data, including in vitro and in vivo studies has been performed and the RMS proposal "No classification for germ cell mutagenicity is warranted" is consistent with the				

previous conclusions at ECHA RAC 40 and by EFSA (List of Endpoint, EFSA Conclusion 2015).
Furthermore, in the frame of the current renewal, new HPRT and in vitro Micronucleus assays (GLP and OECD 2016 test guideline compliant) were carried out and submitted to the RMS. The results of these studies were clearly negative (= no findings), confirming the absence of genotoxic potential and were acceptable and reliable to the RMS.

Any cited reference can be found as a supporting document in the public and confidential attachments, which will be uploaded separately via the large file upload link due to size ("Glyphosate_Supporting documents_public.zip" and "Glyphosate_Supporting documents_confidential.zip").

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Glyphosate_Supporting documents_public.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Glyphosate_Supporting documents_confidential.zip

Dossier Submitter's Response

Noted.
The new HPRT and in vitro micronucleus referenced were already included into the evaluation.

The attachments submitted only contain one report that, among other endpoints, also discusses genotoxicity. This is the NTP toxicity report on glyphosate, which indicates the following: glyphosate did not induce gene mutations in *Salmonella typhimuriumi* strains TA100, TA1535, TA97 or TA98 (preincubation protocol) in presence and absence of S9 mix; no increase in micronuclei was observed in either males or females (13-week dietary study, peripheral blood normochromatic lymphocytes analyzed at termination). The report concludes that available tests showed no evidence that glyphosate is genotoxic and that this is in line with several references from public literature.

This information does not influence the assessment that was conducted by the DS regarding mutagenicity of glyphosate.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	CIAFA (Chamber of the Argentine Industry of Fertilizers and Agrochemicals)	Industry or trade association	67

Comment received

Page 228 "Conclusion on classification and labelling for genotoxicity/germ cell mutagenicity": CIAFA (Chamber of the Argentine Industry of Fertilizers and Agrochemicals) agrees with the assessments and conclusions achieved.

Dossier Submitter's Response

Noted.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
18.11.2021	France	Inserm - French National Institute of Health and Medical Research	Academic institution	68

Comment received

This comment refers to RAR § 2.6.4.3 ; Conclusion on classification and labelling for genotoxicity / germ cell mutagenicity ; page 228

The RAR states (page 177) :
"Genotoxicity and mutagenicity of glyphosate were examined in several test systems covering all relevant endpoints in vitro (in bacterial and mammalian cells) and in vivo (in both somatic and germ cells). In addition, several publications from the open literature have been evaluated and included in the tables below. In the previous CLH report (BAuA, 2016), the following was mentioned: "in addition to the studies with glyphosate, a large number of published studies with formulations containing glyphosate are available which were tested for different mutagenicity and genotoxicity endpoints in a variety of in vitro and in vivo mammalian and non-mammalian test systems. A part of these studies revealed positive or at least equivocal results in particular when testing was performed in non-standard systems and when so-called "indicator tests" were employed. It is likely that such results were rather due to co-formulants than to glyphosate. Therefore, they cannot be taken into account for classification of glyphosate for mutagenicity. Furthermore, against the background of an extremely large database using standard test systems (bacteria, mammalian cells and mammals), data obtained in non-standard test systems (e.g. plant, insect, worm, fish etc.) was not considered for classification of health related endpoints even if performed with the active ingredient." The current assessment has been carried out on the same grounds."

Comment by the Inserm expert panel:
(see also the Inserm report, pages 40-46 ; https://www.inserm.fr/expertise-collective/pesticides-et-sante-nouvelles-donnees-2021/)

Genotoxicity assays, which aim to detect DNA damage such as double-stranded breaks, chromosomal aberrations or adducts, can be performed in different microbial, animal or plant systems using in vitro or in vivo approaches.

The Inserm collective expert review analyzed some twenty studies in the academic literature using these assays to explore the genotoxic potential of glyphosate or GBHs. Due to the large number of studies, the results appear discordant, which can be explained by the different protocols used that vary in terms of models, dose and exposure times, and the types of products tested (glyphosate or formulations). However, the studies showing that glyphosate has genotoxic effects are more important in terms of quality and quantity than those suggesting an absence of effect. A genotoxic effect of glyphosate is consistent with the induction of oxidative stress, observed in different species and cell systems, sometimes at exposure doses consistent with those encountered in the environment.

The difference in opinion between the Inserm collective expert review and the RAR on the question of genotoxicity stems from the fact that the Inserm collective review takes into account both the results using non-standard models (i.e., non-mammalian models such

as fish and crustaceans; not considered for classification in the RAR), and those obtained with formulations (GBHs) that better reflect the reality of exposure in humans. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Inserm EC pesticides 2021_glyphosate_EN_18112021.pdf
Dossier Submitter's Response
We took note of the attachment. This document describes, among other subjects, genotoxicity of glyphosate and glyphosate based herbicides. Articles from public literature are cited in standard and non-standard models. Most of the articles cited were considered in the renewal report for glyphosate and assessed for their relevance and reliability and taken into account into the overall weight of evidence approach to determine the mutagenicity potential of glyphosate. Some of the studies mentioned in the attachment have not been included into the renewal report. A closer look upon these publications shows research conducted with formulations and not the active substance itself, therefore effects of co-formulant cannot be excluded and the use of non-standard models (e.g. eels, shrimp, plant). Overall, DS considers this information does not influence the assessment, therefore, the conclusion remains that glyphosate should not be classified for mutagenicity.
RAC's response
Noted. RAC assessed the studies included in the CLH report as well as relevant infomation submitted during the consultation for the decission on classification for germ cell mutagenicity according to the CLP criteria, including also a weight of evidence assessment. When taking all data into account and based on the overall negative responses in the existing gene mutation and oral mutagenicity tests, RAC concludes that no classification of glyphosate for germ cell mutagenicity is justified based on the data available.

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina		Individual	69
Comment received				
Page 228 "Conclusion on classification and labelling for genotoxicity/germ cell mutagenicity": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina	Bolsa de Cereales de Buenos Aires	Industry or trade association	70
Comment received				
Bolsa de Cereales de Buenos Aires agrees with the assessments and conclusions achieved. Page 228 "Conclusion on classification and labelling for genotoxicity/germ cell mutagenicity"				
Dossier Submitter's Response				

Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina	Fundación INAI	National NGO	71
Comment received				
Fundación INAI Agrees with the assessments and conclusions achieved. Page 228 "Conclusion on classification and labelling for genotoxicity/germ cell mutagenicity"				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	<confidential>	National NGO	72
Comment received				
Page 228 "Conclusion on classification and labelling for genotoxicity/germ cell mutagenicity": <confidential> agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	ACSOJA	National NGO	73
Comment received				
ACSOJA agrees with the assessments and conclusions achieved in the Page 228 "Conclusion on classification and labelling for genotoxicity/germ cell mutagenicity" (CLH report)				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	<confidential>	Industry or trade association	74
Comment received				
<confidential> agrees with Page 228 "Conclusion on classification and labelling for genotoxicity/germ cell mutagenicity"				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Germany	Bund für Umwelt und Naturschutz Deutschland e.V.	National NGO	75
Comment received				
BUND refers to the comments of Pesticide Action Network Germany. ECHA note – An attachment was submitted with the comment above. Refer to public attachment FoE Background on Glyphosate.pdf				
Dossier Submitter's Response				
Noted. The submitted document in the attachment does not contain any specific comments or questions on the mutagenicity section of the CLH report.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.11.2021	Argentina		Individual	76
Comment received				
Page 228 "Conclusion on classification and labelling for genotoxicity/germ cell mutagenicity": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2021	Argentina	CASAFE	Industry or trade association	77
Comment received				
Page 228 "Conclusion on classification and labelling for genotoxicity/germ cell mutagenicity": CASAFE agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2021	Argentina	<confidential>	International NGO	78
Comment received				
Page 228 "Conclusion on classification and labelling for genotoxicity/germ cell mutagenicity". <confidential> agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				

Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
22.10.2021	Germany		Individual	79
Comment received				
As mentioned from <confidential> in this video, Glyphosate can cause serious damage to oranisms in the second or third generation, due to changing mechanism regarding the inter-cellular transport of deuterium (H^3). See video on this page: https://uncutnews.ch/die-beunruhigende-rolle-von-glyphosat-bei-covid-19-neue-erkenntnisse/				
Dossier Submitter's Response				
The video discusses a hypothesis that glyphosate might replace glycine, which would disrupt processes in the mitochondria which would cause deuterium accumulation leading to chronic diseases. The video then further focusses on a possible relation to Covid-19: it is indicated that if a large amount of glyphosate accumulates in your tissues the immune cells will become compromised making it difficult to eliminate viruses such as Covid-19. DS notes that ADME data indicates no evidence for accumulation of glyphosate; elimination via urine and faeces is rapid and nearly complete within 48 h and after repeated dosing less than 0.5% was present in the tissues after 72h. The video does not contain any information relevant for the scientific assessment in relation to the proposal for classification regarding mutagenicity.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
21.10.2021	Germany		Individual	80
Comment received				
unschädlich für das Erbgut				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.10.2021	Germany		Individual	81
Comment received				
According to the latest report of the pesticide authorities from France, The Netherlands, Sweden and Hungary, it is not mutagen; contradicting reports were based on exposure rates which are not relevant in case of good agricultural practice for application. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Literatur.7z				
Dossier Submitter's Response				

Noted. The attachments do not provide data within the scope of the scientific assessment in relation to the proposal for classification.
RAC's response
Noted.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina	Fundación INAI	National NGO	82
Comment received				
Fundación INAI Agrees with the assessments and conclusions achieved. Page 432 "Conclusion on classification and labelling for reproductive toxicity"				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	<confidential>	National NGO	83
Comment received				
Page 432 "Conclusion on classification and labelling for reproductive toxicity": <confidential> agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	ACSOJA	National NGO	84
Comment received				
ACSOJA agrees with the assessments and conclusions achieved in the Page 432 "Conclusion on classification and labelling for reproductive toxicity" (CLH report)				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	<confidential>	Industry or trade association	85
Comment received				
<confidential> agrees with Page 432 "Conclusion on classification and labelling for reproductive toxicity"				
Dossier Submitter's Response				
Noted.				

RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
14.11.2021	Argentina		Individual	86
Comment received				
Page 432 "Conclusion on classification and labelling for reproductive toxicity": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina	Cazenave y Asociados SA	Company-Downstream user	87
Comment received				
Page 432 "Conclusion on classification and labelling for reproductive toxicity": Cazenave y Asociados SA agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina	<confidential>	National NGO	88
Comment received				
Page 432 "Conclusion on classification and labelling for reproductive toxicity": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Italy	Ramazzini Institute	Academic institution	89
Comment received				
Please consider for this section the following cohort studies that we recently published: Lesseur C, Pathak KV, Pirrotte P, Martinez MN, Ferguson KK, Barrett ES, Nguyen RHN, Sathyanarayana S, Mandrioli D, Swan SH, Chen J. Urinary glyphosate concentration in pregnant women in relation to length of gestation. Environ Res. 2021 Jul 30;203:111811. doi: 10.1016/j.envres.2021.111811				

Lesseur C, Pirrotte P, Pathak KV, Manservisi F, Mandrioli D, Belpoggi F, Panzacchi S, Li Q, Barrett ES, Nguyen RHN, Sathyanarayana S, Swan SH, Chen J. Maternal urinary levels of glyphosate during pregnancy and anogenital distance in newborns in a US multicenter pregnancy cohort. Environ Pollut. 2021 Jul 1;280:117002. doi: 10.1016/j.envpol.2021.
Dossier Submitter's Response
The two publications present results indicating a link between glyphosate exposure and pretermbirth and anogenital distance in newborns, respectively. The results presented in the first publication indicate an association between a shortened gestational length and maternal glyphosate and AMPA only among spontaneous deliveries using adjusted Cox proportional hazards models. However, authors recognize that they did not measure additives present in GBH formulations and it is thus not possible to rule out that glyphosate and AMPA are proxies of these adjuvants. The second publication presents interesting results indicating a link between glyphosate exposure and anogenital distance in newborns. In female infants, high maternal urinary glyphosate (above the median) was associated with longer AGD-AC but this was not significant after covariate adjustment. Increased AMPA was associated with longer AGD-AF after adjusting for infant size and age at AGD examination. There were no associations detected in male offspring. Also for this study authors recognized as a limitation of the study[1], that it is not possible to exclude that effects could also result from coformulants as the urinary analysis only included glyphosate and AMPA. Although results are interesting and raise some concern for reproductive toxicity, the relevance here is unclear since classification and labelling is based on a comparison of the data on intrinsic properties of the active substance with the criteria in CLP and any effects of co-formulants must be excluded. [1] "*Nevertheless, exposure to pure glyphosate is unlikely, since this is applied to crops in GBH formulations that contain other "inert" ingredients not listed on the commercial product. Thus, comprehensive quantification of GBH additives is not possible and we used urinary glyphosate and AMPA as biomarkers of exposure. The effects of formulation of GBHs should also be addressed in future studies."*
RAC's response
Noted. RAC agrees with the assessment by the DS that these publications are of limited relevance since it can not be excluded that the effects could also result from exposure to co-formulants in the glyphosate formulations.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Belgium	Health and Environment Alliance (HEAL)	International NGO	90

Comment received

Please refer to the attachment "Reproduction" (Vol 1. 2.6.6/ Vol3 B.6.6) for comments on the reproduction toxicity assessment of glyphosate. The comments highlight some information that has not been properly reported in the studies provided by the applicants. We also provide a short review (Annex R, in the same file) on the evidence of reproduction toxicity from the peer reviewed scientific literature and link it to what has been observed in the applicants' studies. The conclusion that glyphosate causes no adverse effects on reproduction seems incorrect.

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment HEAL_Public consultation Glyphosate ECHA.zip

Dossier Submitter's Response

Thank you for your input. Please find below our response to comments included in the attachment:

Comment 1: The conclusion regarding reproductive toxicity stated in the RAR is based on a large data set of fertility and developmental toxicity studies performed with the substance, the majority performed *in vivo* according to guidelines and GLP. In addition, a huge amount of published articles were reviewed to find any additional reliable and relevant information on the intrinsic properties of glyphosate. The majority of these studies were performed *in vitro* and while such data can be used to provide useful information to explain effects seen *in vivo*, the significance of this information, especially when performed with formulations, is unclear in the absence of correlating *in vivo* findings. Studies performed in accordance with guidelines and the principles of GLP are generally considered to be of higher reliability since the recommendations in guidelines are developed to harmonise and ensure adequate methodology (including relevant doses to study intrinsic properties regardless of exposure (during use) and statistical power) and GLP is the system currently used to prevent fraud.

Comment 2: In three studies: one study conducted 1981 (CA 5.6.1/014), and two studies conducted 1988 (CA 5.6.1/011, CA 5.6.1/012) the top dose levels were considered much too low to reveal any toxic effect. Thus, these studies were not acceptable (studies not suitable for the purpose of classification and labelling). Also, one study conducted 1985 (CA 5.6.1/013) was considered not acceptable. This study was limited due to major deviations and reporting deficiencies). These studies were also considered unreliable in RAR (2015).

Comment 3: In study CA 5.6.1/001-3 cauda epididymis sperm count was measured at high dose level (15000 ppm) but not at low and mid dose, thus a deviation from OECD TG 416 is identified. It could however be noted that no effects on cauda epididymis sperm count was observed in another generational study (B.6.6.1/05, Report No.: IET 96-0031) using higher doses. A statistically significant higher number of large follicles in ovary (38%) was detected for 15000 ppm females ($p<0.01$) when compared to control, however, in the absence of any supporting data retrieved from the uterine examinations or any differences in number of offspring produced at this treatment level, this increase was indicative of normal biological variation and of no toxicological importance according to study author. However, no historical control data is available to confirm this statement. In the F1 generation cortical vacuolation of the adrenal glands was observed with a lower incidence and with generally lower grades of severity among males treated with 15000 ppm (42%), 5000 ppm (33%), and 1500 ppm (42%) when compared to controls (71%).

The group distribution of incidence and of severity grades may also suggest a consequence of treatment. However, the absence of a dose-related response, may suggest that a higher-than-normal background incidence of the condition among control male rats may have contributed to the effect on this occasion. No background data is however available to confirm this statement.

Comment 4: In study CA 5.6.1/04 the proportion of F0 and F1 pups born live was increased (not decreased) in the mid dose group (F0: 94.9%, 96.5%, 99.1%, 97.2% for the 0 (control), 1000, 3000 and 10000 ppm group respectively; F1: 95%, 96.3%, 98.7% and 96.9% for the 0(control), 1000, 3000 and 10000 ppm group respectively). The proportion of F0 and F1 pups born live was slightly higher in the glyphosate acid groups than in the control group. DS does not consider this effect as an adverse effect.

Comment 5:

Study CA 5.6.1/005: Kidney weight: Statistically significant increased absolute kidney weight was found in F1 females at 6000 ppm (11%) and 3000 ppm (17%). At 6000 ppm, this increase was not considered treatment-related because statistical significance in the difference between the control and 6000 ppm groups disappeared when all F1 females were subjected to the weighing of the kidneys fixed in 10% neutral buffered formalin. Furthermore, no dose-response was found. Liver weight: Increased liver weight observed in parental 30000 ppm-animals (F1 males: abs weight: ↑13%; F1 females: abs weight: ↑ 22%, rel weight: ↑ 20%). The magnitude of 13% was considered adverse in the absence of clinical chemistry investigations in the study. Ovary weight: Statistically significant reduced relative ovary weight was observed in F1 females at low dose of 1200 ppm (13%). This effect was not considered treatment related since no effects were observed at mid and high dose, thus no dose-response could be found. Histopathology was only considered for control and high dose animals as recommended by OECD TG 416. At high dose no histopathological changes were observed. Fertility: This comment is not clear for us. Number of implantation sites reported for F1 litter: 13.9, 15.7*, 13.6 and 14.5 for the 0 (control), 1200, 6000 and 30000 ppm group respectively ($p<0.05$). Thus, no reduction in high dose group. Number of pups delivered: 12.8, 13.7, 13.0, 13.1 for the 0 (control), 1200, 6000 and 30000 ppm group respectively. Thus, no reductions were observed in treated groups. Reduced pup weights were observed in F1 and F2 litter animals at 30000 ppm (F1 males:14%, F1 females: 13%; F2 males: 9%, F2 females: 8%). NOAEL for offspring toxicity was set at 6000 ppm (417 mg/kg bw/day) based on reduced pup weights and distension of caecum observed in both F1 and F2 litters at 30000 ppm. The NOAEL for reproductive toxicity was set at 6000 ppm (417 mg/kg bw/day) based on lower fertility indices observed for F1 females at high dose level.

Comment 6: Study CA 5.6.1/07-08. The NOAEL for offspring toxicity in study was set at 10000 ppm (668 mg/kg bw/day). Statistically significant reduced mean pup weight (F0 generation) was observed at PND 21 (7%, 5% and 8% decrease at 1000, 3000 and 10000 ppm respectively). However, no dose response was observed. According to study author it was considered unlikely that the findings were indicative of a real adverse effect of Glyphosate on pre-weaning growth of the offspring due to lack of a dose response or substantiation from any of the other sets of litter data (second mate of the F0 generation and both mates of the F1 generation). Reduced mean pup weight was also observed in the range finding study (CA 5.6.1/009) (9%, 13% and 38% decrease at 3000, 10000 and 30000 ppm, respectively). However, the range finding study was only considered as supplementary data due to limitations (few animals used, no statistically analysis). It could also be noted that no effects on pup weight was observed in study B.6.6.1/001 using the same strain of animal tested up to limit dose.

Comment 7: Study CA 5.6.1/010. NOAEL for offspring was set at 10000 ppm (666-711 mg/kg bw/day for males and 777-804 mg/kg bw/day for females) based on reduced pup weights observed in males and females of both generations at 30000 ppm. Decreases in pup weights at the 10000 ppm dose level (666-771 and 777-804 mg/kg bw/day in males

and females, respectively) did not occur consistently in both sexes from all generations. Therefore, body weight changes in pups at the middle dose level were considered to be of questionable toxicological significance.
Comment 8: The DS agrees that co-formulants may affect (dermal) absorption and bioavailability leading to either an increased or decreased uptake through human skin depending on the type of formulation and the chemical composition. Whereas information on co-formulants is available for the representative product for the renewal, the exact compositions of other formulations used in published studies are not known. However, the aim of the hazard assessment is to elucidate the intrinsic properties of a substance. If studies performed with a formulation should be included in the hazard assessment, we consider it necessary to demonstrate that any influence of co-formulants on the result,i.e. by having a toxic effect or by influencing the toxicity of the active substance e.g., by mechanisms increasing bioavailability, stabilisation, activation etc can be excluded.
Comment 9: Study CA 5.6.1/001. The comment is not clear for us. The NOAEL for reproductive toxicity was set at 5000 ppm based on reduced number of homogenisation resistant spermatid in cauda epididymis observed in F0 generation males at 15000 ppm. Thus, the effect on sperms observed at 15000 ppm was not dismissed.
Comment 10: Study CA 5.6.1/004. DS position remains to set NOAEL for reproductive toxicity at 10000 ppm. Number of pups born live (%) reported for F0 generation: 94.9%, 96.5%, 99.1%** and 97.2% for the 0(control), 1000, 3000 and 10000 ppm group, respectively. Thus, no reduction in mid dose group was seen. Number of post-implantation loss (%) reported for F0 generation: 4%, 6%, 8%, 3% for the 0(control), 1200, 6000 and 30000 ppm group, respectively ($p<0.05$). Thus, no clear dose-response. Number of pups born live (mean) reported for F1 generation: 10.9, 11.4, 12.1 12.2 for the 0 (control), 1000, 3000 and 10000 ppm group, respectively. Thus, no reduction in treated groups. Number of post-implantation loss (%) reported for F1 generation: 2%, 4%, 2%, 3% for the 0 (control), 1200, 6000 and 30000 ppm group. Thus, no clear dose-response. Gestation length (days) was statistically significant lower at 15000 ppm (22.0 compared to 22.3 in control group) but the value seems to be within the average gestational time for rats of 21-23 days according to MSD Veterinary Manual (https://www.msdvetmanual.com/all-other-pets/rats/breeding-and-reproduction-of-rats).
Comment 11: See response to comments 2, 5, 6, 19-28, and Annex R
Comment 12: See response to comments 4, 5, 10, 14, 17, 20, 22, 27, 30 and Annex R
Comment 13: The aim of the hazard assessment is to elucidate the intrinsic properties of a substance. If studies performed with a formulation should be included in the hazard assessment, we consider it necessary to demonstrate that any influence of co-formulants on the result,i.e. by having a toxic effect or by influencing the toxicity of the active substance e.g., by mechanisms increasing bioavailability, stabilisation, activation etc can be excluded. The studies by Dai et al. (2016) and Pham et al. (2019) were considered in this section, and the study by Abarikwu *et al.* (2015) was considered as a data gap (study summary ie requested from applicant). The study by Anifandis *et al.* (2018) (epidemiological data) was not considered further due to limitations in the study. For the Clair *et al*. (2012a) study, RMS suggests that a detailed study summary is requested.
Comment 14: If studies performed with a formulation should be included in the hazard assessment, we consider it necessary to demonstrate that any influence of co-formulants on the result,i.e. by having a toxic effect or by influencing the toxicity of the active substance e.g., by mechanisms increasing bioavailability, stabilisation, activation etc can be excluded. The study by (Ren *et al*. 2018) was considered in this section. In the study, glyphosate and an unknown Roundup formulation were administered to pregnant mice during GD 1-19 via drinking water. DS considers this study restricted (glyphosate used is not sufficiently characterised, only one dose level was tested, there was large inter animal variability observed and too few animals per dose level were analysed). The *in vitro* study

by Coullery *et al.* (2020) (neurotoxicity) and the study by Kubsad *et al.* (2019) were not considered further due to limitations in the studies. In the study by Kubsad *et al.* (2019), the test substance was not sufficiently characterized. In addition, only one dose was tested. For the study by Coullery *et al.* (2020) see response to comment 31.
Comment 15: The decision on classification and labelling is based on whether or not available data indicate that the intrinsic properties of a substance fulfills criteria for classification in Regulation 1272/2008. Such assessment is primarily based on relevant and reliable information on the substance rather than a formulation. Otherwise any impact of co-formulants i.e. by having a toxic effect or by influencing the toxicity of the active substance by mechanisms increasing bioavailability, stabilisation, activation etc must be unequivocally excluded.
The conclusion regarding reproductive toxicity stated in the RAR is based on a large data set of fertility and developmental toxicity studies performed with the substance, the majority performed in vivo according to guidelines and GLP. In addition, a huge amount of published articles were reviewed to find any additional reliable and relevant information on the intrinsic properties of glyphosate. The majority of these studies were performed in vitro and while such data can be used to provide useful information to explain effects seen in vivo, the significance of this information, especially when perfomed with formulations, is unclear in the absence of correlating in vivo findings.
Comment 16: See response to comments 3, 13, 32 and Annex R
Comment 17: For offspring survival and fertility index, see response to comments 3, 4, 10 and 25. For pup weight, see response to comments 5, 6 and 7. For implantation, see response to comments 5, 10, 27 and as follows: Study CA 5.6.1/006: Mean number of implantations for F0 generation: 12.1, 11.2, 11.0 and 12.3 for 0 (control), 100, 1000 and 10000 ppm group respectively. Mean number of implantations for F1 generation: 13.4, 11.6, 12.0, 12.9 for 0 (control), 100, 1000 and 10000 ppm group, respectively. Significant decrease was observed for F1 group animals of low and mid dose but not high dose group. This finding was considered incidental by study author. In the absence of a convincing dose-related response the effect was considered unrelated to treatment. The study was considered as supplementary data due to limitations in the study (no effect dose and limited parameters investigated in study).
Comment 18: Reference to review by Antoniou M, et al. (2012)
The proposal for classification and labelling is based on a comparison between effects observed in the data available and the criteria stating when classification for reproductive toxicity is justified. For this comparison all data considered relevant and reliable is taken into account, regardless if being an industry-sponsored study to address the data requirements of legislation or if being published research. However, studies performed in accordance with guidelines and the principles of GLP are generally considered to be of higher reliability since the recommendations in guidelines are developed to harmonise and ensure adequate methodology (including relevant doses to study intrinsic properties regardless of exposure (during use) and statistical power). GLP is the system currently used to prevent fraud. Since classification and labelling is based on the intrinsic properties of a substance, studies performed with the active substance are considered more relevant than studies performed with formulations since it is difficult to fully exclude any influence of co-formulants on the result.
The adverse effects noted in the industry-sponsored studies such as implantation loss and malformations are discussed in the RAR along with a justification if dismissed based on maternal toxicity or if considered incidental. It is agreed that not all effects show a linear dose-response thus consistency of findings between studies and incidences need to be considered in the assessment to conclude if an effect is incidental or related to treatment. As seen in the RAR, malformations and increased implantation losses are also found in controls.

Comment 19: Study report B.6.6.1/001-003: Statistically significant increased liver weights were observed in adult females of both generations at 15000 ppm (F0 females: absolute weight: ↑13%, relative weight: ↑8%; F1 females: absolute weight: ↑10%, relative weight: ↑8%). DS considers the magnitude of liver weight changes (increase of 13%) as an adverse effect in the absence of clinical chemistry investigations in the study. Statistically significant increased kidney weights were observed in F0 females at 15000 ppm (absolute weight: increased 11%, relative weight: increased 7%). The NOAEL for parental toxicity was set at 5000 ppm based on increased liver and kidney weights observed in females of both generations at 15000 ppm. Statistically significant reductions in relative thyroid weights were observed for F0 males treated at 1500 ppm (22%) and 5000 ppm (24%). No statistically significant changes were detected in the 15000 ppm males, therefore, in the absence of a convincing dose-related response, these intergroup differences were considered to be unrelated to treatment. Anogenitial distance was measured but no measurement according to the cube root of body weight seems to have been done but could be requested from the applicant. For effects on sperm count, cortical vacuolation of the adrenal gland and large follicles, please see response to comment 3.
Comment 20: Study B.6.6.1/004: For effects on pups born live, implantation loss and gestation length, see response to comments 4 and 10. Brain: For the F0 males given 3000 or 10000 ppm glyphosate acid, brain weight adjusted for body weight was statistically significantly greater (↑2%) than in the control group. Absolute values were comparable with the control group. Similar changes were not observed in the F1 animals. The weight changes seen in the brain of the F0 males were therefore considered to be incidental to treatment. Cauda epididymis: Weight of cauda epididymis was statistically significant reduced (8%) in F0 males at low dose only, thus no dose response and no consistency across the generations. The study provides support in the interpretation of effects impacting the EAS modalities. The study follows OECD TG 416 (2001) except for following deviations, these deviations do not invalidate the study:(i) no individual animal data presented in study report, (ii) anogenital distance not examined as no treatment-related differences in sex ratio and sexual maturation were observed, (iii) the thyroid was not weighed, (iv) preimplantation loss not determined, (v) pup development investigations restricted to body weight, vaginal opening and preputial separation
Comment 21: Study B.6.6.1/005: For effects on kidney and ovary weights: See response to comment 5. The study provides support in the interpretation of effects impacting the EAS modalities. The study is performed in accordance with GLP and follows OECD TG 416 (2001) except for following deviations, these deviations do not invalidate the study: (i) testes were not used for enumeration of homogenisation-resistant spermatids but cauda epididymal sperm was enumerated (the guideline recommends both testes and epididymides to be used for enumeration of homogenisation-resistant spermatids and cauda epididymides sperm reserves, respectively), (ii) thyroid and spleen not weighed, (iii) vaginal opening and preputial separation not examined, (iv) anogenital distance not determined, (v) no organ weighed for pups (the guideline recommends brain, spleen and thymus to be weighed), (vi) pre-and post-implantation loss not reported, (vii) number of corpora lutea not given, (viii) time to mating not reported
Comment 22: Study B.6.6.1/006: For effects on implantations: See response to comment 17. The study was considered as supplementary data only.
Comment 23: Study B.6.6.1/007 / B.6.6.1/008: See response to comment 6
Comment 24: Study B.6.6.1/010: See response to comment 7
Comment 25: Study B.6.6.1/013: This study is a pre-guideline study and was conducted before GLP was compulsory. The study was not considered acceptable due to a large number of deviations (for example the glyphosate used is not characterized) and reporting deficiencies. Deviations from the OECD TG 416 (2001) were as follows: (i) purity not specified, (ii) lot/batch number not specified, (iii) no analytical determinations on stability and homogeneity of the test material, (iv) mating period was 6 consecutive

days (the guideline recommends a 2-week mating period), (v) during mating, males changed daily so that each female cohabited with different males (the guideline recommends for each mating each female should be placed with a single male from the same dose level (1:1 mate) until copulation occurs 2 weeks have elapsed), (vi) age of F0 animals at initiating of dosing was 28 days (the guideline recommends the animals to be 5 to 9 weeks old at the start of dosing), (vii) few animals were used. Six F0 animals/sex/dose group were used for production of the F1 generations, F1A and F1B generations. Twelve animals/sex/dose groups of the F1B generation were mated to get F2 generations (the guideline recommends each test and control group should contain a sufficient number of animals to yield preferable not less than 20 pregnant females at or near parturition), (viii) oestrous cycle monitoring not performed, (ix) pre-coital interval not recorded, (x) no sperm analyses, (xi) a quantitative evaluation of primordial follicles not conducted, (xii) sexual maturation not investigated in offsprings, (xiii) uterus, ovaries, seminal vesicles with coagulating glands, pituitary and thyroid not weighed, (xiv) vagina, uterus with cervix, ovaries, testis, epididymidis, prostate, seminal vesicles, coagulating gland not included in the histopathological examination for adults. Due to the large number of deviations and reporting deficiencies, the study was considered insufficient for assessment. It is noteworthy that adverse effects such as histopathological changes in the pancreas, liver and thymus were observed at low dose levels in this study but were not reported in other standard reproductive toxicity studies conducted according to GLP and using much higher doses. Further, in other standard generational studies conducted according to GLP, organ weight changes were observed only at higher dose levels. It could be noted that effects on fertility index was observed in another standard generational study (CA 5.6.1/005) but only at higher dose level.

Comment 26: Study CA 5.6.1/014:

This study is a pre-guideline study and was conducted before GLP was compulsory. The study was not considered acceptable due to a large number of deviations and reporting deficiencies. Dose levels tested were much too low, thus, an effect dose was not reached in this study. Following deviations from the OECD TG 416 (2001) were observed: (i) parental animals were dosed 63 days (males) before the mating period (the guideline recommends that dosing shall be continued for at least 10 weeks before the mating period), (ii) animals were mated in a sex ratio of 1 male:2 females to produce the F1 litters (the guideline recommends that each female shall be placed with a single male from the same dose level (1:1 mating)), (iii) dose levels tested much too low (the guideline recommends that the highest dose level should be chosen with the aim to induce toxicity but not death or severe suffering), (iv) no information on pre-mating dosing period, (ix) oestrous cycle monitoring not performed, (x) pre-coital interval not recorded, (xii) no sperm analyses, (xiii) a quantitative evaluation of primordial follicles not conducted, (xiv) physical and sexual maturation not investigated in offsprings, (xv) thymus of pups not weighed. Pup survival: In the F0 generation, postnatal survival indices for Days 0-4 and 4-21 were comparable between the control and treated groups for the first lactation interval (F1a). For the second litter interval of the F0, postnatal survival indices for the Day 0-4 interval were comparable between the control and treated groups. During the Day 4-21 interval, survival indices were significantly lower than control in each treatment group. The increase in pup mortality during this interval (i.e. Days 4-21) was attributed to high pup mortality within one or more litters at each treatment level. In the low-dose (3 mg/kg bw/day) group the lower pup survival was attributed to one female that experienced complete litter mortality (litter contained 14 live pups at Day 4). In the mid-dose (10 mg/kg bw/day) group, one female died on Day 7 of lactation and all seven pups in her litter died during the Day 4-7 lactation interval. Additionally, three mid-dose litters lost five or more pups from their litters during the Day 4-21 lactation interval. In the high-dose (30 mg/kg bw/day) group, one female lost nine of 12 pups during the Day 4-21 lactation interval. In the F1 and F2 generations postnatal

survival indices for Days 0-4 and 4-21 during both litter intervals were considered comparable between the control and treated groups. Some statistically significant differences in these indices were observed between the control and treated groups; however, no trend was evident through successive generations to indicate an adverse effect of treatment. Organ weights: In the F2 female group, mean liver/body weight ratios were significantly lower than control in each of the treated groups; however, no clear dose-relationship was apparent. Mean liver/brain weight ratios for the treated F2 females were lower than control; however, these differences from control values were not statistically significant. Mean spleen weights (absolute and relative to brain and body weights) were significantly higher than the control value in the F2 mid-dose female group; however, mean spleen weight data for the low- and high-dose F2 females were comparable to control values. In the absence of an effect on spleen weight in the high-dose F2 female group, the change seen in spleen weight data for the mid-dose females was considered spurious and not biologically meaningful. It could also be noted that no effect on spleen weight was observed in other standard reproductive toxicity studies conducted according to GLP at much higher dose levels. Adrenal weight to body ratio was significantly reduced (12%) in mid-dose group F1 females and heart to body ratio was increased (11%) in F2 males from mid-dose group. However, no statistically significant changes were observed at low- or high dose groups or other generations. Thus, no trends were evident within dose levels or through these generations.

Comment 27: There is no dose-response regarding the number of implantations and the pre-implantation loss. If this would be considered a treatment-related effect, it could be similarly argued that treatment reduces the incidence of post-implantation loss since this parameter is statistically significantly reduced in low and high dose groups and also lower in the mid-dose compare to controls.

Comment 28: Thank you for noticing this mistake. In study 5.6.2/002 the mean number of implantations in control, low, mid and high dose groups were 14.8±4.4, 16.1±1.7, 16.1±2,5 and 16.8±1.4. There was no statistical significant difference between the control group and any of the treated groups for this parameter or with respect to the mean numbers of corpora lutea and implants, mean number of live fetuses and the mean percent incidence of resorptions and fetal deaths.

Comment 29: Reference to article Perego et al. (2017). This study investigated ovarian function in bovine granulosa and theca cells after glyphosate stimulation. A slight, non-dose-related alteration in bovine granulosa cell proliferation and estradiol production was observed at 5 µg/mL. Due to the isolated occurrence of the observed effects without any dose-response relationship, the biological significance of those findings was questioned. Further, the source of glyphosate tested was not sufficiently characterised, no positive controls were used and the tests were conducted with only one or 2 test concentrations of glyphosate.

Comment 30: Reference to article by Lorenz V, Pacini G, Luque EH, Varayoud J, Milesi MM (2020).

This article presents interesting results indicating impaired fertility (decrease number of implanted embryos and increase of the preimplantation embryo losses) in pregnant rats exposed to low concentrations of glyphosate or a glyphosate-formulation. This was associateted with an increase in E2 levels, ERalpha protein and hormone responsive genes in utero indicating disruption of hormone signalling. This information should be taken into consideration in a weight of evidence assessment along with results from the other studies performed in accordance with GLP and guidelines. The number of animals examined, parameters included for analysis and the transparency of results presented should be taken into account (actual number of implantation sites per animals are not reported and the number of corpora lutea, resorption sites and preimplantation loss are only reported in graphics).

Comment 31: Reference to article by Coullery R, Pacchioni AM, Rosso SB. (2020)

The article states that "*pregnancy exposure to Glyph induces a delay in the development of neonatal reflexes and a reduction in locomotion as well as deficits in learning and memory processes, at different post-natal ages in a range from 5 to 45 days after the end of the treatment. Importantly, Glyph exposure affects neither maternal weight gain throughout pregnancy, nor gestational length, litter size or the age of eye opening of rat pups. However, prenatal Glyph exposure produces a 10–20% decrease on pups body weights mainly from PND 29. Moreover, pups treated with the higher dose of Glyph showed a delay in the acquisition of the righting reflex.*"
It is noted that the number of animals per group (8) was much smaller than recommended in OECD 426 (i.e. 20 litters at each dose level). Consequently, the number of pups used for motor activity (16 in total) was lower than recommended (20/sex (1/sex/litter)), a total of 8 was used for motor and sensory function compared to the recommendation of 20/sex (1/sex/litter) and a total of 8 pups were used instead of 10/sex (1/litter, depending on type of test).
It is also noted that rats were treated via intraperitoneal route every 48 hour rather than daily by the oral route as recommended in TG 426 (e.g., gavage, dietary, via drinking water), but other routes (e.g., dermal, inhalation) may be used depending on the characteristics and anticipated or known human exposure routes).
Comment 32: The study by Anifandis *et al.* (2018) (epidemiological data) was not considered further due to limitations in the study (test substance not characterized, only on test concentration used, no positive control)
Comment 33: Mohammadi et al. (2021): This study is a systematic review and meta-analysis on the studies in which the alteration of at least one sexual hormone including testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol was reported as a measured outcome in rats. According to study report glyphosate intake could have major effects on the health of reproductive system. Consequently, strict monitoring of the residual glyphosate content in the drinking water, agricultural crops, and food products is necessary. For the assessment of this hazard class we think this type of information must be considered along with the results from similar studies as well as studies performed in accordance with GLP and guidelines and the in vivo effects observed. In the absence of detailed information on the individual studies included in the analysis, the relevance for C& L is unclear.
Comment 34/35: Reference to study by Lesseur, et al. 2022 Lesseur, et al. 2021.
The two publications present interesting results indicating a link between glyphosate exposure and pretermbirth and anogenital distance in newborns, respectively. In female infants, high maternal urinary glyphosate (above the median) was associated with longer AGD-AC but this was not significant after covariate adjustment. Increased AMPA was associated with longer AGD-AF after adjusting for infant size and age at AGD exam.
No associations were detected in male offspring.
While seemingly robust, the relevance of these studies for classification and labelling is unclear since it is not possible to exclude that effects could also result from coformulants as the urinary analysis only included glyphosate and AMPA.
Comment (Annex R): The studies included in Annex R have been checked with available literature search provided by the applicant. The studies reported in Annex R were also considered in the RAR with exception of following references:
•Arbuckle *et al.* (2001). An exploratory analysis of the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population. Environmental Health Perspectives 109(8):851-57.
•Lesseur *et al.* (2021). Urinary glyphosate concentration in pregnant women in relation to length of gestation. Environ Res. 2021 Jul 30;203:111811
•Lesseur *et al*. (2021). Maternal urinary levels of glyphosate during pregnancy and anogenital distance in newborns in a US Multicenter pregancy cohort. Environ Pollut. 2021 Jul 1;280:117002

•Lorenz *et al.* (2020). Perinatal exposure to glyphosate or a glyphosate-based formulation disrupts hormonal and uterine milieu during the receptive state in rats. Food and Chemical Toxicology 143 (September): 111560 •Richard *et al.* (2005). Differential effects of glyphosate and Roundup on Human placental cells and aromatase. Environmental Health Perspectives 113 (6): 716-20. •Spinaci *et al.* (2020). Glyphosate and its formulation Roundup Impair pig oocyte maturation. Scientific Reports 10(1):12007. In the study by Spinaci *et al.* (2020) nuclear maturation, cytoplasmic maturation and developmental competence of oocytes, steroidogenic activity of cumulus cells as well as intracellular levels of glutathione (GSH) and ROS of oocytes were invstigated using an *in vitro* model of pig oocytes. It was concluded that Roundup adjuvants enhance glyphosate toxic effect and/or are biologically active in their side-effect. However, *in vitro* methods can only be considered to be of limited *in vivo* relevance. Thus, this study was not given appropriate weight of evidence. It could also be noted that there are no *in vivo* studies conducted for this endpoint using pigs. The studies by Richard *et al.* (2005) and Arbuckle *et al.* (2001) were published before the period "last ten years before the date of dossier submission" and therefore not included in the literature search by the applicant. However, the studies were included in old RAR (2015). Richard *et al.* (2005) studied effects of glyphosate and Roundup formulation on human placental cells and aromatase. Also in this study it was concluded that the formulation is more toxic than its active ingredient. However, the extrapolations to *in vivo* effects was considered unjustifiable based on both the unsuitability of surfactants in such test systems and the supraphysiological cytotoxic concentrations at which *in vitro* effects are reported. In the study by Arbuckle *et al.* (2001), glyphosate and other pesticides were weakly associated with spontaneous abortion. However, the author did not control for important personal confounding factors or for multiple exposures and no actual exposure data was used, casting doubt on the validity of the findings in this study. Thus, this study was not given appropriate weight of evidence.
RAC's response
RAC notes the in depth evaluation of the reproductive toxicity studies by HEAL and the thorough responses from the RMS. RAC assessed the reproductive toxicity studies included in the CLH report as well as relevant studies provided during the consultation according to the CLP criteria also including a weight of evidence assessment.

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2021	Argentina	<confidential>	International NGO	91
Comment received				
Page 432 "Conclusion on classification and labelling for reproductive toxicity". <confidential> agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina		Individual	92
Comment received				

Page 432 "Conclusion on classification and labelling for reproductive toxicity":<confidential> agrees with the assessments and conclusions achieved.
Dossier Submitter's Response
Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
22.10.2021	Germany		Individual	93
Comment received				
As mentioned from <confidential> in this video, Glyphosate can cause serious damage to oranisms in the second or third generation, due to changing mechanism regarding the inter-cellular transport of deuterium (H^3). See video on this page: https://uncutnews.ch/die-beunruhigende-rolle-von-glyphosat-bei-covid-19-neue-erkenntnisse/				
Dossier Submitter's Response				
RAC's response				
Noted. Not considered relevant for the process of classification.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Denmark		MemberState	94
Comment received				
2.6.6.4: Agree. No classification for reproductive or developmental effects is warranted for glyphosate.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.10.2021	Germany		Individual	95
Comment received				
According to the latest report of the pesticide authorities from France, The Netherlands, Sweden and Hungary, it has no effect on reproductivity; contradicting reports were based on exposure rates which are not relevant in case of good agricultural practice for application. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Literatur.7z				
Dossier Submitter's Response				
Noted. The attachments do not provide data within the scope of the scientific assessment in relation to the proposal for classification.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
21.10.2021	Germany		Individual	96
Comment received				
nicht rerprodunktionstoxisch!				
Dossier Submitter's Response				
Noted.				

RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2021	Argentina	Asociación Argentina de Consorcios Regionales de Experimentación Agrícola (AACREA)	National NGO	97
Comment received				
Page 432 "Conclusion on classification and labelling for reproductive toxicity": AACREA agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2021	Argentina		Individual	98
Comment received				
Page 432 "Conclusion on classification and labelling for reproductive toxicity": Ing. Agr. <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	<confidential>	National Authority	99
Comment received				
Page 432 "Conclusion on classification and labelling for reproductive toxicity": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2021	Argentina	CASAFE	Industry or trade association	100
Comment received				
Page 432 "Conclusion on classification and labelling for reproductive toxicity": CASAFE agrees with the assessments and conclusions achieved.				

Dossier Submitter's Response
Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	Asociación Argentina de Trigo	National NGO	101
Comment received				
Page 432 "Conclusion on classification and labelling for reproductive toxicity": Argentrigo agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Germany	Glyphosate Renewal Group	Company-Manufacturer	102
Comment received				
The applicant is in agreement with the proposal by the RMS (Glyphosate_RAR_01_Volume_1_2021-08-10, "No classification for reproductive or developmental toxicity"), that no classification for reproductive or developmental effects is warranted. This is consistent with the conclusion of the ECHA Committee for Risk Assessment (RAC 40, March 2017, "No classification for reproductive or developmental toxicity is justified"). This conclusion is based on a rigorous analysis of all the available data on glyphosate which included regulatory studies carried out according the OECD testing guidelines, in compliance with the Good Laboratory Practice (GLP), and also all the peer-reviewed scientific publications available till June 2021. When such a comprehensive and rich database exists, it is possible to assess, in a sound scientific manner, the relevance and reliability of scattered and random effects observed in some experiments or reported in some publications. The conclusion of 'no relevant effects on the reproductive function' is supported by the absence of consistent effects across the studies and /or among effects reported in the public literature (epidemiology data included). In addition, specific studies investigating the potential effects on androgenic, estrogenic and steroidogenesis function ruled out any potential effect on the reproductive function. No specific reproductive toxicity potential was shown in studies conducted with glyphosate. Treatment-related effects in parent animals were similar to those seen in subchronic and chronic toxicity studies and occurred at comparable dose levels. Developmental toxicity of glyphosate was tested in numerous studies in rats and rabbits. Glyphosate provided no evidence of teratogenicity. Further, no convincing evidence on developmental effects of glyphosate is evident in epidemiological data. The conclusion on whether to classify glyphosate for effects on reproductive and developmental toxicity must be based on reliable data obtained from internationally accepted and validated protocols and on experiments carried out in qualified laboratories. In conclusion, based on an entire body of evidence, there is no consistent indication of an				

effect on the sexual function and fertility, or an effect on embryo and fetal development, that would trigger classification and concern for human health. Any cited reference can be found as a supporting document in the public and confidential attachments, which will be uploaded separately via the large file upload link due to size ("Glyphosate_Supporting documents_public.zip" and "Glyphosate_Supporting documents_confidential.zip"). ECHA note – An attachment was submitted with the comment above. Refer to public attachment Glyphosate_Supporting documents_public.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Glyphosate_Supporting documents_confidential.zip
Dossier Submitter's Response
Thank you for your input.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	CIAFA (Chamber of the Argentine Industry of Fertilizers and Agrochemicals)	Industry or trade association	103
Comment received				
Page 432 "Conclusion on classification and labelling for reproductive toxicity": CIAFA (Chamber of the Argentine Industry of Fertilizers and Agrochemicals) agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
18.11.2021	France	Inserm - French National Institute of Health and Medical Research	Academic institution	104
Comment received				
This comment refers both to the sections of the RAR pertaining to assessment of reproductive effects (Volume 1 - § 2.6.6.4; page 432 and Volume 3 - § B.6.6.3 (AS); pages 364-450), as well as endocrine disruptor effects (§ 2.10.4; page 764). Conclusions RAR : "Overall summary (open literature): A review of the available published literature did not provide conclusive evidence that glyphosate exposure negatively affects reproduction". (Vol 1 - § 2.6.6.1.1 ; page 373) "No classification and labelling of glyphosate for reproductive or developmental effects is proposed". (Vol 1 - § 2.6.6.4 ; page 432) "It is agreed with overall conclusion of the applicant regarding human health. Based on				

the available data on glyphosate, the ED criteria are not met. "(Vol 1- § 2.10.4 ; page 764)

Comment by the Inserm expert panel :
(see also the Inserm report, pages 50-60 ; https://www.inserm.fr/expertise-collective/pesticides-et-sante-nouvelles-donnees-2021/)

The Inserm collective expert review analyzed the findings of a dozen academic studies using rodent models that investigated the effects of glyphosate and GBHs on different aspects of endocrine function (Walsh et al., 2000; Dallegrave et al., 2007; Romano et al., 2012; De Liz Oliveira Cavalli et al., 2013; Cai et al., 2017; Guerrero Schimpf et al., 2017 and 2018; Owagboriaye et al., 2017; Altamirano et al., 2018; Anifandis et al., 2018a and b; Jiang et al., 2018; Milesi et al., 2018; Gomez et al., 2019; Manservisi et al., 2019; Pham et al., 2019). The results are convergent and suggest an interaction of both GBHs and glyphosate with sex hormone regulatory pathways. Specifically, the studies show that glyphosate and GBHs have inhibitory effects on aromatase and can activate estrogen signaling pathways through mechanisms that may not involve receptor binding and that exhibit complex dose-effect relationships. These changes are associated with deleterious effects on reproductive function: for example, exposure of male rodents during the prenatal period or in adult life is associated with disruption of spermatogenesis and mammary gland anomalies, whereas early exposure to GBH in females is associated with uterine anomalies.

Our analysis of the academic literature thus suggests that both GBHs and glyphosate may exhibit endocrine disrupting properties that impact reproductive function. The difference between the conclusions reached by the Inserm collective expert review and the RAR stems from the inclusion or not of peer-reviewed academic studies studied by different groups that tested formulations (considered not relevant in the RAR), and that better reflect the reality of exposure in humans.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Inserm EC pesticides 2021_glyphosate_EN_18112021.pdf

Dossier Submitter's Response

Thank you for your input.
The decision on classification and labelling is based on whether or not available data indicate that the intrinsic properties of a substance fulfills criteria for classification in Regulation 1272/2008. Such assessment is primarily based on relevant and reliable information on the substance since any impact of co-formulants in a formulation must be unequivocally excluded. Moreover, since classification and labelling is based on the intrinsic properties of a substance, real exposure situations and exposure levels are less relevant for this type of assessment.
The conclusion regarding reproductive toxicity stated in the RAR is based on a large set of fertility and developmental toxicity studies with the substance, the majority performed in vivo according to guidelines and GLP. In addition, many published articles were reviewed to assess if these provide reliable and relevant information on the intrinsic properties of glyphosate. The majority of these studies were performed in vitro and while such data can be used to provide useful information to explain effects seen in vivo, the significance of this information, especially when perfomed with formulations, is unclear in the absence of correlating in vivo findings.
The studies included in section "Impaired reproductive function" of the Inserm report have been checked with available literature search provided by the applicant. The studies considered in the Inserm report for this section were also considered in the draft RAR with exception of following references:

- Dallegrave et al. (2007). Pre-and postnatal toxicity of the commercial glyphosate formulation in Wistar rats. Arch Toxicol 2007; 81:665-73
- Walsh et al. (2000). Roundup inhibits steroidogenesis by disrupting steroidogenic acute regulatory (StAR) protein expression. Environ Health Perspec 2000; 108:769-76
- Niemeyer et al. (2018). Do recommended doses of glyphosate-based herbicides affect soil invertebrates? Field and laboratory screening tests to risk assessment. Chemosphere 2018; 198:154-60.

Formulations were also the test substance used in the majority of the studies in the INSERM report which makes it difficult to distinguish between effects caused by the active substance and co-formulations.

The study by Dallegrave et al. (2007) was published before the period "last ten years before the date of dossier submission" and therefore not included in the literature search by the applicant. However, this study was included in old RAR (2015). It could be noted that a glyphosate based formulation containing POEA (not permitted for use in EU) was used in this study, and effects caused by co-formulants cannot be excluded.

Also, the study by Walsh et al. (2000) was published before the period "last ten years before the date of dossier submission" and therefore not included in the literature search by the applicant. This study was included in old RAR (2015) and reported that a glyphosate- based formulation affected the steroidogenesis pathway by inhibiting the progesterone production resulting in downstream reduction of mitochondrial levels of the StAR protein. Effects caused by co-formulants cannot be excluded.

The study by Niemeyer et al. (2018) (there seems to be a typo regarding study year) is relevant for the section of ecotox. A data gap is set to provide summary and a detailed assessment of reliability for the paper of Niemeyer J. C. *et al.* 2012 (see Vol. 1 section 3.4.1 "List of studies to be generated, still ongoing or available but not peer reviewed"). Regarding developmental toxicity: the document briefly informs about data showing lack of association between glyphosate exposure and birth defects and on the opposite, i.e., data indicating an association. In the absence of further information on exposure etc., the relevance for the hazard and risk assessment of glyphosate is unclear since it is not possible to exclude that effects could also result from co-formulants or for some studies, results seem to be based on simultaneous exposure to several pesticides.

RAC's response

Noted. RAC agrees with the RMS that the three studies identified that were not included in the assessment by the RAR are of very limited relevance for this opinion since it cannot be excluded that effects observed could be due to co-formulants or simultaneous exposure to other pesticides.

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina		Individual	105

Comment received

Page 432 "Conclusion on classification and labelling for reproductive toxicity": <confidential> agrees with the assessments and conclusions achieved.

Dossier Submitter's Response

Noted.

RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina	Bolsa de Cereales de Buenos Aires	Industry or trade association	106
Comment received				
Bolsa de Cereales de Buenos Aires agrees with the assessments and conclusions achieved. Page 432 "Conclusion on classification and labelling for reproductive toxicity"				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina	Fundación INAI	National NGO	107
Comment received				
Fundación INAI Agrees with the assessments and conclusions achieved. Page 84 ""Conclusion on classification and labelling for oral toxicity""Page 91 ""Conclusion on classification and labelling for dermal toxicity""Page 98 ""Conclusion on classification and labelling for inhalation toxicity""				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	<confidential>	National NGO	108
Comment received				
"Page 84 ""Conclusion on classification and labelling for oral toxicity"" Page 91 ""Conclusion on classification and labelling for dermal toxicity"" Page 98 ""Conclusion on classification and labelling for inhalation toxicity""" <confidential> agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	ACSOJA	National NGO	109
Comment received				

ACSOJA agrees with the assessments and conclusions achieved in the "Page 84 "Conclusion on classification and labelling for oral toxicity"; Page 91 "Conclusion on classification and labelling for dermal toxicity" and Page 98 "Conclusion on classification and labelling for inhalation toxicity" (CLH report)
Dossier Submitter's Response
Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	<confidential>	Industry or trade association	110
Comment received				
<confidential> agrees with: Page 84 "Conclusion on classification and labelling for oral toxicity" Page 91 "Conclusion on classification and labelling for dermal toxicity" Page 98 "Conclusion on classification and labelling for inhalation toxicity"				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.11.2021	Argentina		Individual	111
Comment received				
"Page 84 ""Conclusion on classification and labelling for oral toxicity"" Page 91 ""Conclusion on classification and labelling for dermal toxicity"" Page 98 ""Conclusion on classification and labelling for inhalation toxicity"": <confidential> agrees with the assessments and conclusions achieved."				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina	Cazenave y Asociados SA	Company-Downstream user	112
Comment received				
"Page 84 ""Conclusion on classification and labelling for oral toxicity"" Page 91 ""Conclusion on classification and labelling for dermal toxicity"" Page 98 ""Conclusion on classification and labelling for inhalation toxicity"": Cazenave y Asociados SA agrees with the assessments and conclusions achieved."				

Dossier Submitter's Response
Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina	<confidential>	National NGO	113
Comment received				
"Page 84 ""Conclusion on classification and labelling for oral toxicity"" Page 91 ""Conclusion on classification and labelling for dermal toxicity"" Page 98 ""Conclusion on classification and labelling for inhalation toxicity"": <confidential> agrees with the assessments and conclusions achieved."				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2021	Argentina	<confidential>	International NGO	114
Comment received				
Page 84 "Conclusion on classification and labelling for oral toxicity". Page 91 "Conclusion on classification and labelling for dermal toxicity". Page 98 "Conclusion on classification and labelling for inhalation toxicity". <confidential> agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.10.2021	Germany		Individual	115
Comment received				
Very low ECHA note – An attachment was submitted with the comment above. Refer to public attachment Literatur.7z				
Dossier Submitter's Response				
Noted. The attachments do not provide data within the scope of the scientific assessment in relation to the proposal for classification.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina		Individual	116

Comment received
"Page 84 ""Conclusion on classification and labelling for oral toxicity"" Page 91 ""Conclusion on classification and labelling for dermal toxicity"" Page 98 ""Conclusion on classification and labelling for inhalation toxicity"": <confidential> agrees with the assessments and conclusions achieved."
Dossier Submitter's Response
Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Denmark		MemberState	117
Comment received				
Not reviewed.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2021	Argentina	Asociación Argentina de Consorcios Regionales de Experimentación Agrícola (AACREA)	National NGO	118
Comment received				
Page 84 "Conclusion on classification and labelling for oral toxicity" Page 91 "Conclusion on classification and labelling for dermal toxicity" Page 98 "Conclusion on classification and labelling for inhalation toxicity": AACREA agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2021	Argentina		Individual	119
Comment received				
"Page 84 ""Conclusion on classification and labelling for oral toxicity"" Page 91 ""Conclusion on classification and labelling for dermal toxicity"" Page 98 ""Conclusion on classification and labelling for inhalation toxicity"": Ing. Agr. <confidential> agrees with the assessments and conclusions achieved."				

Dossier Submitter's Response
Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	<confidential>	National Authority	120
Comment received				
Page 84 "Conclusion on classification and labelling for oral toxicity" Page 91 "Conclusion on classification and labelling for dermal toxicity" Page 98 "Conclusion on classification and labelling for inhalation toxicity": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2021	Argentina	CASAFE	Industry or trade association	121
Comment received				
Page 84 "Conclusion on classification and labelling for oral toxicity" Page 91 "Conclusion on classification and labelling for dermal toxicity" Page 98 "Conclusion on classification and labelling for inhalation toxicity": CASAFE agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	Asociación Argentina de Trigo	National NGO	122
Comment received				
Page 84 "Conclusion on classification and labelling for oral toxicity" Page 91 "Conclusion on classification and labelling for dermal toxicity" Page 98 "Conclusion on classification and labelling for inhalation toxicity" Argentrigo agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number

19.11.2021	Germany	Glyphosate Renewal Group	Company-Manufacturer	123
Comment received				

The applicant is in agreement with the proposal by the RMS (Glyphosate_RAR_01_Volume_1_2021-08-10, "Glyphosate does not need to be classified for acute oral toxicity according to the CLP Regulation (EU) No 1272/2008"), that is consistent with the conclusion of the ECHA Committee for Risk Assessment (RAC 40, March 2017, "no classification for acute oral toxicity").
The applicant is in agreement with the proposal by the RMS (Glyphosate_RAR_01_Volume_1_2021-08-10, "Glyphosate does not need to be classified for acute dermal toxicity according to the CLP Regulation (EU) No 1272/2008"), that is consistent with the conclusion of the ECHA Committee for Risk Assessment (RAC 40, March 2017, "no classification for acute dermal toxicity").
The applicant is in agreement with the proposal by the RMS (Glyphosate_RAR_01_Volume_1_2021-08-10, "Glyphosate does not need to be classified for acute inhalation toxicity according to the CLP Regulation (EU) No 1272/2008"), that is consistent with the conclusion of the ECHA Committee for Risk Assessment (RAC 40, March 2017, "no classification for acute inhalation toxicity").

In the dRAR prepared by the RMS, in the table 3.1.4 "List of studies to be generated, still ongoing or available but not peer reviewed", point 3.1.4.6, the RMS provided the following request:

"1) Volume 1, section 2.6.1.1 short summary on toxicokinetic information.
A public literature study is available in which 13 poisoning incidents with glyphosate-based herbicides in France (Zouaoui et al., 2012) were analysed. This publication was evaluated during the previous assessment of glyphosate by RMS DE. However, it is not re-submitted by the applicant. The applicant is requested to submit this publication together with a summary and a relevance and reliability assessment of this publication."

This information is provided in the supporting documents "RMS request dRAR 1_113898-001" and Zouaoui et al., 2012, "Supporting document 8", in the public and confidential attachments.

"2) Volume 1, section 2.6.2 acute toxicity
The applicant is requested to justify why for the same batch different conclusions are drawn regarding the purity and the acceptability of acute toxicity studies.
Study CA 5.2.1/020 acceptable
Study CA 5.2.3/016 acceptable
Study CA 5.2.4/012 supportive due to low purity
Study CA 5.2.5/015 supportive due to low purity
Study CA 5.2.6/016 acceptable"

This information is provided in the supporting document "RMS request dRAR 2_113898-002" in the public and confidential attachments.

Any cited reference can be found as a supporting document in the public and confidential attachments, which will be uploaded separately via the large file upload link due to size ("Glyphosate_Supporting documents_public.zip" and "Glyphosate_Supporting documents_confidential.zip").

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Glyphosate_Supporting documents_public.zip

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Glyphosate_Supporting documents_confidential.zip

Dossier Submitter's Response

Response relating to the request stated in Volume 1, section 2.6.1.1 (short summary on toxicokinetic information):
A public literature study is available in which 13 poisoning incidents with glyphosate-based herbicides in France (Zouaoui et al., 2012) were analysed. This literature study was not summarised by the applicant. Therefore, a summary was made available by the applicant (see attachment).

Zouaoui et al. (2012) reported 13 cases of acute oral intoxication with glyphosate. The patients were classified by the intoxication severity using simple clinical criteria. Various symptoms were observed following intoxication, which are considered not relevant for the data point under consideration (i.e. toxicokinetics and -dynamics) and are therefore not further discussed here.

In the study, however, concentrations of glyphosate and AMPA have also been determined in blood and/or urine. Blood glyphosate concentrations had a mean value of 61 mg/L (range 0.6–150 mg/L) and 4146 mg/L (range 690–7480 mg/L) respectively in mild–moderate intoxication and fatal cases. In the severe intoxication case for which blood has been sampled, the blood glyphosate concentration was found at 838 mg/L.

This study also showed that there is at least strong evidence that biotransformation of ingested glyphosate to AMPA is very limited in man. The glyphosate:AMPA ratio in blood analyses varied between 12:1 and 6933:1 with a median value of 235:1. In urine, with data from 7 cases available, the individual ratios ranged from 243:1 to 7863:1 with a median of 422:1. These ratios were independent from the severity of symptoms or a fatal outcome.

Although it is difficult to assign a reliability score to this study, the relevance of the study is limited. The study investigates the symptomatology and blood/urine glyphosate concentrations following oral ingestion of different glyphosate-containing plant protection products, i.e. not the active substance itself. It is not possible to allocate effects to glyphosate, to other components within the formulation, or to a combination of different formulations. Likewise it is not known how the different compositions influence the toxicokinetics and -dynamics of glyphosate. In addition, in two cases, co-exposure with another active substance occurred.

In conclusion, although the study gives indications that glyphosate is converted only to a very limited extend to AMPA in humans, the results need to be considered with caution. Nevertheless, it is noted that the results are in line with the available data from rats and with the in vitro comparative metabolism study, which also indicated limited metabolism of glyphosate in mammals.

Response relating to the request stated Volume 1, section 2.6.2 (acute toxicity):
The applicant was requested to justify why for the same batch of test item, different conclusions were drawn regarding the purity and the acceptability of acute toxicity studies. In the attachment provided by the applicant, it is explained that the study summaries incorrectly stated that they should be considered "supportive due to low purity." Instead, they should indeed be considered acceptable.

The dossier submitted agrees with the reasoning provided by the applicant and the purity of the test item is considered acceptable for conducting the acute toxicity tests.

RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	CIAFA (Chamber of the Argentine Industry of Fertilizers and Agrochemicals)	Industry or trade association	124
Comment received				
Page 84 "Conclusion on classification and labelling for oral toxicity" Page 91 "Conclusion on classification and labelling for dermal toxicity" Page 98 "Conclusion on classification and labelling for inhalation toxicity": CIAFA (Chamber of the Argentine Industry of Fertilizers and Agrochemicals) agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina		Individual	125
Comment received				
"Page 84 ""Conclusion on classification and labelling for oral toxicity"" Page 91 ""Conclusion on classification and labelling for dermal toxicity"" Page 98 ""Conclusion on classification and labelling for inhalation toxicity"": <confidential> agrees with the assessments and conclusions achieved."				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina	Bolsa de Cereales de Buenos Aires	Industry or trade association	126
Comment received				
Bolsa de Cereales de Buenos Aires agrees with the assessments and conclusions achieved. "Page 84 ""Conclusion on classification and labelling for oral toxicity", Page 91 ""Conclusion on classification and labelling for dermal toxicity", Page 98 "Conclusion on classification and labelling for inhalation toxicity"				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina	Fundación INAI	National NGO	127
Comment received				
Fundación INAI Agrees with the assessments and conclusions achieved. Page 104 "Conclusion on classification and labelling for skin corrosion/irritation"				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	<confidential>	National NGO	128
Comment received				
Page 104 "Conclusion on classification and labelling for skin corrosion/irritation"				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	ACSOJA	National NGO	129
Comment received				
ACSOJA agrees with the assessments and conclusions achieved in the Page 104 "Conclusion on classification and labelling for skin corrosion/irritation" (CLH report)				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	<confidential>	Industry or trade association	130
Comment received				
<confidential> agrees with Page 104 "Conclusion on classification and labelling for skin corrosion/irritation"				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.11.2021	Argentina		Individual	131
Comment received				
Page 104 "Conclusion on classification and labelling for skin corrosion/irritation": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina	Cazenave y Asociados SA	Company-Downstream user	132
Comment received				
Page 104 "Conclusion on classification and labelling for skin corrosion/irritation": Cazenave Asociados SA agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina	<confidential>	National NGO	133
Comment received				
Page 104 "Conclusion on classification and labelling for skin corrosion/irritation": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2021	Argentina	<confidential>	International NGO	134
Comment received				
Page 104 "Conclusion on classification and labelling for skin corrosion/irritation". <confidential> agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.10.2021	Germany		Individual	135
Comment received				
This has only been reported in case of repeated and direct application on the skin (for example in the coca control applications which were done by airplanes over populated areas). ECHA note – An attachment was submitted with the comment above. Refer to public attachment Literatur.7z				
Dossier Submitter's Response				
Noted. The attachments do not provide data within the scope of the scientific assessment in relation to the proposal for classification.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina		Individual	136
Comment received				
Page 104 "Conclusion on classification and labelling for skin corrosion/irritation": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Denmark		MemberState	137
Comment received				
Not reviewed.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2021	Argentina	Asociación Argentina de Consorcios Regionales de Experimentación Agrícola (AACREA)	National NGO	138
Comment received				
Page 104 "Conclusion on classification and labelling for skin corrosion/irritation": AACREA agrees with the assessments and conclusions achieved.				

Dossier Submitter's Response
Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2021	Argentina		Individual	139
Comment received				
Page 104 "Conclusion on classification and labelling for skin corrosion/irritation": Ing. Agr. <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	<confidential>	National Authority	140
Comment received				
Page 104 "Conclusion on classification and labelling for skin corrosion/irritation": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2021	Argentina	CASAFE	Industry or trade association	141
Comment received				
Page 104 "Conclusion on classification and labelling for skin corrosion/irritation": CASAFE agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	Asociación Argentina de Trigo	National NGO	142
Comment received				
Page 104 "Conclusion on classification and labelling for skin corrosion/irritation": Argentrigo agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				

Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Germany	Glyphosate Renewal Group	Company-Manufacturer	143
Comment received				
The applicant is in agreement with the proposal by the RMS (Glyphosate_RAR_01_Volume_1_2021-08-10, "Glyphosate does not need to be classified for skin corrosion or irritation according to the CLP Regulation (EU) No 1272/2008"), that is consistent with the conclusion of the ECHA Committee for Risk Assessment (RAC 40, March 2017, "no classification skin irritation/corrosion is warranted"). Any cited reference can be found as a supporting document in the public and confidential attachments, which will be uploaded separately via the large file upload link due to size ("Glyphosate_Supporting documents_public.zip" and "Glyphosate_Supporting documents_confidential.zip"). ECHA note – An attachment was submitted with the comment above. Refer to public attachment Glyphosate_Supporting documents_public.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Glyphosate_Supporting documents_confidential.zip				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	CIAFA (Chamber of the Argentine Industry of Fertilizers and Agrochemicals)	Industry or trade association	144
Comment received				
Page 104 "Conclusion on classification and labelling for skin corrosion/irritation": CIAFA (Chamber of the Argentine Industry of Fertilizers and Agrochemicals) agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina		Individual	145
Comment received				

Page 104 "Conclusion on classification and labelling for skin corrosion/irritation": <confidential> agrees with the assessments and conclusions achieved.
Dossier Submitter's Response
Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina	Bolsa de Cereales de Buenos Aires	Industry or trade association	146
Comment received				
Bolsa de Cereales de Buenos Aires agrees with the assessments and conclusions achieved. Page 104 "Conclusion on classification and labelling for skin corrosion/irritation"				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina	Fundación INAI	National NGO	147
Comment received				
Fundación INAI Agrees with the assessments and conclusions achieved. Page 116 "Conclusion on classification and labelling for serious eye damage/irritation"				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	<confidential>	National NGO	148
Comment received				
Page 116 "Conclusion on classification and labelling for serious eye damage/irritation": <confidential> agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	ACSOJA	National NGO	149
Comment received				
ACSOJA agrees with the assessments and conclusions achieved in the Page 116 "Conclusion on classification and labelling for serious eye damage/irritation" (CLH report)				

Dossier Submitter's Response
Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	<confidential>	Industry or trade association	150
Comment received				
<confidential> agrees with Page 116 "Conclusion on classification and labelling for serious eye damage/irritation"				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.11.2021	Argentina		Individual	151
Comment received				
Page 116 "Conclusion on classification and labelling for serious eye damage/irritation": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina	Cazenave y Asociados SA	Company-Downstream user	152
Comment received				
Page 116 "Conclusion on classification and labelling for serious eye damage/irritation": Cazenave y Asociados agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina	<confidential>	National NGO	153
Comment received				
Page 116 "Conclusion on classification and labelling for serious eye damage/irritation": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				

Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2021	Argentina	<confidential>	International NGO	154
Comment received				
Page 116 "Conclusion on classification and labelling for serious eye damage/irritation". <confidential> agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.10.2021	Germany		Individual	155
Comment received				
Not relevant ECHA note – An attachment was submitted with the comment above. Refer to public attachment Literatur.7z				
Dossier Submitter's Response				
Noted. The attachments do not provide data within the scope of the scientific assessment in relation to the proposal for classification.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina		Individual	156
Comment received				
Page 116 "Conclusion on classification and labelling for serious eye damage/irritation": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Denmark		Individual	157
Comment received				
Serious eye damage: this accounts for the global increases in cataracts and macular degeneration therefore glyphosate's licence should not be renewed.				

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Five books about the toxicity of Monsanto.docx
Dossier Submitter's Response
Noted. Not within the scope of the scientific assessment in relation to the proposal for classification. Besides, in the attachement submitted by the individual, no information regarding the global increases in cataracts and macular degeneration were provided.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Denmark		MemberState	158
Comment received				
2.6.2.5.3: Agree. A classification for eye damage is warranted for glyphosate.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2021	Argentina	Asociación Argentina de Consorcios Regionales de Experimentación Agrícola (AACREA)	National NGO	159
Comment received				
Page 116 "Conclusion on classification and labelling for serious eye damage/irritation": AACREA agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2021	Argentina		Individual	160
Comment received				
Page 116 "Conclusion on classification and labelling for serious eye damage/irritation": Ing. Agr. <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	<confidential>	National Authority	161

Comment received
Page 116 "Conclusion on classification and labelling for serious eye damage/irritation": <confidential> agrees with the assessments and conclusions achieved.
Dossier Submitter's Response
Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2021	Argentina	CASAFE	Industry or trade association	162
Comment received				
Page 116 "Conclusion on classification and labelling for serious eye damage/irritation": CASAFE agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	Asociación Argentina de Trigo	National NGO	163
Comment received				
Page 116 "Conclusion on classification and labelling for serious eye damage/irritation": Argentrigo agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Germany	Glyphosate Renewal Group	Company-Manufacturer	164
Comment received				
The applicant is in agreement with the classification proposal by the RMS (Glyphosate_RAR_01_Volume_1_2021-08-10, "Classification for Serious Eye Damage, category 1 (H318)"), for glyphosate acid but not for the glyphosate salts. The applicant disagrees with classifying both the acid and salts with serious eye damage, as the results of the eye irritation studies with glyphosate salts do not trigger any classification. The glyphosate salts are the neutralized form of glyphosate acid, the result of a combination of acid and base, and are thus exhibiting completely different properties. The studies carried out with glyphosate isopropylamine salt, were considered not valid or acceptable with restriction because of low purity. The batch tested in these studies (lot/batch # 290-JaK-146-4), had a purity of 62.2% (glyphosate isopropylamine salt, a.i.) which is equivalent to 46.1% (glyphosate technical acid equivalents, a.e.). The applicant is of the opinion that the test material glyphosate isopropylamine salt has an acceptable purity, representative of manufacturing, and the studies should therefore be considered				

acceptable and supportive to conclude for no classification. In conclusion, no classification for Serious Eye Damage, category 1 (H318) is warranted for glyphosate salts. Any cited reference can be found as a supporting document in the public and confidential attachments, which will be uploaded separately via the large file upload link due to size ("Glyphosate_Supporting documents_public.zip" and "Glyphosate_Supporting documents_confidential.zip"). ECHA note – An attachment was submitted with the comment above. Refer to public attachment Glyphosate_Supporting documents_public.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Glyphosate_Supporting documents_confidential.zip
Dossier Submitter's Response
In contrast to glyphosate acid, studies with glyphosate salts indeed do not exhibit eye irritating/damaging properties that would warrant classification (see Section 2.6.2.5 of the CLH report). It might be considered by the RAC to propose different harmonised classifications for glyphosate (acid) and glyphosate salts.
RAC's response
Noted. RAC is assessing the classification of glyphosate with CAS 1071-83-6. If salts of glyphosate should be considered for classification, separate CLH proposals should be submitted.

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	CIAFA (Chamber of the Argentine Industry of Fertilizers and Agrochemicals)	Industry or trade association	165
Comment received				
Page 116 "Conclusion on classification and labelling for serious eye damage/irritation": CIAFA (Chamber of the Argentine Industry of Fertilizers and Agrochemicals) agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina		Individual	166
Comment received				
Page 116 "Conclusion on classification and labelling for serious eye damage/irritation": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina	Bolsa de Cereales de Buenos Aires	Industry or trade association	167
Comment received				
Bolsa de Cereales de Buenos Aires agrees with the assessments and conclusions achieved. Page 116 "Conclusion on classification and labelling for serious eye damage/irritation"				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina	Fundación INAI	National NGO	168
Comment received				
Fundación INAI Agrees with the assessments and conclusions achieved. Page 126 "Conclusion on classification and labelling for skin sensitisation"				
Dossier Submitter's Response				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	<confidential>	National NGO	169
Comment received				
Page 126 "Conclusion on classification and labelling for skin sensitisation": <confidential> agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	ACSOJA	National NGO	170
Comment received				
ACSOJA agrees with the assessments and conclusions achieved in the Page 126 "Conclusion on classification and labelling for skin sensitisation" (CLH report)				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON GLYPHOSATE (ISO); *N*-(PHOSPHONOMETHYL)GLYCINE

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	<confidential>	Industry or trade association	171
Comment received				
<confidential> agrees with Page 126 "Conclusion on classification and labelling for skin sensitisation"				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.11.2021	Argentina		Individual	172
Comment received				
Page 126 "Conclusion on classification and labelling for skin sensitisation": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina	Cazenave y Asociados SA	Company-Downstream user	173
Comment received				
Page 126 "Conclusion on classification and labelling for skin sensitisation": Cazenave y Asociados agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina	<confidential>	National NGO	174
Comment received				
Page 126 "Conclusion on classification and labelling for skin sensitisation": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON GLYPHOSATE (ISO); *N*-(PHOSPHONOMETHYL)GLYCINE

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2021	Argentina	<confidential>	International NGO	175
Comment received				
Page 126 "Conclusion on classification and labelling for skin sensitisation". <confidential> agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.10.2021	Germany		Individual	176
Comment received				
Not relevant ECHA note – An attachment was submitted with the comment above. Refer to public attachment Literatur.7z				
Dossier Submitter's Response				
Noted. The attachments do not provide data within the scope of the scientific assessment in relation to the proposal for classification.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina		Individual	177
Comment received				
Page 126 "Conclusion on classification and labelling for skin sensitisation": <confidential> with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Denmark		MemberState	178
Comment received				
Ned reviewed.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number

20.11.2021	Argentina	Asociación Argentina de Consorcios Regionales de Experimentación Agrícola (AACREA)	National NGO	179
Comment received				
Page 126 "Conclusion on classification and labelling for skin sensitisation": AACREA agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2021	Argentina		Individual	180
Comment received				
Page 126 "Conclusion on classification and labelling for skin sensitisation": Ing. Agr. <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	<confidential>	National Authority	181
Comment received				
Page 126 "Conclusion on classification and labelling for skin sensitisation": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2021	Argentina	CASAFE	Industry or trade association	182
Comment received				
Page 126 "Conclusion on classification and labelling for skin sensitisation": CASAFE agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON GLYPHOSATE (ISO); *N*-(PHOSPHONOMETHYL)GLYCINE

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	Asociación Argentina de Trigo	National NGO	183
Comment received				
Page 126 "Conclusion on classification and labelling for skin sensitisation": Argentrigo agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Germany	Glyphosate Renewal Group	Company-Manufacturer	184
Comment received				
The applicant is in agreement with the proposal by the RMS (Glyphosate_RAR_01_Volume_1_2021-08-10, "no classification according to the CLP Regulation (EU) No 1272/2008 is warranted"), that is consistent with the conclusion of the ECHA Committee for Risk Assessment (RAC 40, March 2017, "no classification for skin sensitization is warranted"). Any cited reference can be found as a supporting document in the public and confidential attachments, which will be uploaded separately via the large file upload link due to size ("Glyphosate_Supporting documents_public.zip" and "Glyphosate_Supporting documents_confidential.zip"). ECHA note – An attachment was submitted with the comment above. Refer to public attachment Glyphosate_Supporting documents_public.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Glyphosate_Supporting documents_confidential.zip				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	CIAFA (Chamber of the Argentine Industry of Fertilizers and Agrochemicals)	Industry or trade association	185
Comment received				
Page 126 "Conclusion on classification and labelling for skin sensitisation": CIAFA (Chamber of the Argentine Industry of Fertilizers and Agrochemicals) agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina		Individual	186
Comment received				
Page 126 "Conclusion on classification and labelling for skin sensitisation": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				

RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina	Bolsa de Cereales de Buenos Aires	Industry or trade association	187
Comment received				
Bolsa de Cereales de Buenos Aires agrees with the assessments and conclusions achieved. Page 126 "Conclusion on classification and labelling for skin sensitisation"				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina	Fundación INAI	National NGO	188
Comment received				
Fundación INAI Agrees with the assessments and conclusions achieved. Page 130 "Conclusion on classification and labelling for STOT-SE"				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	<confidential>	National NGO	189
Comment received				
Page 130 "Conclusion on classification and labelling for STOT-SE": <confidential> agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	ACSOJA	National NGO	190
Comment received				
ACSOJA agrees with the assessments and conclusions achieved in the Page 130 "Conclusion on classification and labelling for STOT-SE" (CLH report)				
Dossier Submitter's Response				
Noted.				
RAC's response				

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	<confidential>	Industry or trade association	191
Comment received				
<confidential> agrees with Page 130 "Conclusion on classification and labelling for STOT-SE"				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.11.2021	Argentina		Individual	192
Comment received				
Page 130 "Conclusion on classification and labelling for STOT-SE": <confidential>agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina	Cazenave y Asociados SA	Company-Downstream user	193
Comment received				
Page 130 "Conclusion on classification and labelling for STOT-SE": Cazenave y Asociados SA agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina	<confidential>	National NGO	194
Comment received				
Page 130 "Conclusion on classification and labelling for STOT-SE": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2021	Argentina	<confidential>	International NGO	195
Comment received				
Page 130 "Conclusion on classification and labelling for STOT-SE". <confidential> agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.10.2021	Germany		Individual	196
Comment received				
According to the latest report of the pesticide authorities from France, The Netherlands, Sweden and Hungary, it is not toxic for organs; contradicting reports were based on exposure rates which are not relevant in case of good agricultural practice for application. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Literatur.7z				
Dossier Submitter's Response				
Noted. The attachments do not provide data within the scope of the scientific assessment in relation to the proposal for classification.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina		Individual	197
Comment received				
Page 130 "Conclusion on classification and labelling for STOT-SE":<confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Denmark		MemberState	198
Comment received				
Not reviewed.				
Dossier Submitter's Response				
Noted.				
RAC's response				

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2021	Argentina	Asociación Argentina de Consorcios Regionales de Experimentación Agrícola (AACREA)	National NGO	199
Comment received				
Page 130 "Conclusion on classification and labelling for STOT-SE": AACREA agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2021	Argentina		Individual	200
Comment received				
Page 130 "Conclusion on classification and labelling for STOT-SE": Ing. Agr. <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	<confidential>	National Authority	201
Comment received				
Page 130 "Conclusion on classification and labelling for STOT-SE": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2021	Argentina	CASAFE	Industry or trade association	202
Comment received				
Page 130 "Conclusion on classification and labelling for STOT-SE": CASAFE agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				

Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	Asociación Argentina de Trigo	National NGO	203
Comment received				
Page 130 "Conclusion on classification and labelling for STOT-SE": Argentrigo agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Germany	Glyphosate Renewal Group	Company-Manufacturer	204
Comment received				
The applicant is in agreement with the proposal by the RMS that is consistent with the conclusion of the ECHA Committee for Risk Assessment (RAC 40, March 2017). Volume 1, section 2.6.2.10.2 notes, based on the large acute toxicity data set, "no classification for STOT-SE category 1 or 2 is warranted as neither significant nor severe toxic effects were observed at non-lethal doses attributed to the acute exposure to glyphosate. Further, there is no evidence for narcotic effects or respiratory irritation and therefore no classification for STOT- SE category 3 is warranted." This proposal is consistent with previous conclusions at ECHA RAC 40 and by EFSA (List of Endpoints, EFSA Conclusion 2015, EFSA Journal 2015;13(11):4302). Any cited reference can be found as a supporting document in the public and confidential attachments, which will be uploaded separately via the large file upload link due to size ("Glyphosate_Supporting documents_public.zip" and "Glyphosate_Supporting documents_confidential.zip"). ECHA note – An attachment was submitted with the comment above. Refer to public attachment Glyphosate_Supporting documents_public.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Glyphosate_Supporting documents_confidential.zip				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	CIAFA (Chamber of the Argentine Industry of Fertilizers and Agrochemicals)	Industry or trade association	205
Comment received				
Page 130 "Conclusion on classification and labelling for STOT-SE": CIAFA (Chamber of the Argentine Industry of Fertilizers and Agrochemicals) agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
18.11.2021	France	Inserm - French National Institute of Health and Medical Research	Academic institution	206
Comment received				
This comment refers to RAR § 2.6.2.6 Respiratory sensitization, page 117 ; RAR § 2.6.2.10.1 Short summary and overall relevance of the provided information on specific target organ toxicity - single exposure (STOT-SE), page 129 ; RAR § 2.6.3.1 Specific target organ toxicity - repeated exposure (STOT-RE). Conclusion RAR (page 129): "In humans, there is no evidence for respiratory tract irritation by the active substance. However, it should be acknowledged that such an exposure will seldomly occur. During the previous assessment, it was noted that for formulations, Burger et al. (2009, refer to Volume 1 2.6.9) reported cases from Germany that might indicate respiratory irritation but these findings were considered to be likely due to POEA surfactants (tallowamines) present in the formulation. [.....] Overall, there is no sufficient evidence to classify glyphosate for respiratory tract irritation." Comment by the Inserm expert panel: (see also the Inserm report, pages 30-31 ; https://www.inserm.fr/expertise-collective/pesticides-et-sante-nouvelles-donnees-2021/) The Inserm collective expert review concluded from epidemiological studies, that there is a weak presumption of a link (for definition, see Annex 2 of the Inserm report) between glyphosate exposure and deleterious effects on respiratory health, and in particular with an excess risk of wheezing (allergic or not) and asthma. It was noted, however, that this conclusion is based on the results of a limited number of epidemiological studies, most of which are from the AHS cohort. This conclusion is supported by experimental toxicology studies that show glyphosate has pro-oxidant and mitotoxic effects, two biological mechanisms likely to be involved in pathophysiology of asthma and chronic obstructive pulmonary disease. Although the				

experimental models used involve different species and cellular systems, and do not directly focus on the lung toxicity, the results indicate a potential pro-inflammatory effect in the lung, which also depends on the duration and intensity of exposure.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Inserm EC pesticides 2021_glyphosate_EN_18112021.pdf

Dossier Submitter's Response

According to the DS, based on the publication by Burger et al. (2009), it cannot be concluded that glyphosate should be classified for respiratory tract irritation. Based on the available information in the publication (which is only an abstract of one case) the effects observed cannot be (solely) attributed to glyphosate. Examples of shortcomings are:
- Composition of the formulation: 600 mL of a pesticide containing glyphosate (no details as if other a.i. is present);
- No information on previous health status of the person involved.

In animal studies, in one acute inhalation study, nasal irritation was observed in rats (refer to Vol 1 2.6.3.2; report no ES.877.AIN). However, this study was not considered acceptable due to the too low exposure concentration (0.644 mg/L air) and due the inconsistency of the results compared to the other studies, casting doubt on the validity of this study. In the other acute inhalation toxicity studies (no specific studies for respiratory irritation are available), no pathological findings were reported in the respiratory tract. In the current CLP guidance, it is stated that evaluation, in the absence of validated animal tests, will be based primarily on human data.
In humans, there is no evidence for respiratory tract irritation by the active substance based on the available data.
Overall, there is not sufficient evidence to classify glyphosate for respiratory tract irritation.

RAC's response

Noted. The emidemiological studies mentioned in the Inserm report have been addressed under the hazard class respiratory sensitisation in the draft opinion. RAC is of the opinion that the studies mainly from the AHS cohort showing only a weak correlation between exposure to glyphosate-based herbicide (GBH) and respiratory sensitisation are not sufficient for a classification of glyphosate for respiratory sensitisation. It is further noted that no information on respiratory sensitisation is available on glyphosate as such. In conclusion, RAC agrees with the DS that no classification for respiratory sensitisation is justified.

As for respiratory irritation (STOT SE 3) RAC is of the opinion that a classification is not justified, based on the results from the acute and the repeated dose toxicity studies when compared with the CLP criteria.

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina		Individual	207

Comment received

Page 130 "Conclusion on classification and labelling for STOT-SE": <confidential> agrees with the assessments and conclusions achieved.

Dossier Submitter's Response

Noted.

RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina	Bolsa de Cereales de Buenos Aires	Industry or trade association	208
Comment received				
Bolsa de Cereales de Buenos Aires agrees with the assessments and conclusions achieved. Page 130 "Conclusion on classification and labelling for STOT-SE"				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina	Fundación INAI	National NGO	209
Comment received				
Fundación INAI Agrees with the assessments and conclusions achieved. Page 177 "Conclusion on classification and labelling for STOT-RE"				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	<confidential>	National NGO	210
Comment received				
Page 177 "Conclusion on classification and labelling for STOT-RE": <confidential> agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	ACSOJA	National NGO	211
Comment received				
ACSOJA agrees with the assessments and conclusions achieved in the Page 177 "Conclusion on classification and labelling for STOT-RE" (CLH report)				
Dossier Submitter's Response				
Noted.				

RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Argentina	<confidential>	Industry or trade association	212
Comment received				
<confidential> agrees with Page 177 "Conclusion on classification and labelling for STOT-RE"				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.11.2021	Argentina		Individual	213
Comment received				
Page 177 "Conclusion on classification and labelling for STOT-RE": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina	Cazenave y Asociados SA	Company-Downstream user	214
Comment received				
Page 177 "Conclusion on classification and labelling for STOT-RE": Cazenave y Asociados SA agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina	<confidential>	National NGO	215
Comment received				
Page 177 "Conclusion on classification and labelling for STOT-RE": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				

RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2021	Argentina	<confidential>	International NGO	216
Comment received				
Page 177 "Conclusion on classification and labelling for STOT-RE". <confidential> agrees with the assessments and conclusions achieved				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.10.2021	Germany		Individual	217
Comment received				
According to the latest report of the pesticide authorities from France, The Netherlands, Sweden and Hungary, it is not toxic for organs even with repeated exposure with exposure meaning normal application use with good agricultural practices; contradicting reports were based on exposure rates which are not relevant in case of good agricultural practice for application. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Literatur.7z				
Dossier Submitter's Response				
Noted. The attachments do not provide data within the scope of the scientific assessment in relation to the proposal for classification.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Argentina		Individual	218
Comment received				
Page 177 "Conclusion on classification and labelling for STOT-RE": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.10.2021	Germany		Individual	219
Comment received				
As mentioned from <confidential> in this video, Glyphosate can cause serious damage to oranisms in the second or third generation, due to changing mechanism regarding the				

inter-cellular transport of deuterium (H^3). See video on this page: https://uncutnews.ch/die-beunruhigende-rolle-von-glyphosat-bei-covid-19-neue-erkenntnisse/
Dossier Submitter's Response
The video discusses a hypothesis that glyphosate might replace glycine, which would disrupt processes in the mitochondria which would cause deuterium accumulation leading to chronic diseases. The video then further focusses on a possible relation to Covid-19: it is indicated that if a large amount of glyphosate accumulates in your tissues the immune cells will become compromised making it difficult to eliminate viruses such as Covid-19. DS notes that ADME data indicates no evidence for accumulation of glyphosate; elimination via urine and faeces is rapid and nearly complete within 48 h and after repeated dosing less than 0.5% was present in the tissues after 72h. The video does not contain any information relevant for the scientific assessment in relation to the proposal for classification regarding STOT-RE.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Denmark		MemberState	220
Comment received				
Not reviewed.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
21.10.2021	Germany		Individual	221
Comment received				
nicht organschädigend! Zielorgan-Toxizität				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2021	Argentina	Asociación Argentina de Consorcios Regionales de Experimentación Agrícola (AACREA)	National NGO	222
Comment received				

Page 177 "Conclusion on classification and labelling for STOT-RE": AACREA agrees with the assessments and conclusions achieved.
Dossier Submitter's Response
Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2021	Argentina		Individual	223
Comment received				
Page 177 "Conclusion on classification and labelling for STOT-RE": Ing. Agr. <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	<confidential>	National Authority	224
Comment received				
Page 177 "Conclusion on classification and labelling for STOT-RE": <confidential> agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2021	Argentina	CASAFE	Industry or trade association	225
Comment received				
Page 177 "Conclusion on classification and labelling for STOT-RE": CASAFE agrees with the assessments and conclusions achieved.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	Asociación Argentina de Trigo	National NGO	226
Comment received				
Page 177 "Conclusion on classification and labelling for STOT-RE": Argentrigo agrees with the assessments and conclusions achieved				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON GLYPHOSATE (ISO); *N*-(PHOSPHONOMETHYL)GLYCINE

Dossier Submitter's Response
Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Germany	Glyphosate Renewal Group	Company-Manufacturer	227

Comment received

The applicant is in agreement with the proposal by the RMS (Glyphosate RAR Volume 1, 2.6.3.1.3, "No classification is proposed for glyphosate for STOT-RE"), which is consistent with the conclusion of the ECHA Committee for Risk Assessment (RAC 40, March 2017). A thorough review of the extensive repeat dose toxicity data, including sub-acute, sub-chronic, chronic, developmental, reproductive and neurotoxicity studies assessed at this review cycle and the proposal "STOT-RE classification is not justified" are consistent with previous conclusions at ECHA RAC 40 and by EFSA (List of Endpoints, EFSA Conclusion 2015, EFSA Journal 2015;13(11):4302).
The applicant concurs with the RMS that the mild nature of histopathological changes to the parotid salivary gland in some repeat dose dietary studies in rodents are not considered a significant effect warranting classification. However, the applicant also notes that subsequent to the AIR2 RAR, guidance to the global toxicological pathology community regarding these salivary gland histopathology observations, International Harmonization of Nomenclature and Diagnostic Criteria (INHAND) for Lesions in Rats and Mice (Nolte, 2016, "Supporting document 11"), clearly establishes these effects are adaptive and non-adverse;
"Differential diagnoses
Hypertrophy, acinar cell: Cells in single or multiple acini (foci) enlarged without increased cytoplasmic basophilia.
Comment:… several chemicals such as … glyphosate (NTP, 1992a), … induce basophilic hypertrophic foci in rodents. These foci are considered adaptive hypertrophic lesions".
Furthermore, of more significance to human health risk assessment, in 2021 INHAND guidance was published including the same histopathology finding in salivary glands of non-human primates, "focus, hypertrophic, basophilic". These salivary gland alterations are today considered by the international toxicological pathology community as not applicable in routine toxicological examination (i.e. non-adverse) (Colman et al., 2021, Table 8, "Supporting document 12").
No new maternal toxicity data from developmental toxicity studies in rabbit via gavage are available since the previous ECHA RAC 40 conclusion that "the overall weight of evidence for classification is unconvincing" for STOT-RE classification based on excessive rabbit maternal toxicity. The applicant is in agreement with the seven separate discussion points cited in Vol. 1, section 2.6.3.1.1, pages 175 and 176, which directly quotes page 21 of the RAC 40 opinion in 2017, clearly articulating there is no basis for STOT-RE classification of glyphosate.

In the dRAR prepared by the RMS, in the table 3.1.4 "List of studies to be generated, still ongoing or available but not peer reviewed", point 3.1.4.6, the RMS provided the following request:

"5) Volume 3 CA B.6.3.2.6 and B.6.3.2.13 and Volume 1 sections 2.6.3.1.1, 2.6.8.2 and 2.6.10
Cellular alterations in the parotid gland were also reported in a NTP study in rats and mice (Chan and Mahler, 1992). However, this study was not submitted. The applicant is requested to submit this study with an OECD summary and an evaluation of the results in rats and mice including the mechanistic study on the salivary gland and including effects on toxicity to reproduction."
The applicant is addressing this request by submitting an additional stand-alone

document, "RMS request dRAR 5_113898-004", as well as Chan and Mahler, 1992, "Supporting document 13" in the public and confidential attachment.

Any cited reference can be found as a supporting document in the public and confidential attachments, which will be uploaded separately via the large file upload link due to size ("Glyphosate_Supporting documents_public.zip" and "Glyphosate_Supporting documents_confidential.zip").

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Glyphosate_Supporting documents_public.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Glyphosate_Supporting documents_confidential.zip

Dossier Submitter's Response

The DS notes that the applicant agrees with the proposal that no classification is warranted for STOT-RE (Glyphosate RAR Volume 1, 2.6.3.1.3).
The comment by the applicant that the salivary gland histopathology observations should be considered as adaptive effects and should not be considered as adverse effects is further discussed within the EFSA procedure as it is not relevant for classification and labelling.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Argentina	CIAFA (Chamber of the Argentine Industry of Fertilizers and Agrochemicals)	Industry or trade association	228

Comment received

Page 177 "Conclusion on classification and labelling for STOT-RE": CIAFA (Chamber of the Argentine Industry of Fertilizers and Agrochemicals) agrees with the assessments and conclusions achieved.

Dossier Submitter's Response

Noted.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
18.11.2021	France	Inserm - French National Institute of Health and Medical Research	Academic institution	229

Comment received

This comment refers to RAR § 2.6.7 Summary of neurotoxicity

Conclusion RAR (page 436) :
"Overall, the available information does not indicate a neurotoxic potential for glyphosate"

Comment by the Inserm expert panel :
(see the Inserm report, pages 60-62 ; https://www.inserm.fr/expertise-collective/pesticides-et-sante-nouvelles-donnees-2021/)

Recent academic studies have shown that GBHs as well as glyphosate alone alter the concentrations of several neurotransmitters in various regions of the brain in rodents (Hernandez-Plata et al., 2015; Cattani et al., 2017; Gallegos et al., 2018; Martinez et al, 2018; Yu et al., 2018). This could explain the locomotor deficits and depressive behavior observed in rodents exposed to glyphosate or formulations (Ait Bali et al., 2017 and 2018; Cattani et al., 2017; Gallegos et al., 2018). This deserves to be analyzed and taken into consideration in the RAR. In addition, results using non-standard models such as those in fish also merit consideration (Bridi et al., 2017; Pereira et al., 2018).

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Inserm EC pesticides 2021_glyphosate_EN_18112021.pdf

Dossier Submitter's Response

In the dossier both studies submitted by the applicant as well as studies from public literature were taken into account. All studies were assessed for their relevance and reliability. The studies mentioned were mostly conducted with formulations, therefore, possible effects of co-formulants cannot be excluded.
The studies mentioned in the comment were considered following the literature search. These studies were either considered to be non-relevant for the risk assessment or reliable with restrictions due to methodological limitations (e.g. no HCD provided, no positive control included).

Regarding data from non-standard test systems (e.g. fishes): these data could present an interesting approach, provided that the data are generated according to a recognised and validated scienfitic design. So far there are no scientific robust guidances on this available. It is noted that the study by Pereira (2018) was evaluated in the ecotox section and was considered not relevant due to the fact that the study was conducted using a formulation containing POEA.

The dossier includes OECD-guideline compliant neurotoxicity studies conducted with the active substance glyphosate. These studies did not indicate a neurotoxic potential.

All available information was taken into account into a weight of evidence approach to determine the neurotoxic potential of glyphosate. Based on this assessment, the DS is of the opinion that glyphosate was sufficiently investigated for neurotoxicity in line with the data requirements and that it does not have a neurotoxic potential.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina		Individual	230

Comment received

Page 177 "Conclusion on classification and labelling for STOT-RE": <confidential> agrees with the assessments and conclusions achieved.

Dossier Submitter's Response

Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2021	Argentina	Bolsa de Cereales de Buenos Aires	Industry or trade association	231
Comment received				
Bolsa de Cereales de Buenos Aires agrees with the assessments and conclusions achieved. Page 177 "Conclusion on classification and labelling for STOT-RE"				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
21.10.2021	Germany		Individual	232
Comment received				
nicht bekannt				
Dossier Submitter's Response				
Noted.				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
20.10.2021	Germany		Individual	233
Comment received				
In aquatic environment glyphosate can be more stable than in active healthy soils and it can have negative effects on aquatic fauna. In fact, glyphosate accumulation has been reported in several European water bodies. It is therefore important to exclude glyphosate use in conditions, where it can enter into surface or groundwater bodies. With this glyphosate use should be limited to no-till farming with permanent mulch cover as pre-emergence herbicide. It should not be used on bare soil, on tilled soil, on paved surfaces, in gardening or not agricultural use. It should also not be used as desiccant to accelerate ripening of crops or applied by airplane (drift danger into water bodies). ECHA note – An attachment was submitted with the comment above. Refer to public attachment Literatur.7z				
Dossier Submitter's Response				
The attachments do not provide data within the scope of the scientific assessment in relation to the proposal for classification. No action required.				
RAC's response				
Noted.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON GLYPHOSATE (ISO); *N*-(PHOSPHONOMETHYL)GLYCINE

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Germany	Glyphosate Renewal Group	Company-Manufacturer	234

Comment received

The applicant DOES NOT agree with the chronic classification proposal by the RMS, based on the Brachydanio rerio chronic fish study (study CA 8.2.2.1/002, provided as "Supporting document 14");

Glyphosate_RAR_01_Volume_1_2021-08-10: "The lowest reliable chronic effect concentration is considered to be the 7-day NOEC of 1 mg a.s./L (nominal) for Brachydanio rerio. As the lowest NOEC/EC10 is ≤ 1 mg/L and the substance is considered as non rapidly degradable, glyphosate is classified as Aquatic chronic 2 and should be labelled H411"), and with the conclusion of the ECHA Committee for Risk Assessment (RAC-40, March 2017, "classification as Aquatic chronic 2").

There are multiple deficiencies with the chronic B. rerio study ("Supporting document 14"), which make it invalid for chronic classification purposes. Critical to the classification, deficiencies linked to test design, analytical verifications and the age of fish used, are discussed briefly below.
[The study report – which includes the raw data record from the study, is provided with this response document for full disclosure.]

TEST DESIGN: According to CLP guidance - section point 4.1 (Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, 2017), studies used for chronic classification, should be conducted according to 'validated and internationally recognized test guidelines.' Specifically, under point A9.3.2.5.2 'Chronic testing', of the GHS guidance, it states 'Tests consistent with OECD guideline 210 (fish early life stage), the fish life cycle test (US EPA 850.1500), or equivalent can be used for the classification scheme.' This section also states that observational endpoints can include hatching success, growth (length and weight changes) and spawning success.
This chronic fish study was not conducted according to any particular test guideline, and observations - typically required in chronic fish early life stage tests, such as growth and hatching success were not recorded / reported.
The report of the chronic B. rerio study ("Supporting document 14") states the test design as being 'semi-static' test design with '48 h test media renewal intervals'. The raw data record confirms only a single occasion of test media preparation (at 0 h) supported by the water quality measurements for a single set of test vessels on each day of the test. There are no water quality measurements for a second set of test vessels that would be required for a semi-static test design. Fish transfer to fresh test media cannot also be confirmed from the raw data record. Thus, the study was conducted using a 168 h static test design - without test media renewal.

ANALYTICAL VERIFICATIONS: According to CLP guidance, for chronic exposure studies, measured concentrations of test media at the start and the end of the test (static test design), or at the start and end of test media renewal periods (semi-static test design) - should be available. The guidance states specifically that if measured concentrations are absent, 'no valid interpretation can be made and the test should be considered as invalid for classification purposes.'
In this test, there was no measurement of the concentration in the test media at the start or end of the static exposure period. Concentrated stock solutions only were analysed at

0, 24, 72 and 120 h. No other analytical information is recorded. Adequate exposure of fish to glyphosate for the full 168 h static test duration cannot therefore be confirmed based on the available concentrated stock solution analysis results.

AGE OF THE FISH: The age of fish added to the test are reported as '48 h post fertilization'. The raw data record confirms only that 'larvae' were added. No other 'age / developmental stage' related information is recorded in the raw data record. The age of the fish used in the test, cannot therefore be confirmed. This is important, as B. rerio depend on yolk-sac for nutrition for ca. 160 h post fertilization (at 24 °C) (Straehle et al., 2012, "Supporting document 15"). In the test, yolk-sacs would have been depleted after approximately 110-115 h into the test, with fish held a further 56 hours without food until the end of the test. This 56 h period coincides with reductions in dissolved oxygen levels and increased incidence of lethal and sub-lethal observations in the study. Growth parameters were not recorded at the end of the test, therefore, effects on growth and also fish loading rates (g fish/L water) were not determined.

Therefore, as there were no measured test media concentrations at start or the end of the 168 h exposure period, and that the available chemical analysis of the concentrated stock solutions is not adequate to support exposure for the full 168 h duration of the study, the relevance to the observations recorded from 96 -120 hours onwards cannot be confirmed / concluded on. Overall, as no valid interpretation can be made, the test should be considered invalid for chronic classification purposes.
Based on the above points, the applicant strongly objects to the chronic fish study, conducted with B. rerio (Volume 3, CA 8.2.2.1/002) being considered suitable for chronic hazard classification purposes. Effect values from this study should not be used for hazard classification.
Therefore, glyphosate does not fulfil the criteria to be classified and labelled for chronic aquatic hazards.

Any cited reference can be found as a supporting document in the public and confidential attachments, which will be uploaded separately via the large file upload link due to size ("Glyphosate_Supporting documents_public.zip" and "Glyphosate_Supporting documents_confidential.zip").

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Glyphosate_Supporting documents_public.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Glyphosate_Supporting documents_confidential.zip

Dossier Submitter's Response

In the attachment, two documents are in relation with this comment.
Supporting document 14_sanitized.pdf corresponds to the study report of the chronic Toxicity of to Zebrafish larvae (*Brachydanio rerio*) that has been assessed under Volume 3 CA B.9. Study reference is CA 8.2.2.1/002.
The other one Supporting document 15.pdf is a publication with the following title : Zebrafish embryos as an alternative to animal experiments—A commentary on the definition of the onset of protected life stages in animal welfare regulations. This publication is not related to glyphosate.
Glyphosate Renewal Group made similar comments in the EFSA consultation : 5(184), 5(186), 5(232) and 5(238). Comments 5(170) and 5(176) also concern the same study on Zebrafish larvae (*Brachydanio rerio*). The first one is an agreement with proposal of EC10 and the second one questioned the reliability of the study.
The RMS/dossier submitter already assessed the study and considered the concern expressed by the Glyphosate Renewal Group. The assessment of CA 8.2.2.1/002 study

could be found in Volume 3 CA B.9. Please note that a data gap has been set to the Applicant to provide a statistical reanalysis (NOEC, LC10/20) and information on the extent of lethargy. The outcome of this request may influence the classification proposal. In addition, in the reporting table, Dossier Submitter proposed an expert meeting has been proposed on the chronic endpoint for fish to be considered based on available information (e.g Dias Correa and Tavares (2000), outcome of literature review…).

RAC's response

RAC notes that the study from Dias Correa Tavares, was the Key study for previous chronic classification (RAC Opinion 2017). While not designed for regulatory purposes, it was however conducted in compliance with IBAMA (Environmental Regulations of Brazil) and based on the principle of GLP. RAC also notes that the study can be compared to OECD 212 which in turn can provide useful information on lethal and sublethal effects caused by exposure to chemicals. The OECD 212 has been previously used for classification purposes. In RAC's opinion, the study from Dias Correa Tavares, despite the presence of minor deviations, fulfils all the validity criteria of the OECD 212 and thus can be considered valid and relevant for the purpose of glyphosate classification.

Regarding test design, RAC recognizes that only in a single occasion the authors provide evidence of fresh medium preparation, despite having declared that the test was run under semi-static conditions, with renewals every 48h. However, RAC also notes that the study contains a complete description of the key physicochemical parameters (i.e. conductivity, pH, temperature, dissolved oxygen) in each replicate for all the testing conditions. Since glyphosate is hydrolytically stable and does not undergo photolysis, RAC considers that the choice of a static or semi-static condition is not expected to alter the exposure of the larvae to the substance across the whole testing period. RAC also notes that the analysis of water quality provided in the study was of sufficient quality.

Regarding the analytical verification, RAC recognizes that the results of the study are based on nominal glyphosate concentrations while the analytical measurement of the substance at the end of the testing period is missing. RAC agrees that this is normally an important limitation of an ecotoxicological study which does not allow to confirm the appropriate exposure of the tested organism to the substance. However, RAC also notes that the analytical glyphosate concentration measured in the stock solutions did not show apparent deviations from the nominal concentrations for 6 days. Taking into account that glyphosate is stable in water solutions, RAC deems reasonable to assume that the glyphosate remained in the acceptable range (80%-120% of the nominal concentration) across the whole test duration. As a result, in RAC's opinion it is unlikely that potential fluctuations of glyphosate levels might have led to an overestimation of its ecotoxicological effects.

Regarding the age of fish, RAC notes that the OECD 212 suggests to initiate the exposure as soon as possible after fertilization, ideally from 30 min to 8hpf and that this represents a deviation from the guideline indications. However, RAC also considers that normally zebrafish embryos rely on the yolk sac for the first 7 days post fertilization, while in general starvation and mortality
are observed after 10 days post-fertilization in absence of external feeding (Wilson C, ILAR J. 2012;53(2):169-78). RAC notes that the test was initiated with a certain delay compared to what indicated by the OECD 212 guideline, yet the duration of the test was consistent with what reported in the OECD 212 (7 days versus 8-10 days from the guidance) and no signs of starvation were observed in the control groups at latest time points. Based on these considerations, RAC concludes that fish starvation is not expected to have significantly contributed to the observed effects (lethal and sub lethal).

RAC recognizes that other important parameters such as the survival rate of fertilized eggs or the length of the larvae were missing from the full study report. However, RAC also notes that no mortality was observed in the control group at the end of testing. RAC recognizes that the OECD 212 TG suggests to report the length and weight of the larvae in the experimental groups at the end of the exposure to account for potential effects on individuals that accidentally might have remained smaller. However, in the RAC's opinion this is not a major drawback of the study. In conclusion, RAC considers that all the validity criteria of the OECD 212 were fulfilled and that the study from Dias Correa Tavares 2000, despite the presence of some minor deviations from the TGs, can be considered relevant for the purpose of glyphosate classification.

Date	Country	Organisation	Type of Organisation	Comment number
18.11.2021	Germany	Landwirtschaftskammer Nordrhein Westfalen	Regional or local authority	235
Comment received				
Als Landwirtschaftskammer arbeiten wir in Wasserkooperationen eng mit den regionalen Wasserversorgen zusammen. Die Wasserversorger überprüfen bei der Brauch-/Trinkwasserversorgung die Qualität des Wassers laufend. In Gesprächen mit den Wasserversorgern wird von diesen immer wieder betont, dass Glyphosat zu keiner Zeit ein Problem dargestellt hat. Zum einen lässt es sich nur sehr selten nachweisen. Wenn es messbar ist, dann in der Regel in einem Umfang der unterhalb des zulässigen Grenzwertes liegt. Durch das Verbot von Glyphosat in Wasserschutzgebieten, sind die Landwirte dort gezwungen in Zukunft zur Unkrautbekämpfung wieder vermehrt auf Bodenbearbeitung zu setzen, unter anderem mit dem Pflug. Das hat zur Folge, dass die Mineralisation angeregt wird und vermehrt Nitrat ausgewaschen werden kann. Gerade in Wasserschutzgebieten hat aber der Schutz des Wassers vor Eintrag von Nährstoffen wie Nitrat oberste Priorität. Die neuen Pflanzenschutzanwendungsverordnung (Deutschland) ist vor diesem Hintergrund aus fachlicher Sicht nicht nachvollziehbar.				
Dossier Submitter's Response				
Noted. Not within the scope of the scientific assessment in relation to the proposal for classification.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	United Kingdom	Heath and Safety Executive	National Authority	236
Comment received				
Glyphosate (CAS: 1071-83-6) Chronic fish toxicity We disagree with the use of the Danio rerio 7-day NOEC of 1 mg a.s./L based on lethargy (not assessed statistically) as the key chronic endpoint for the proposed classification on the basis of the following points. Feedback for the OECD TG 203 moribund and mortality considerations highlighted that lethargy is subjective and it is also difficult to demonstrate a causal link between sub-lethal lethargy and future mortality or other population-relevant effects, unless individual test organisms have been marked / tracked with individual level observations. Although				

lethargy was observed at the next test concentration of 3.2 mg a.s./L in the key Danio rerio study, the number of fish exhibiting lethargy in each treatment group was not recorded in the study report and lethargy was not clearly described. As a result a clear concentration-response relationship cannot be determined.

In addition, the study was conducted according to the Brazilian national IBAMA 1990 guideline which although comparable to OECD TG 212, has some important differences. Notably, the IBAMA 1990 Danio rerio study was initiated with freshly hatched fry (48 hours post hatch), whereas OECD TG 212 studies are initiated with freshly fertilised eggs. No feeding is performed in either of these study types. In order to prevent starvation, OECD TG 212 studies are terminated before the yolk sac of any larvae has been completely absorbed. The typical duration of OECD TG 212 studies with Danio rerio is 8-10 days from as soon as possible after fertilisation to 5 days post hatch. Considering the age at initiation, the larvae in the IBAMA 1990 study would be 9 days post hatch at the end of the test. We consider that the test animals were therefore potentially starving by the end of the study which may have contributed to the observed lethargy.

Comparatively, the statistical 7-day NOEC of 3.2 mg a.s./L based on mortality for the Danio rerio study would lead to no Aquatic Chronic classification. A number of other limitations have been discussed in the RAR and CLH report for this study which we believe cannot be discounted. All other chronic fish toxicity endpoints included in the CLH report that are considered reliable are also >1 mg/L.

Overall, we are unclear how relevant and reliable the lethargy endpoint is and note that reliable, relevant endpoints are in the hazard classification range >1-10 mg/L.

Toxicity to aquatic plants

We agree that the available Myriophyllum aquaticum study with glyphosate acid cannot be used for hazard classification because it does not meet the OECD TG 239 validity criteria for control growth. Therefore, there is a data gap for rooted aquatic macrophytes and the active substance. However, we note that a study with the same species using the glyphosate formulation MON-52276 is available in the RAR. This study meets the OECD TG 239 validity criteria for control growth, is GLP compliant and is accepted for the PPP risk assessment. The lowest growth rate endpoints from the study expressed as mg glyphosate acid/L based on mean measured concentrations are within the 0.1 – 1 mg/L range:

- 14-d NOErC = <0.3 mg/L based on shoot fresh weight
- 14-d ErC10 = 0.16 mg/L based on shoot fresh weight
- 14-d ErC20 = 0.66 mg/L based on shoot fresh weight
- 14-d ErC10 = 0.44 mg/L based on shoot dry weight

Given the mode of action of glyphosate as a herbicide, we think this formulation study should be considered further for hazard classification, noting that the above endpoints would lead to a classification as Aquatic Chronic 2. RAC previously agreed the environmental classification of mecoprop-P (ECHA, 2019) based on a Myriophyllum study with a formulation product due to similar reasons, including its mode of action as a herbicide and the sensitivity of the species indicated by the study. Other reasons were the low concentration of co-formulants and the high purity of the technical product. Information on the co-formulants in the glyphosate formulation used in the study above has not been provided in the CLH report / RAR. To enable further consideration of the Myriophyllum formulation study endpoints, please can the CLH DS provide information on

what the other components in the formulation are, what concentrations were used and whether these meet the classification criteria as hazardous to the aquatic environment?

The final reason given by RAC for using the formulation study as the key study for the classification of mecoprop-P was the similar toxicities between the active substance and the formulated product. We note the Lemna gibba 7-day ErC50 of >46.31 mg a.e./L from a study with the glyphosate formulation MON-52276 is higher than the lowest reliable Lemna minor 7-day ErC50 of 30.3 mg a.e./L in the CLH report for the active substance. The 7-day Lemna gibba NOErC of 5.9 mg a.e./L from the same formulation study is within the same concentration range as the Lemna minor 7-day ErC10 of 8.16 mg a.e./L from the study with active substance. Reliable algal data are not available for the formulation according to the RAR, although all other data for fish and aquatic invertebrates indicate that fish and invertebrates are less sensitive to the formulation than the active substance. This information supports the use of the formulation study with Myriophyllum aquaticum for the classification of glyphosate.

Amphibian toxicity

We note that a number of amphibian studies considered to be reliable, or reliable with restrictions are included in Table 2.9.1.6-2 on page 601 and 602 in the terrestrial vertebrates section of the RAR / CLH report. The report states that "all amphibian studies tested the aquatic life stages and should therefore be assessed in relation to the available data on aquatic organisms".

These data include endpoints as sensitive as a NOEC value of 0.0006 mg a.i./L based on survival. Following an evaluation of the data, the PPP RMS considered that "effects on amphibians cannot be excluded even from low glyphosate exposure levels. Hence, the aquatic risk assessment may not be sufficiently protective for amphibians and therefore it is proposed that further consideration is needed". These data do not however appear to have been considered for their suitability in relation to the aquatic hazard classification. Given the sensitivity of the aquatic life-stages of amphibians indicated, please could the CLH DS consider whether these data are relevant to the hazard classification of glyphosate?

Surrogate approach

Depending on the findings for the amphibian data, if the chronic fish NOEC of 1 mg/L based on lethargy and the formulation study with Myriophyllum above are considered not relevant for hazard classification, we note that the surrogate approach with the Crassostrea gigas 48-h LC50 of 40 mg a.e./L would lead to an Aquatic Chronic 3 classification. According to the CLH report, there are no reliable chronic toxicity data for this species, or other oysters.

References

ECHA (2019) Committee for Risk Assessment (RAC) Opinion (including Annexes) proposing harmonised classification and labelling at EU level of mecoprop-P (ISO) [1] and its salts; (R)-2-(4-chloro-2-methylphenoxy)propionic acid [1] and its salts; Reference CLH-O-0000006713-73-01/F; Date: 20/09/2019, Accessed date: 11/2021.

Dossier Submitter's Response

For chronic toxicity to fish, a data gap has been set by RMS for the *Danio rerio* study (Dias 1 Tavares, 2000) in order to obtain a statistical re-analysis of the study, including

LC10 values. The outcome of this request may influence the classification proposal. In addition, in the reporting table, Dossier Submitter proposed an expert meeting has been proposed on the chronic endpoint for fish to be considered based on available information (e.g Dias Correa and Tavares (2000), outcome of literature review…).

For toxicity to aquatic plants, in accordance with CLP regulation, the active substance should be classified with active substance data. Formulation studies should only be used for formulation classification as it also takes into account other components of the formulation. The only exception may be when the formulation contains only the active substance and inert co-formulants (water). Even with information on aquatic hazard for other components, it cannot be determined precisely if the endpoint determined with the formulation expressed as active substance is mainly due to the active substance without a comparison with a study conducted with active substance alone. In addition, RMS agrees that the formulation do not seem to indicate a higher toxicity to fish, aquatic invertebrates and Lemna. Nevertheless, as Myriophyllum could be the more sensitive species based on available formulation data, it cannot be known without an active substance study if the formulation do not indicate a higher toxicity to all taxonomic groups. This is why a data gap has been set and that a study with Myriophyllum with the active substance has to be submitted. This may influence the hazard classification proposal.

For amphibians, RMS agrees to not disregard toxicity data on aquatic phase of amphibians for classification purpose as CLP regulation states that data on other species (e.g. Lemna spp.) shall also be considered if the test methodology is suitable and do not precise to exclude other aquatic species. Nevertheless, the endpoint specified in the comment (NOEC = 0.0006 mg a.i./L) comes from a study with several methodology limitations for classification of the active substance(lack of analytical measurements, formulation study). Therefore, this endpoint is not considered suitable for aquatic hazard classification. No action needed.

RAC's response

For chronic fish toxicity, RAC considers that lethargy is a well recognized alteration of zebrafish behavior caused by chronic distress (Kalueff AV et al.2013,DOI:10.1089/zeb.2012.0861). Lethargy can potentially reduce the fish mating capacity by altering the courtship behavior and impair an effective escape response from predators, leading to enhanced fish mortality. Therefore lethargy is an important biological effect caused by long term exposure to chemical substances and a relevant chronic endpoint for the purpose of classification, providing that it is clearly demonstrated. In this respect, RAC also notes that the study from Dias Correa Tavares 2000 lacks a detailed description of lethargy in terms of morphological or behavioral changes. Moreover, the number of lethargic embryos in the treated groups is not clearly indicated, precluding any possible statistical analysis of this endpoint. In RAC's opinion this is an important limitation of the study. RAC agrees that according to OECD 212 indications the test "should start preferably within 30 minutes after the eggs have been fertilised. As the sensitivity of the test may be seriously influenced by delaying the start of the test, the test should be initiated within 8 hours after fertilisation. As larvae are not fed during the exposure period, the test should be terminated just before the yolk sac of any larvae in any of the test chambers has been completely absorbed or before mortalities by starvation start in controls". RAC also recognizes that embryos at 48h post hatch were used and exposed to glyphosate for additional 7 days and that normally zebrafish embryos rely on the yolk sac for the first 7 days post fertilization, requiring external feeding after its reabsorption. However, RAC considers that the duration of the test was consistent with the indications of the OECD 212 (7 days in comparison to the 8-10 days suggested by the TG) and no signs of starvation were observed in the control

groups. Taking into account that delayed or absent exogenous feeding normally results in starvation and decreased survival rates at around 10 days post-fertilization (Wilson C, ILAR J. 2012;53(2):169-78), in the view of RAC the potential contribute of starvation to the observed lethargy/mortality is expected to be negligible.
RAC notes that the statistical analysis provided by the authors derived a LOEC of 5.2 mg/L, that would lead to a NOEC of 3.2 mg/L, based on mortality, leading to no chronic classification of glyphosate according to CLP regulation. RAC also notes that the exposure to 3.2 mg/L of glyphosate resulted in 10% mortality after 7d, revealing that the effects of glyphosate followed a clear dose-response relationship. However, RAC considers that the derivation of a NOEC = 1 mg/L is not supported by the statistical analysis provided by the authors, despite it is reasonable to assume that a real NOEC value from a chronic toxicity study would be lower than 3.2 mg/L. For this reason, RAC considers that the study would require a statistical reassessment of the data set and the derivation of novel NOEC and ECx values, in addition to a more detailed description of the lethargy endpoint, in line also with the DS observations.

Regarding the toxicity to aquatic plants, RAC agrees with DS and MS that glyphosate formulation MON 52276 do not seem to indicate a higher toxicity to fish, aquatic invertebrates and Lemna. Moreover, as Myriophyllum could be the more sensitive species, a comparative study with active substance alone should be conducted. Although valid studies on Myriophyllum with glyphosate are missing from the RAR, other literature data seem to support the results obtained with the formulation. Based on the reliability of these studies, data on glyphosate formulation MON 52276 could be used for classification purposes.

RAC agrees to take amphibian studies into account for aquatic classification in case the tests are suitable eg. aquatic exposure, relevant endpoints and the effects can be related to glyphosate. RAC agrees with the DS to consider the test mentioned in the comment not suitable for classification of glyphosate.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Denmark		Individual	237
Comment received				
This accounts for the decreases in catches of trout and salmon in the rivers where farmers allow Roundup to leach into the rivers. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Five books about the toxicity of Monsanto.docx				
Dossier Submitter's Response				
The comment and document do not provide information that could be used for hazard classification purpose in accordance with Regulation 1272/2008. No action.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Denmark		MemberState	238
Comment received				
Not reviewed.				

Dossier Submitter's Response
Noted No action.
RAC's response
Noted No action.

Date	Country	Organisation	Type of Organisation	Comment number
18.11.2021	Germany		MemberState	239
Comment received				
Thank you for the comprehensive evaluation. We disagree with the classification as Aquatic chronic 2. Based on the available studies it is also in our view reasonable to use the 7-d study with Brachydanio rerio for classification purposes. When correctly evaluated (according to OECD 54) the NOEC derived from the study is 1 mg/L based on a Cochran-Armitage test for trend (R package RSCABS, version: 0.9.3). The 3.7 mg/L treatment is highly significant compared to the control (p = 0.007). However, according to the Guidance on the Application of the CLP Criteria (p. 490), the EC10 should be preferred over the NOEC. A reliable EC10 can be clearly derived from the study and is 4.6 mg /L (Confidence intervals: 2.45 – 6.75 mg/L; based on a 2-parameter log-normal model, R drc package, version: 3.0.1). Therefore, the EC10 should be used as relevant endpoint for classification. The EC10 is also in line with the ELS study, showing no adverse effects at concentrations up to 2.804 mg/L, whereas at 9.63 mg/L adverse effects cannot be excluded due to uncertainty caused by the limited number of replicates and an unfortunate choice of test concentrations preventing the derivation of effect concentrations. In our view the classification as Aquatic chronic 2 should not be applied just because there is a missing statistical evaluation of the study with Brachydanio rerio, which can be easily conducted. The labelling for environmental hazards should be dropped.				
Dossier Submitter's Response				
Please also refer to answer to comment 234. A data gap has been set to the Applicant to provide a statistical reanalysis (NOEC, LC10/20) and information on the extent of lethargy regarding the 7-d study with *Brachydanio rerio*. The outcome of this request may influence the classification proposal. In addition, in the reporting table, Dossier Submitter proposed an expert meeting has been proposed on the chronic endpoint for fish to be considered based on available information (e.g Dias Correa and Tavares (2000), outcome of literature review…).				
RAC's response				
As previously reported, RAC also agrees that a statistical reanalysis of the data set might be necessary to substantiate the NOEC value. RAC also notes that according to OECD 212 TGs a number of different statistical methods can be used, including ANOVA or contingency tables to estimate LOEC/NOEC while fitting the data to logistic curves by using least squares or non-linear least squares is indicated in case LC/ECx needs to be determined. RAC notes that the authors performed a statistical analysis of the data by using the Fisher's exact test with a confidence limit (upper and lower) of 95% and a significance level set to 0.05. In RAC's opinion the Fisher's exact test is appropriate to estimate the statistical significance of a two-by-two contingency table, yet in case when one or both of the row or column totals are unconditioned, the Fisher's exact test is				

conservative and less powerful than other alternatives. Nevertheless, in line with DS observations, RAC recognizes that the derivation of EC10 or a novel NOEC value might change the classification proposal of glyphosate, in case the current study will still be retained as the key study.

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2021	Germany	Bund für Umwelt und Naturschutz Deutschland e.V.	National NGO	240
Comment received				
Glyphosate reaches aquatic systems, too. According to the assessment report (page 570/571 - Summary of surface water monitoring data), the number of detections above LOQ (respectively ~40% and ~64% samples EU-wide for Glyphosate and AMPA) tends to indicate that the active substance and its main metabolite is widely and regularly found in surface water. Aquatic organisms are thus exposed to them. The following literature showing negative effects on a range of aquatic organisms should be taken into account: - Bonansea et al. 2017, The Fate of Glyphosate and AMPA in a Freshwater Endorheic Basin: An Ecotoxicological Risk Assessment. Toxics https://www.mdpi.com/2305-6304/6/1/3 . - Tresnakova et al. 2021, Effects of glyphosate and their metabolite AMPA on aquatic organisms. Appl Sci, https://www.mdpi.com/2076-3417/11/19/9004 Also marine organisms can be negatively affected: - Matozzo et al. (2020) The Effects of Glyphosate and Its Commercial Formulations to Marine Invertebrates: A Review. J Mar Sci Eng 8:399; https://www.mdpi.com/2077-1312/8/6/399 ECHA note – An attachment was submitted with the comment above. Refer to public attachment FoE Background on Glyphosate.pdf				
Dossier Submitter's Response				
Same attachment as PCSF-176241 submitted to EFSA. The study of Bonansea et al. 2017 was already included in the dRAR in the environmental fate section (Vol 3 CA B.8) (year was 2018 in the dRAR but same title/study). The studies of Tresnakova et al. 2021 and Matozzo et al. (2020) were not part of the literature review from the dRAR. They should be submitted by the applicant (both study summary, full-text document and proposed analysis). A data requirement has been proposed in answer to comment 5(3) in the EFSA reporting table 19 on comments from public. These studies may be considered for classification purpose depending on their relevance and reliability assessment that will be done during the peer-review process.				
RAC's response				
RAC agrees with the DS. The cited studies will be considered for classification purpose depending on relevance and reliability assessment.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Ozone Layer

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Denmark		MemberState	241
Comment received				
Not reviewed.				
Dossier Submitter's Response				
Noted.				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Germany	Glyphosate Renewal Group	Company-Manufacturer	242
Comment received				
The applicant is in agreement with the proposal by the RMS (Glyphosate_RAR_01_Volume_1_2021-08-10, "based on the available data presented under 2.8.3, there is no evidence that glyphosate may present a danger to the structure and/or the functioning of the stratospheric ozone layer."). Any cited reference can be found as a supporting document in the public and confidential attachments, which will be uploaded separately via the large file upload link due to size ("Glyphosate_Supporting documents_public.zip" and "Glyphosate_Supporting documents_confidential.zip"). ECHA note – An attachment was submitted with the comment above. Refer to public attachment Glyphosate_Supporting documents_public.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Glyphosate_Supporting documents_confidential.zip				
Dossier Submitter's Response				
Noted. The supporting documents are not within the scope of the scientific assessment in relation to the "Hazardous to the ozone layer"section.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
21.10.2021	Germany		Individual	243
Comment received				
Wichtig bleibt die Zulassung um eine CO2-Reduktion weiterhin mit Minimalbodenbearbeitung (jede Bearbeitung des Bodens führt zu Freisetzung von CO2, Nährstoffverlagerung ,,Nitrat-Auswaschung, etc.´`) durchführen zu können.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.10.2021	Germany		Individual	244
Comment received				
Not relevant. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Literatur.7z				
Dossier Submitter's Response				
Noted. The attachments do not provide data within the scope of the scientific assessment in relation to the proposal for classification.				

RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2021	Denmark		MemberState	245
Comment received				
Not reviewed.				
Dossier Submitter's Response				
Noted				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2021	Germany	Glyphosate Renewal Group	Company-Manufacturer	246
Comment received				
2.2.1.1.1 Explosives [equivalent to section 8.1 of the CLH report template] The applicant is in agreement with the proposal done by the RMS in Glyphosate_RAR_01_Volume_1_2021-08-10, page 58. 2.2.1.1.2 Flammable gases (including chemically unstable gases) [equivalent to section 8.2 of the CLH report template The applicant is in agreement with the proposal done by the RMS in Glyphosate_RAR_01_Volume_1_2021-08-10, page 58. 2.2.1.1.3 Oxidising gases [equivalent to section 8.3 of the CLH report template] The applicant is in agreement with the proposal done by the RMS in Glyphosate_RAR_01_Volume_1_2021-08-10, page 59. 2.2.1.1.4 Gases under pressure [equivalent to section 8.4 of the CLH report template] The applicant is in agreement with the proposal done by the RMS in Glyphosate_RAR_01_Volume_1_2021-08-10, page 59. 2.2.1.1.5 Flammable liquids [equivalent to section 8.5 of the CLH report template] The applicant is in agreement with the proposal done by the RMS in Glyphosate_RAR_01_Volume_1_2021-08-10, page 59. 2.2.1.1.6 Flammable solids [equivalent to section 8.6 of the CLH report template] The applicant is in agreement with the proposal done by the RMS in Glyphosate_RAR_01_Volume_1_2021-08-10, page 60. 2.2.1.1.7 Self-reactive substances [equivalent to section 8.7 of the CLH report template] The applicant is in agreement with the proposal done by the RMS in Glyphosate_RAR_01_Volume_1_2021-08-10, page 60. 2.2.1.1.8 Pyrophoric liquids [equivalent to section 8.8 of the CLH report template] The applicant is in agreement with the proposal done by the RMS in Glyphosate_RAR_01_Volume_1_2021-08-10, page 60.				

2.2.1.1.9 Pyrophoric solids [equivalent to section 8.9 of the CLH report template]
The applicant is in agreement with the proposal done by the RMS in Glyphosate_RAR_01_Volume_1_2021-08-10, page 61.

2.2.1.1.10 Self-heating substances [equivalent to section 8.10 of the CLH report template]
The applicant is in agreement with the proposal done by the RMS in Glyphosate_RAR_01_Volume_1_2021-08-10, page 61.

2.2.1.1.11 Substances which in contact with water emit flammable gases [equivalent to section 8.11 of the CLH report template]
The applicant is in agreement with the proposal done by the RMS in Glyphosate_RAR_01_Volume_1_2021-08-10, page 61.

2.2.1.1.12 Oxidising liquids [equivalent to section 8.12 of the CLH report template]
The applicant is in agreement with the proposal done by the RMS in Glyphosate_RAR_01_Volume_1_2021-08-10, page 62.

2.2.1.1.13 Oxidising solids [equivalent to section 8.13 of the CLH report template]
In subsection 2.2.1.1.13.3 RMS commented that
„The negative A.17 result is not sufficient to conclude the substance is not oxidizing. The chemical structure contains oxygen atoms which are not bonded only to carbon or hydrogen". The conclusion is: „Not classified as oxidising due to lack of data".
Furthermore RMS stated „Glyphosate does not fulfil the criteria in 2.14.4.1 (b) and should have been tested according to UN O.1 method".
In the same document (RAR vol. 01) point 2.2.1 Summary of physical and chemical properties of the active substance it is however given:
Glyphosate acid is not an oxidising substance. Result can be extrapolated to CLP regulation
Important: in Volume 3 – B.2 (AS), point B.2.13 the study performed in accordance with EEC A.17 by Wollerton & Husband (1997) was accepted. RMS commented „Acceptable. The result can be extrapolated to the CLP regulation".
There are discrepancies between information provided in Vol.1 / CLH report. The applicant kindly asks for the acceptance of summary given in point 2.2.1 of RAR vol. 1.

2.2.1.1.14 Organic peroxides [equivalent to section 8.14 of the CLH report template]
The applicant is in agreement with the proposal done by the RMS in Glyphosate_RAR_01_Volume_1_2021-08-10, page 62.

2.2.1.1.15 Corrosive to metals [equivalent to section 8.15 of the CLH report template]
The applicant is in agreement with the proposal done by the RMS in Glyphosate_RAR_01_Volume_1_2021-08-10, page 63.

Any cited reference can be found as a supporting document in the public and confidential attachments, which will be uploaded separately via the large file upload link due to size ("Glyphosate_Supporting documents_public.zip" and "Glyphosate_Supporting documents_confidential.zip").

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Glyphosate_Supporting documents_public.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Glyphosate_Supporting documents_confidential.zip

Dossier Submitter's Response
Agree. For oxidising property, based on test results the active substance is not classified oxidising.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
18.11.2021	Germany		MemberState	247
Comment received				
Self-reactive substances It is stated that glyphosate acid does not contain chemical groups associated with self-reactive properties according to table A6.3 of the UN RTDG Appendix 6. However, as glyphosate contains a P-O group the criteria in 2.8.4.2 (a) are not fulfilled. This should be corrected. Consequence for table 80 on p. 793 would be "data lacking".				
Dossier Submitter's Response				
Agree. The glyphosate contains a P-O group. However, the P-O group is a phosphonate functional group (Phosphorus in a P^{5+} oxidation state) and not phosphite group (phosphorus in a P^{3+} oxidation state) which is known to be of a limited thermal stability. Therefore, the conclusion "not classified as self-reactive" is still valid.				
RAC's response				
RAC agrees with the DS response.				

Date	Country	Organisation	Type of Organisation	Comment number
21.10.2021	Germany		Individual	248
Comment received				
nicht organschädigend, nicht gefährlich von Hormonhaushalt!				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.10.2021	Germany		Individual	249
Comment received				
Not relevant ECHA note – An attachment was submitted with the comment above. Refer to public attachment Literatur.7z				
Dossier Submitter's Response				
Noted. The attachments do not provide data within the scope of the scientific assessment in relation to the proposal for classification.				
RAC's response				
Noted.				

PUBLIC ATTACHMENTS
1. <confidential>_HEAL_Glyphosate_carcinogenicity_ATTACHMENT.pdf [Please refer to comment No. 25]
2. Comments of Générations Futures on the litterature search and genotoxicity endpoint.pdf [Please refer to comment No. 8, 57]
3. ATTACHMENT_.pdf [Please refer to comment No. 27]
4. Five books about the toxicity of Monsanto.docx [Please refer to comment No. 157, 237]
5. EFFAT Position Paper - Ending the use of glyphosate and building a more sustainable agriculture EN.pdf [Please refer to comment No. 11, 30]
6. Comments.zip [Please refer to comment No. 12, 31]
7. Glyphosate_Supporting documents_public.zip [Please refer to comment No. 17, 37, 66, 102, 123, 143, 164, 184, 204, 227, 234, 242, 246]
8. Inserm EC pesticides 2021_glyphosate_EN_18112021.pdf [Please refer to comment No. 18, 39, 68, 104, 206, 229]
9. FoE Background on Glyphosate.pdf [Please refer to comment No. 4, 48, 75, 240]
10. Literatur.7z [Please refer to comment No. 14, 53, 81, 95, 115, 135, 155, 176, 196, 217, 233, 244, 249]

CONFIDENTIAL ATTACHMENTS
1. HEAL_Public consultation Glyphosate ECHA.zip [Please refer to comment No. 6, 24, 56, 90]
2. sumofus-archive.zip [Please refer to comment No. 59]
3. Glyphosate_Supporting documents_confidential.zip [Please refer to comment No. 17, 37, 66, 102, 123, 143, 164, 184, 204, 227, 234, 242, 246]