EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Food Safety, Sustainability, and Innovation
Pesticides and Biocides

Annex

ASSESSMENT OF THE GROUNDS FOR THE REQUEST FOR INTERNAL REVIEW OF COMMISSION IMPLEMENTING REGULATION (EU) 2023/2660 OF 28 NOVEMBER 2023 RENEWING THE APPROVAL OF THE ACTIVE SUBSTANCE GLYPHOSATE

I. INTRODUCTION

1. On 24 January 2024, the Commission received a request for internal review (the 'IRR') from Pesticide Action Network Europe, ClientEarth, Générations futures, GLOBAL 2000, Pesticide Action Network Germany, Pesticide Action Network Netherlands (the 'Requestors'), for the internal review of Commission Implementing Regulation (EU) 2023/2660 of 28 November 2023 renewing the approval of the active substance glyphosate ([1]) (the 'Reviewed Regulation').
2. The Requestors put forward several grounds for the review of the Reviewed Regulation. This assessment will first describe the facts and procedure (Section II), and subsequently address the grounds for review (Section III), following the order in the IRR.
3. This assessment also draws on the technical and scientific input provided by the European Food Safety Authority ('EFSA') and the European Chemicals Agency ('ECHA') at the request of the Commission to respond to the points in the IRR directly related to their scientific assessments ([2]).

II. FACTS AND PROCEDURE

1. THE PROCEDURE FOR THE RENEWAL OF THE GLYPHOSATE APPROVAL

4. Glyphosate is an active substance contained in plant protection products ('PPPs') used as herbicides in agriculture, horticulture and other areas, e.g. for the removal of weeds from railway tracks or other infrastructures. On 20 November 2001, glyphosate was approved as an active substance and included, by Commission Directive 2001/99/EC ([3]), in Annex I to Council Directive 91/414/EEC ([4]). Upon the entry into force of Regulation (EC) 1107/2009

([1]) Commission Implementing Regulation (EU) 2023/2660 of 28 November 2023 renewing the approval of the active substance glyphosate in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council and amending Commission Implementing Regulation (EU) No 540/2011, OJ L, 2023/2660, 29.11.2023.
([2]) Available at: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2024.EN-8737.
([3]) Commission Directive 2001/99/EC of 20 November 2001 amending Annex I to Council Directive 91/414/EEC concerning the placing of plant protection products on the market to include glyphosate and thifensulfuron-methyl as active substances, OJ L 304, 21.11.2001, p. 14.
([4]) Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market. OJ L 230, 19.8.1991, p. 1.

(the 'PPP Regulation') ([5]), glyphosate was deemed to have been approved under that Regulation pursuant to its Article 78(3) and was consequently listed in Part A of the Annex to Commission Implementing Regulation (EU) No 540/2011 ([6]) with expiry date on 30 June 2012.

5. The approval of glyphosate was extended several times in order to complete the first renewal process. Commission Directive 2010/77/EU ([7]) extended, for the first time, the approval to 31 December 2015. Commission Implementing Regulation (EU) 2015/1885 ([8]) extended the approval to 30 June 2016. Subsequently, Commission Implementing Regulation (EU) 2016/1056 ([9]) extended the approval to "*6 months from the date of receipt of the opinion of the Committee for Risk Assessment of the European Chemicals Agency by the Commission or 31 December 2017, whichever is earlier*," due to the time required to assess the dossier concerning the harmonised classification of glyphosate's carcinogenicity before deciding on a renewal of approval.

6. The approval was amended on 1 August 2016 by Commission Implementing Regulation (EU) 2016/1313 ([10]), which revised the conditions of use, particularly excluding the co-formulant polyethoxylated tallowamine ('POE-tallowamine') from PPPs containing glyphosate due to concerns over its toxicity and impact on human health.

7. In December 2017, the approval of glyphosate was renewed for a period of five years by Commission Implementing Regulation (EU) 2016/1313 ([11]), and it was consequently listed in Part B of the Annex to Implementing Regulation (EU) No 540/2011 with an expiry date of 15 December 2022.

8. In May 2019, in light of the experience with the extraordinarily voluminous amount of data and other information dealt with during the risk assessment of the renewal procedure that ran from 2012 to 2017, the Commission attributed the role of the rapporteur Member State

([5]) Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC, OJ L 309, 24.11.2009, p. 1 ('PPP Regulation').

([6]) Commission Implementing Regulation (EU) No 540/2011 of 25 May 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the list of approved active substances, OJ L 153, 11.6.2011, p. 1.

([7]) Commission Directive 2010/77/EU of 10 November 2010 amending Council Directive 91/414/EEC as regards the expiry dates for inclusion in Annex I of certain active substances, OJ L 293, 11.11.2010, p. 48.

([8]) Commission Implementing Regulation (EU) 2015/1885 of 20 October 2015 amending Implementing Regulation (EU) No 540/2011 as regards the extension of the approval periods of the active substances 2,4-D, acibenzolar-s-methyl, amitrole, bentazone, cyhalofop butyl, diquat, esfenvalerate, famoxadone, flumioxazine, DPX KE 459 (flupyrsulfuron-methyl), glyphosate, iprovalicarb, isoproturon, lambda-cyhalothrin, metalaxyl-M, metsulfuron methyl, picolinafen, prosulfuron, pymetrozine, pyraflufen-ethyl, thiabendazole, thifensulfuron-methyl and triasulfuron, OJ L 276, 21.10.2015, p. 48.

([9]) Commission Implementing Regulation (EU) 2016/1056 of 29 June 2016 amending Implementing Regulation (EU) No 540/2011 as regards the extension of the approval period of the active substance glyphosate, OJ L 173, 30.6.2016, p. 52.

([10]) Commission Implementing Regulation (EU) 2016/1313 of 1 August 2016 amending Implementation Regulation (EU) No 540/2011 as regards the conditions of approval of the active substance glyphosate, OJ L 208, 2.8.2016, p. 1.

([11]) Commission Implementing Regulation (EU) 2017/2324 of 12 December 2017 renewing the approval of the active substance glyphosate in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending the Annex to Commission Implementing Regulation (EU) No 540/2011, OJ L 333, 15.12.2017, p. 10.

for any upcoming renewal procedure concerning the approval of glyphosate to several Member States acting jointly ([12]): the 'Assessment Group on Glyphosate' or 'AGG' ([13]).

9. In December 2019, a consortium of companies (the 'Glyphosate Renewal Group' or 'GRG') ([14]) submitted a joint application for the renewal of the approval of glyphosate to the AGG. The admissibility check of the application, carried out by the AGG, found that it was not complete and the AGG requested the GRG to submit a completed application by 23 January 2020. On 30 January 2020, following receipt of the updated application, the AGG declared the application complete ([15]).

10. On 8 June 2020, the GRG submitted the supplementary dossiers, thereby meeting the requirement of Article 6(3) of Commission Implementing Regulation (EU) No 844/2012 ([16]) to submit these dossiers at least 30 months before the approval's expiry date of 15 December 2022 ([17]).

11. On 10 July 2020, following an admissibility check of the supplementary dossiers, the AGG informed the GRG that the submitted supplementary dossiers were inadmissible and requested the GRG to provide the missing elements by 24 July 2020. On 23 July 2020, the GRG submitted revised supplementary dossiers. On 18 August 2020, the AGG informed the GRG, the Commission and the European Food Safety Authority ('EFSA') that the application, including the supplementary dossiers, was admissible ([18]).

([12]) Commission Implementing Regulation (EU) 2019/724 of 10 May 2019 amending Implementing Regulation (EU) No 686/2012 as regards the nomination of rapporteur Member States and co-rapporteur Member States for the active substances glyphosate, lambda-cyhalothrin, imazamox and pendimethalin and amending Commission Implementing Regulation (EU) No 844/2012 as regards the possibility that a group of Member States assumes jointly the role of the rapporteur Member State (OJ L 124, 13.5.2019, p. 32).

([13]) France, Hungary, the Netherlands and Sweden.

([14]) Current members: Albaugh Europe SARL, Barclay Chemicals Manufacturing Ltd., Bayer Agriculture bvba, Ciech Sarzyna S.A., Industrias Afrasa S.A., Nufarm GMBH & Co.KG, Sinon Corporation and Syngenta Crop Protection AG.

([15]) Each member of the AGG confirmed the application of the application separately
https://food.ec.europa.eu/document/download/9eb04b89-855e-404f-9cdd-6648111290d1_en?filename=pesticides_renew_glyphosate_letter-to-grg_se_outcome.pdf
https://food.ec.europa.eu/document/download/558f5e73-15d5-474d-a623-247ec2396aab_en?filename=pesticides_renew_glyphosate_letter-to-grg_nl_outcome.pdf
https://food.ec.europa.eu/document/download/77f5bb43-4d20-4a3e-9be3-b68fb097cbb2_en?filename=pesticides_renew_glyphosate_letter-to-grg_hu_outcome.pdf
https://food.ec.europa.eu/document/download/47806f22-3e0f-4edf-b8af-cd82f853fd07_en?filename=pesticides_renew_glyphosate_letter-to-grg_fr_outcome.pdf

([16]) Commission Implementing Regulation (EU) No 844/2012 of 18 September 2012 setting out the provisions necessary for the implementation of the renewal procedure for active substances, as provided for in Regulation (EC) No 1107/2009, OJ L 252, 19.9.2012, p. 26–32. This Regulation applies to the procedure for the renewal of approval of glyphosate despite its repeal by Commission Implementing Regulation (EU) No 2020/1740 in accordance with Article 17 of that Regulation.

([17]) Following the amendment of Commission Implementing Regulation (EU) No 844/2012 by Commission Implementing Regulation (EU) 2020/103 of 17 January 2020 amending Implementing Regulation (EU) No 844/2012 as regards the harmonized classification of active substances (OJ L 19, 24.1.2020, p.1), which applies to the renewal of approvals set to expire on or after 13 May 2023 (unless the supplementary dossier has been submitted before), this time frame has been changed into 33 months. At the time when the application for a renewal of the glyphosate approval was submitted, its expiry date was 15 December 2022. Therefore, the original version of Article 6 (3) of Commission Implementing Regulation (EU) No 844/2012, which provides for the submission of the supplementary dossiers at least 30 months before the expiry date, applies in the present case.

([18]) https://food.ec.europa.eu/document/download/bf05c0bc-312c-43e1-85f4-90b700d1346b_en?filename=pesticides_renew_glyphosate_supp-doss_202008_anses.pdf

12. The AGG assessed the information submitted by the GRG and prepared a draft Renewal Assessment Report ('RAR') which it submitted to EFSA on 15 June 2021.

13. At the same time, on 15 June 2021, the AGG submitted a proposal for harmonised classification and labelling (the 'CLH dossier') of glyphosate under Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures ([19]) ('CLP Regulation') to the European Chemicals Agency ('ECHA').

14. On 23 September 2021, EFSA and ECHA launched public consultations on the draft RAR and the CLH dossier, which ended on 22 November 2021. EFSA also invited all Member States and the GRG to provide comments on the draft RAR simultaneously by the same deadline. The AGG invited the GRG to react to the comments received after the public consultation ended. EFSA also established a dedicated Working Group on Glyphosate Renewal ([20]) composed of experts from EFSA as well as independent experts appointed by EFSA. The EFSA Working Group took up its work on 14 October 2021 ([21]).

15. On 28 February 2022, the AGG informed EFSA and the Commission that more time was needed to provide an updated draft RAR, given the number of comments received during the public consultation as well as from Member States and EFSA experts (which included new information to be analysed and/or assessed) and the amount of additional information that EFSA, based on its analysis of the comments and the reactions from the GRG and after consultation with the AGG, intended to request from the GRG.

16. On 14 March 2022, EFSA requested additional information from the GRG to be delivered within one month.

17. On 10 May 2022, EFSA and ECHA announced that, due to the expected delay in the delivery of the updated draft RAR by the AGG, and in order to complete the process established by Article 13(1) of Implementing Regulation (EU) No 844/2012, which involves organising a consultation of experts (part of the Peer Review process[22], there would be a delay in delivering the EFSA Conclusion [pursuant to Article 13 of Implementing Regulation (EU) No 844/2012] following the Peer Review. They estimated that the Conclusion would become available only in July 2023.

https://food.ec.europa.eu/document/download/43b449a3-b39c-41ea-83a3-b43c7759f6eb_en?filename=pesticides_renew_glyphosate_supp-doss_202008_nebih.pdf
https://food.ec.europa.eu/document/download/3f1c1ec5-259d-48e3-be8d-4078e1093a1d_en?filename=pesticides_renew_glyphosate_supp-doss_202008_ctgb.pdf
https://food.ec.europa.eu/document/download/6e4eb3ac-ef81-4ccf-a8a7-25f288d1971f_en?filename=pesticides_renew_glyphosate_supp-doss_202008_kemi.pdf

([19]) Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, OJ L 353, 31.12.2008, p. 1.

([20]) Members and Declarations of Interest can be found here: https://open.efsa.europa.eu/working-group/300000017681253

([21]) Minutes from the meetings of the Working Group were published by EFSA: https://www.efsa.europa.eu/sites/default/files/2021-11/wg-minutes-glyphosate-peer-review-renewal-assessment.pdf

([22]) The Peer Review process includes the scrutiny of the draft RAR during the public consultation period, where experts from Member States and EFSA review and provide comments on the assessment performed by the RMS, as well as the following discussions by experts from EFSA and Member States.

18. On 30 May 2022, ECHA's Committee for Risk Assessment ('RAC') adopted its Opinion ([23]) by consensus ('RAC Opinion 2022'), as previously done on 15 March 2017 ([24]) on the harmonised classification of glyphosate 'as causing serious eye damage and being toxic to aquatic life' ('RAC Opinion 2017'). Based on a wide-ranging review of the available scientific evidence, the RAC concluded ([25]), as in 2017, that it was not justified to classify glyphosate as either carcinogenic, or as mutagenic or as toxic to reproduction ([26]).

19. On 22 September 2022, following its assessment of the comments and the additional information gathered through consultations of the public and the Member States, and of the additional data submitted by the GRG on request of EFSA, the AGG submitted the updated RAR to EFSA.

20. As part of the Peer Review, EFSA scheduled expert meetings to discuss the assessment carried out by the AGG which were held between 14 November and 2 December 2022 in the areas of mammalian toxicology, residues, environmental fate and behaviour and ecotoxicology.

21. On 2 December 2022, the Commission adopted on the basis of Article 17 of the PPP Regulation, Implementing Regulation (EU) 2022/2364 ([27]), which postponed the expiry of the approval of glyphosate until 15 December 2023 in light of the delay announced by EFSA for the delivery of the EFSA Conclusion.

22. On 6 July 2023, EFSA communicated to the Commission, the Member States and to the GRG its conclusion ('the EFSA Conclusion') on whether the active substance glyphosate can be expected to meet the approval criteria provided for in Article 4 of the PPP Regulation ([28]).

23. On 13 July 2023, the Commission presented its draft renewal report on glyphosate and a draft Implementing Regulation renewing the approval of glyphosate to the Standing Committee on Plants, Animals, Food and Feed ('PAFF Committee') for discussion. Revised versions of both documents were presented at the next meeting of the PAFF Committee on 22 September 2023.

24. On 26 July 2023, EFSA published the EFSA Conclusion ([29]).

25. On 13 October 2023, the PAFF Committee discussed, and Member States voted on the draft Implementing Regulation renewing the approval of glyphosate subject to conditions put forward by the Commission, but it did not deliver an opinion. Therefore, the Commission submitted the draft Implementing Regulation to the Appeal Committee (as foreseen in Article 5 (4) of Regulation (EU) No 182/2011).

([23]) European Chemicals Agency (2022). Opinion of the Committee for Risk Assessment proposing harmonised classification and labelling of glyphosate (ISO); N-(phosphonomethyl)glycine (EC Number: 213-997-4; CAS Number: 1071-83-6).

([24]) European Chemicals Agency (ECHA) (2017). Opinion of the Committee for Risk Assessment proposing harmonised classification and labelling of glyphosate (ISO); N-(phosphonomethyl)glycine (EC Number: 213-997-4; CAS Number: 1071-83-6).

([25]) https://echa.europa.eu/-/glyphosate-no-change-proposed-to-hazard-classification.

([26]) See the summary table on page 3 of the RAC Opinion, as well as the individual sections on germ cell mutagenicity, carcinogenicity and reproductive toxicity.

([27]) Commission Implementing Regulation (EU) 2022/2364 of 2 December 2022 amending Implementing Regulation (EU) No 540/2011 as regards the extension of the approval period of the active substance glyphosate OJ L 312, 5.12.2022, p. 99.

([28]) European Food Safety Authority (EFSA), (2023). Peer review of the pesticide risk assessment of the active substance glyphosate (EFSA Journal, 21(7), 1-52, https://doi.org/10.2903/j.efsa.2023.8164).

([29]) https://www.efsa.europa.eu/en/efsajournal/pub/8164.

26. On 16 November 2023, the Appeal Committee discussed and Member States voted on the draft Implementing Regulation renewing the approval of glyphosate subject to conditions put forward by the Commission, but it did not deliver an opinion.

27. On 28 November 2023, the Commission adopted the Reviewed Regulation, which renews the approval of glyphosate until 15 December 2033 subject to conditions and restrictions, as set out in sub-section 3 below.

2. MAIN FINDINGS OF THE SCIENTIFIC RISK ASSESSMENT ON GLYPHOSATE AS AN ACTIVE SUBSTANCE USED IN PPPS

28. Article 4(1) of the PPP Regulation requires, inter alia, active substances to be approved "*in the light of current scientific and technical knowledge*". This is the scientific evidence basis for decisions on the approval of active substances (or the renewal thereof) which primarily results from the risk assessment procedures provided for by the PPP Regulation and its implementing measures.

29. It therefore appears useful to consider the main findings of the risk assessment, which has been carried out in the procedure for the renewal of approval of glyphosate between 2019 and 2023, before addressing the merits of the Requestor's grounds for review. The entirety of the findings from that risk assessment are found in a number of documents, in particular in the RAR prepared by the AGG and updated during the Peer Review ([30]), the EFSA Conclusion of 6 July 2023 as well as its background documents, including the Peer Review Report which includes, amongst others, the reports from expert meetings ([31]).

30. As a general remark, it is important to underline that, given the significant body of evidence available on glyphosate, a weight of evidence ('WoE') approach ([32]) was employed in assessing the toxicological impacts and effects of glyphosate, as recommended by EFSA's Scientific Committee ([33]). This approach integrates all relevant data, weighing the reliability, relevance, and consistency of findings across different studies. Under this approach, higher relevance is given to studies performed on mammalian species and those conducted according to internationally recognised protocols. This prioritisation, as set out in the relevant guidance of the EFSA Scientific Committee ([34]), is based on the higher relevance of such studies to human health risk assessment.

31. Although the EFSA Conclusion notes several issues that could not be finalised and identifies some missing information (or 'data gaps') ([35]), it is important to note that, throughout this risk assessment, no critical area of concern was identified ([36]).

32. The following parts of the outcome of the risk assessment seem particularly important for the assessment of the grounds for review's merits further below.

([30]) Final version of the RAR published by EFSA: https://open.efsa.europa.eu/study-inventory/EFSA-Q-2020-00140

([31]) https://open.efsa.europa.eu/study-inventory/EFSA-Q-2020-00140.

([32]) Weight of Evidence ('WoE') is an approach in which all of the evidence considered relevant for a risk assessment is evaluated and weighted and taken into account accordingly in the assessment. For example, it may be that one particular study shows a certain effect but that several others do not. In such a case it is not scientifically correct to only rely on the single study showing an effect.

([33]) EFSA Scientific Committee, Hardy A, Benford D, Halldorsson T, Jeger MJ, Knutsen HK, More S, Naegeli H, Noteborn H, Ockleford C, Ricci A, Rychen G, Schlatter JR, Silano V, Solecki R, Turck D, Benfenati E, Chaudhry QM, Craig P, Frampton G, Greiner M, Hart A, Hogstrand C, Lambre C, Luttik R, Makowski D, Siani A, Wahlstroem H, Aguilera J, Dorne J-L, Fernandez Dumont A, Hempen M, Valtuena Martınez S, Martino L, Smeraldi C, Terron A, Georgiadis N and Younes M, 2017.Scientific Opinion on the guidance on the use of the weight of evidence approach in scientific assessments.

([34]) idem.

([35]) See Sections 9 and 10 of the EFSA Conclusion.

([36]) See Section 9.2 of the EFSA Conclusion: "Critical areas of concern were not identified."

a) Genotoxicity (cfr. Article 4, point 3.6.2 of Annex II, of the PPP Regulation)

33. Genotoxicity or 'genotoxic potential' refers to the potential of a substance to damage the genetic material of cells. Such damage may lead to adverse outcomes such as cancer or other diseases. Genotoxicity is a broad term that includes mutagenicity (i.e. substances that can cause permanent and heritable changes to the DNA of organisms).

34. Article 4(1) of the PPP Regulation requires, *inter alia*, that the specific approval criteria in Annex II, points 2 and 3, to the PPP Regulation are met. Point 3.6.2 of Annex II specifies that an active substance must not be approved if it is, or has to be, classified as mutagen category 1A or 1B under the CLP Regulation.

35. Glyphosate has never been classified as mutagenic in accordance with the CLP Regulation (or its predecessor, Directive 67/548/EEC ([37])).

36. With regards to mutagenicity, ECHA, in its RAC Opinion 2022, concluded that *"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 warranted*" ([38]). This conclusion reached by RAC is congruent with its earlier RAC Opinion 2017.

37. Moreover, a full assessment of the potential for genotoxicity was also undertaken by EFSA as part of the risk assessment of glyphosate. Even where, as stated with regard to glyphosate in paragraph 34, an active substance is not, and does not have to be, classified as mutagenic category 1A or 1B (or category 2), any risks related to its genotoxicity are also relevant under the approval criterion, laid down in Article 4(3)(b) of the PPP Regulation, that PPPs (or their residues, cfr. Article 4(2) of the PPP Regulation) must not have any harmful effects on human health. The risk assessment for glyphosate in respect of potential genotoxicity was based on an extensive body of evidence of over 70 studies, including those adhering to internationally recognised protocols as well as scientific literature. A specific sub-group of the Working Group on Glyphosate Renewal was also set up by EFSA to look at specific aspects of the genotoxicity assessment ([39]) and in addition experts from EFSA and Member States discussed the assessment during the expert meetings arranged by EFSA as part of the Peer Review. Experts from Member States and EFSA concluded that *"Glyphosate is unlikely to be genotoxic or mutagenic based on a weight of evidence approach. The formulation for the representative uses is unlikely to be genotoxic or mutagenic based on a weight of evidence approach"* ([40]).

b) *Carcinogenicity (cfr. Article 4, and point 3.6.3 of Annex II of the PPP Regulation)*

38. Carcinogenicity refers to the potential of a substance to cause cancer. The assessment of carcinogenicity is a fundamental element of the safety assessment for human health carried out for active substances.

39. Article 4(1) of the PPP Regulation requires, *inter alia*, that the specific approval criteria in Annex II, points 2 and 3, to the PPP Regulation are met. Point 3.6.3 of Annex II to the PPP

([37]) Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances OJ 196, 16/08/1967, p. 1.

([38]) See page 48 of the RAC Opinion: https://echa.europa.eu/documents/10162/5702e99d-d503-f154-226f-d8ab070ac47a.

([39]) The Working Group was asked to perform a preliminary assessment on DNA damage by the Comet assay as well as other genotoxicity studies including mode of action studies. See Annex 3 to Part 3 of 6 Annexes to Peer Review Meeting Report TC 80 'of the Peer Review Report.

([40]) See Experts' consultation 2.1 identified following comments by public, as discussed at Pesticide Peer Review TC 80 (14 – 25 November 2022) as found in Peer Review Report on Glyphosate (AIR V) Part 3 of 6. See also page 11 of the EFSA Conclusion.

Regulation specifies that an active substance must not be approved if it is, or has to be, classified as a carcinogen in categories 1A or 1B under the CLP Regulation, unless human exposure under realistic conditions of use is considered negligible.

40. Glyphosate has never been classified as carcinogenic in accordance with the CLP Regulation (or its predecessor, Directive 67/548/EEC).

41. Both the RAC Opinions of 2017 and 2022 conclude that glyphosate does not warrant classification as carcinogenic. It is noted that, in the context of the latest renewal procedure for glyphosate leading to the RAC Opinion 2022, RAC carried out an assessment based on the CLH dossier submitted by Sweden, which took into account an even greater amount of information than previously available.

42. Moreover, a full assessment of the potential for carcinogenicity was also undertaken by EFSA as part of the risk assessment of glyphosate, even though it is not classified as carcinogen category 1A or 1B, since any risks related to its carcinogenicity could result in not meeting the approval criterion, laid down in Article 4(3)(b) of the PPP Regulation, that PPPs (or their residues, cfr. Article 4(2) of the PPP Regulation) must not have any harmful effects on human health. The risk assessment carried out for the renewal of the glyphosate approval under the PPP Regulation concluded in this respect that it is not carcinogenic: neither EFSA nor any Member States identified any indication that glyphosate would be carcinogenic in the Peer Review carried out as part of the risk assessment. The EFSA Conclusion states in this respect: "*Based on all the available evidence, it was agreed that glyphosate is not carcinogenic in rats up to the highest dose level tested of 1,214 mg/kg bw per day in males and 1,498 mg/kg bw per day in females. In the mouse studies, no carcinogenic effects were seen up to 988 mg/kg bw per day in males and 1,081 mg/kg bw per day in females. The currently available human epidemiological studies do not provide conclusive evidence that glyphosate exposure is associated with any cancer-related health effect* ([41])".

43. The conclusion, reached by both ECHA and EFSA, that glyphosate as an active substance used in PPPs is not carcinogenic is in line with the scientific assessments of glyphosate that have been carried out under the remit of regulatory agencies worldwide ([42]). Solely the International Agency for Research on Cancer (IARC) concluded in 2015 that glyphosate should be classified as "*probably carcinogenic to humans*" ([43]). The scientific assessment carried out by IARC was also assessed in the CLH dossier and was taken into account by RAC as part of the scientific assessment underpinning both of its RAC Opinions delivered in 2017 and in 2022 respectively.

c) Reproductive toxicity (cfr. Article 4, point 3.6.4 of Annex II of the PPP Regulation)

44. Reproductive toxicity refers to adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring. These effects can include alterations in reproductive organs, endocrine functions, pregnancy outcomes, and developmental impairments in the foetus or young.

45. Article 4(1) of the PPP Regulation requires, *inter alia*, that the specific approval criteria in Annex II, points 2 and 3, to the PPP Regulation are met. Point 3.6.4 of Annex II to the PPP Regulation specifies that an active substance must not be approved if it is, or has to be,

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([41]) See page 11 of the EFSA Conclusion: Peer review of the pesticide risk assessment of the active substance glyphosate, doi: 10.2903/j.efsa.2023.8164.

([42]) Including regulatory authorities in the US, Canada, Australia, New Zealand and Japan as well as the FAO-WHO Joint Meeting on Pesticide Residues (JMPR).

([43]) See page 398 of the IARC monographs on the evaluation of carcinogenic risks to humans; volume 112 https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Some-Organophosphate-Insecticides-And-Herbicides-2017.

classified as toxic for reproduction category 1A or 1B under the CLP Regulation unless human exposure under realistic conditions of use is considered negligible.

46. Glyphosate has never been classified as toxic for reproduction under the CLP Regulation (or its predecessor, Directive 67/548/EEC).

47. Both the RAC Opinions 2017 and 2022 conclude that glyphosate does not warrant classification for adverse effects on reproduction or development. Moreover, a full assessment of the possible impacts of glyphosate on reproduction and development was also undertaken as part of the risk assessment of glyphosate by the AGG and EFSA, even though it is not classified as toxic for reproduction, since any risks could result in not meeting the approval criterion, laid down in Article 4(3)(b) of the PPP Regulation, that PPPs (or their residues, cfr. Article 4(2) of the PPP Regulation) must not have any harmful effects on human health. That assessment did not lead to the identification of any risks to human health from reproductive toxicity ([44]).

d) Endocrine disrupting properties (cfr. Article 4, points 3.6.5 and 3.8.2 of Annex II of the PPP Regulation)

48. Endocrine active substances are substances that can interact or interfere with normal hormonal action. When this leads to adverse effects, they are called endocrine disruptors ('ED').

49. Article 4(1) of the PPP Regulation requires, inter alia, that the specific approval criteria in Annex II, points 2 and 3, to the PPP Regulation are met. Point 3.6.5 of Annex II to the PPP Regulation specifies that an active substance must not be approved if it is considered to have endocrine disrupting properties that may cause adverse effects in humans, unless human exposure under realistic conditions of use is considered negligible. In addition, point 3.8.2 of Annex II to the PPP Regulation stipulates that an active substance must not be approved if it is considered to have endocrine disrupting properties that may cause adverse effects in non-target organisms, unless exposure of non-target organisms under realistic conditions of use is considered negligible.

50. According to these provisions, an active substance is considered as having endocrine disrupting properties if it meets three cumulative criteria: an adverse effect in an intact organism or its progeny; an endocrine mode of action; and the adverse effect is a consequence of the endocrine mode of action (cfr. points 3.6.5 and 3.8.2. of Annex II to the PPP Regulation).

51. EFSA, supported by the EFSA Working Group on Endocrine Disruptors (EFSA ED WG), conducted an assessment in line with the relevant ECHA/EFSA guidance ([45]) (as required by Article 4(1), read in conjunction with points 3.6.5. and 3.8.2 of Annex II to the PPP Regulation) ([46]).

52. EFSA found that, for humans, the complete dataset provided in the supplementary dossiers showed no adverse effects on the thyroid, or any issues related to estrogen, androgen, and steroidogenesis pathways. Consequently, based on this finding that there is no endocrine

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([44]) See EFSA Conclusion, sections 2 and 3. See also Table 7 where no risks are identified for operators, workers, bystanders or residents, or consumers.

([45]) https://doi.org/10.2903/j.efsa.2018.5311.

([46]) See Section 2.10 of Volume 1 of the RAR –including the separate Volume 1 containing the ED assessment for humans. See Renewal Assessment Report (final): https://open.efsa.europa.eu/study-inventory/EFSA-Q-2020-00140.

adverse effect, glyphosate does not meet the criteria for being considered an endocrine disruptor according to point 3.6.5 of Annex II to the PPP Regulation ([47]).

53. For non-target species, such as mammals, fish, birds, amphibians, reptiles, and various invertebrates, EFSA found that the overall WoE did neither show any convincing pattern of adversity nor of endocrine activity ([48]). Therefore, EFSA concluded that glyphosate neither meets the endocrine disruption criteria for non-target organisms ([49]).

e) Environmental effects of using PPPs containing glyphosate as regards biodiversity

54. Article 4(1) of the PPP Regulation establishes that active substances must be approved if it can be expected, based on the identification of at least one representative use of one product (Article 4(5) of the PPP Regulation) that PPPs containing that active substance meet the requirements laid down in Article 4(2) and 4(3) of that Regulation. This includes the requirement, according to Article 4(3)(e) of the PPP Regulation, that PPPs containing a given active substance can be expected not to have any unacceptable effects on the environment. Subject to the availability of scientific methods accepted by EFSA to assess such effects on the environment, the assessment of an active substance's effects on the environment includes a consideration of the impact which the use of PPPs containing a specific active substance may have on biodiversity and the ecosystem (cfr. Article 4(3)(e)(iii) of the PPP Regulation).

55. The risk assessment for glyphosate carried out in the renewal procedure under the PPP Regulation by the AGG, EFSA and Member State experts did not identify any risks to biodiversity from direct exposure to glyphosate ([50]) - apart from a risk to wild small herbivorous mammals at the first tier ([51]) of the risk assessment for certain representative uses ([52]).

56. Overall, the experts involved in the Peer Review recognised that the risks associated with the representative uses of glyphosate for biodiversity are complex and depend on multiple factors ([53]).

The risk assessment also did not identify substantive indirect risks or impacts on biodiversity from the representative uses of PPPs containing glyphosate ([54]). However, as stated in the EFSA Conclusion ([55]), there are currently no agreed harmonised methodologies for carrying out assessments of indirect effects via trophic interactions and that the assessment of such potential impacts, which are multifactorial, is extremely complex ([56]). Therefore, EFSA

([47]) See page 26 of the EFSA Conclusion: "*For humans, with regard to the T-modality, the data set was considered complete and a pattern of T-mediated adversity was not identified. With regard to the EAS-modalities, the dataset was also considered complete and a pattern of EAS-mediated adversity was not observed*".

([48]) See page 27 of the EFSA Conclusion: "*The overall WoE did not show any convincing pattern of EATS-mediated adversity and/or endocrine activity*".

([49]) See page 27 of the EFSA Conclusion: "*Overall, based on the available evidence and assessment, glyphosate does not meet the criteria for the EATS-modalities as laid down in point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605*".

([50]) See Section 5 of the EFSA Conclusion.

([51]) i.e. a risk assessment using conservative assumptions and default values rather than information on actual and realistic field exposure.

([52]) For further details see Table 7 in the EFSA Conclusion which summarises the findings of the risk assessment.

([53]) See EFSA Conclusion, page 25.

([54]) See pages 25-26 of the EFSA Conclusion.

([55]) See page 24 of the EFSA Conclusion: "In general, the current lack of a harmonised approach to assess biodiversity within the prospective risk assessment was recognised by the experts."

([56]) See EFSA Conclusion, page 25.

could not fully exclude potential impacts risks ([57]), but notes that "*risk mitigation measures for the off-field (e.g. the use of the proposed 75% drift reduction nozzles) as well as the implementation of a MFFM ([58]) could be beneficial*" ([59]).

3. THE REVIEWED REGULATION

57. The Reviewed Regulation was published in the Official Journal of the European Union on 29 November 2023, entered into force 3 days following its publication and became applicable from 16 December 2023.

58. The Reviewed Regulation renews the approval of glyphosate, subject to a number of conditions and restrictions, until 15 December 2033.

59. Some of the conditions and restrictions already imposed in the approval of glyphosate prior to the adoption of the Reviewed Regulation have been maintained, namely:

i. glyphosate can only be authorised for use as an herbicide;

ii. a minimum purity of glyphosate of 950 g/kg;

iii. the setting of maximum limits for two toxicologically relevant impurities (formaldehyde and *N*-nitroso-glyphosate) – as part of the renewal this provision was strengthened by setting maximum limits for 3 additional toxicologically relevant impurities (see below);

iv. the obligation for Member States to pay particular attention to certain issues (protection of groundwater, protection of operators and amateur users, the risk terrestrial vertebrates and non-target terrestrial plants and the risk to diversity and abundance of non-target terrestrial arthropods and vertebrates via trophic interactions) when carrying out assessments for authorisation of PPPs – as part of the renewal this provision was strengthened (see below);

v. conditions of use shall include risk mitigation measures, where appropriate – as part of the renewal this provision was strengthened (see below);

vi. compliance of pre-harvest uses with good agricultural practices – as part of the renewal this provision was strengthened (see below);

vii. the use of glyphosate should be minimised or banned in sensitive locations such as public parks, gardens, sports and recreation grounds, school grounds, children's playgrounds, and near healthcare facilities to reduce exposure risks.

60. Other conditions and restrictions imposed in the renewal of approval of glyphosate have been introduced with the Reviewed Regulation, in particular:

i) maximum limits for 5 impurities considered toxicologically relevant (as opposed to 2 in the previous renewal). This means that these impurities are recognised as having potential harmful effects on human and animal health or the environment, and their presence must be kept below specified safe levels;

([57]) See pages 25-26 of the EFSA Conclusion: "*Overall, on the basis of the information provided, the experts agreed that a conclusion cannot be reached to exclude possible negative impacts on non-target species, habitats and ecosystems due to indirect effects via trophic interactions for all the representative uses of glyphosate, including uses where less than 50% of the surface is treated (i.e. band and spot applications) and railway uses*".

([58]) MFFM – multi-functional field margin.

([59]) See page 26 of the EFSA Conclusion.

ii) Member States must pay particular attention to several additional aspects of the risk assessment when evaluating applications for the authorisation of PPPs containing glyphosate, namely:

- **Assessment of co-formulants**: all co-formulants in PPPs containing glyphosate must be evaluated to ensure they are safe for humans and the environment. When doing so Member States must take into account in particular the criteria for identification of unacceptable co-formulants as set out in Commission Implementing Regulation (EU) 2023/574 ([60]);
- **Consumer exposure assessment:** where relevant for the use being assessed, Member States must consider the consumer exposure from residues that may be present in crops grown in fields where glyphosate was used in the preceding growing season;
- **Protection of water sources**: As well as the need to ensure protection of groundwater, Member States must ensure also that surface waters, especially those used for drinking water, are protected from contamination. Special consideration shall be given to uses of glyphosate on sealed surfaces, which might increase runoff;
- **Maximum application doses**: to protect wild mammals, maximum allowable doses of glyphosate are established. Applicants for authorisation must provide additional data proving safety if they seek to use higher doses;
- **Protection of non-target terrestrial and aquatic plants:** Member States must consider exposure of non-target plants to spray drift;
- **Indirect impacts on biodiversity:** Member States must consider indirect effects on biodiversity via trophic interactions once relevant methods and guidance to identify such effects are agreed at EU level. In the absence of such methods and guidance, Member States may apply methods which they consider appropriate to determine the potential indirect effects of PPPs containing glyphosate and which take into account their specific agro-environmental conditions. When doing so, if they identify any such possible indirect effects on biodiversity, Member States shall set specific conditions or restrictions of use for PPPs containing glyphosate, considering in particular if practical alternative control or prevention methods with lower impacts on biodiversity are available;

iii) Member States must pay attention to the compliance of pre-harvest uses with the provisions of Directive 2009/128/EC in conjunction with Article 55 of the PPP Regulation. The authorisation of glyphosate-containing products for desiccation, which is the use of glyphosate to dry out crops before harvest to control the timing or optimise threshing, may not be authorised;

iv) The conditions of use established in the authorisation for any PPP containing glyphosate (cfr. Article 31 of the PPP Regulation) must include risk mitigation measures, including combinations thereof, as required. In particular, drift has to be reduced for spray applications made by professional users in agricultural fields. Certain default mitigation measures must be applied unless the outcome of the risk assessment undertaken for the specific use indicates that such risk mitigation measures are not needed or can be lowered because there are no unacceptable risks caused by spray drift;

([60]) Commission Implementing Regulation (EU) 2023/574 of 13 March 2023 setting out detailed rules for the identification of unacceptable co-formulants in plant protection products in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council, OJ L 75, 14.03.2023, p. 7.

v) the GRG must provide confirmatory information on the possible indirect effects on biodiversity via trophic interactions, within 3 years from the date when relevant guidance is agreed at EU level. If this information is not provided or its assessment leads to the conclusion that there are unacceptable impacts on biodiversity via trophic interaction, the approval will be withdrawn in accordance with Article 21 of the PPP Regulation.

vi) Member States may set additional monitoring requirements when granting authorisations for PPPs containing glyphosate. This is to complement existing monitoring under Directives 2000/60/EC ([61]) and 2009/128/EC ([62]) of the European Parliament and of the Council ensuring comprehensive oversight of glyphosate's environmental impact.

III. RESPONSE TO THE GROUNDS FOR REVIEW

61. The Requestors base their request for internal review on several grounds, contesting:

first, the methodology and outcome of the risk assessment, concerning more specifically:

1) the toxicity assessment of the representative formulation;

2) the genotoxicity of glyphosate;

3) the carcinogenicity of glyphosate;

4) the effect of glyphosate on the microbiome;

5) the neurotoxicity and reproductive toxicity of glyphosate;

6) the endocrine disrupting properties of glyphosate;

7) the toxicity of glyphosate to animals (including ecotoxicity);

8) the effect of glyphosate on biodiversity;

9) exposure to glyphosate via inhalation; and

10) a systematic failure to take independent scientific literature into account; and

second, the appreciation of the outcome of the risk assessment by the Commission as risk manager.

These grounds will be examined in Sections III.1, and III.2 respectively, below.

III.1 ALLEGED DEFICIENCIES AT THE RISK ASSESSMENT STAGE

1. Alleged illegalities and manifest errors in the toxicity assessment of the product for representative uses "MON 52276" (paragraphs 10 to 30 of the IRR)

62. As its first ground for review, the Requestors claim that the AGG and EFSA would not have assessed the long-term toxicity and carcinogenicity of the product for representative uses "MON 52276", which contains glyphosate and various co-formulants, and thereby infringed the obligations in Article 4(1), (2), and (3) of the PPP Regulation. The Requestors criticise, in particular, that, despite numerous literature studies pointing to the chronic toxicity of the product, the GRG has not submitted any long-term toxicity or carcinogenicity studies and

([61]) Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy, OJ L 327, 22.12.2000, p. 1.

([62]) Directive 2009/128/EC of the European Parliament and of the Council of 21 October 2009 establishing a framework for Community action to achieve the sustainable use of pesticides, OJ L 309, 24.11.2009, p. 71.

that neither the AGG nor EFSA have demanded such studies. They also criticise that no toxicological information is available for one of the co-formulants, only limited information for another, and no ecotoxicological information for any of them. Lastly, they claim that no evaluation of the ecotoxicity of the product in relation to amphibians, birds and mammals would have been carried out.

1.a Absence of assessment of long-term toxicity and carcinogenicity despite serious indications from independent literature (paragraphs 14 and 17 to 21 of the IRR)

63. Contrary to the claim put forward by the Requestors that no assessment of the long-term toxicity and carcinogenicity of the product for representative uses MON 52276 took place, the product for representative uses MON 52276 did undergo thorough examination, encompassing an assessment of data on MON 52276 itself and its components, first by the AGG and then by EFSA together with Member States during the Peer Review. This assessment examined all possible effects, both short and long term. This is evidenced by the EFSA Conclusion ([63]) and background documents ([64]).

64. Contrary to the Requestors' assertions about data reliability and validity of tests, the procedures followed by EFSA and ECHA ensured that all relevant studies, including those by independent researchers and academics, were evaluated and considered in the assessment, as further demonstrated below The EFSA Conclusion is not only based on guideline regulatory studies submitted by the applicant, but also includes a review of all relevant scientific literature, which is documented and referenced ([65]). In this context, the WoE as explained in Section II.2 above was key, in particular as for glyphosate a very extensive body of evidence exists.

65. In paragraph 14 of the IRR, the Requestors claim that the conclusion of the absence of chronic toxicity in the product for representative uses was allegedly reached "*solely on the basis of three in vivo ([66]) tests affected by methodological errors and too targeted to reverse the positive results provided by independent literature*".

66. However, the claim that the three in vivo studies are too specific to counter results from studies from the literature is not substantiated nor based on any scientific evidence. On the contrary, those genotoxicity studies were carried out on the actual product for representative use MON 52276 and therefore are completely relevant for the assessment of that product.

67. In paragraphs 17 and 18 of the IRR, the Requestors refer to four studies allegedly proving the long-term toxicity of the product for representative uses. However, as clearly

([63]) See EFSA Conclusion, Section 2, page 14.

([64]) Such as the public version of the Peer Review Report on Glyphosate (AIR V) Part 3 of 6 - Pages 275-296/672.

([65]) See various Volumes of the RAR, available in the Peer Review Report in the Open EFSA under 'Supporting documents' under EFSA Question number EFSA-Q-2020-00140: https://open.efsa.europa.eu/study-inventory/EFSA-Q-2020-00140 (refer to Glyphosate_Final RAR_public.zip)

([66]) The reference made by the Requestors to three *in vivo* studies was likely intended as a reference to *in vitro* studies concerning genotoxicity on the formulation.

documented in the RAR ([67])each study referred to by the Requestors was assessed in the renewal process but considered as either supplementary, supportive or unreliable ([68]).

68. In particular, with regard to the fourth study referred to (Ren et al. 2018), the Requestors claim that the study would have been dismissed due to the composition of the PPP tested being unknown. However, this is not the main reason. As indicated in the final RAR ([69]) "*the study is considered unacceptable (less relevant/unreliable) due to different reasons: the study was not conducted according to any international guideline, no GLP status, the test substances are not sufficiently characterised, unknown dose of exposure following administration via drinking water, small group size (n=5), exposure during GD1-19 without justification for this window of exposure, only one dose tested, individual data missing, no historical control data or positive control.*". Additionally, in Volume 1 of the RAR ([70]), it becomes even more evident why the AGG deemed the study unreliable, namely particularly due to the uncertainty surrounding the presence in the tested PPP of POE tallowamine, a substance banned for use in PPPs in the EU.

69. Moreover, at the end of paragraph 18 of the IRR, the Requestors' claim that the competent authorities should have sought clarifications on the composition from the study authors. However, detailed information on the full composition would not have resolved the other deficiencies identified for the studies. In addition, the AGG and EFSA are not entitled to

([67]) For Mesnage et al. see "RAR_01_Volume_1_2023-04-21_public", page 240: "*the study is considered to provide no information that will directly impact the risk assessment of glyphosate*.". The study is a review paper describing the chemical identification and toxicity profile of some co-formulants (notably including co-formulants currently not allowed for use in plant protection products in the EU, namely polyethoxylated tallowamine surfactants), and their replacements. No original data are presented and therefore this publication does not provide any specific information on glyphosate or MON 52276. For Manservisi et al., see "RAR_01_Volume_1_2023-04-21_public", see pages 483, 502, 514, 569 and 573. For Q. Mao et al., the study was considered by the EFSA WG on glyphosate and the outcome is reported in Annex 9 of the Pesticides Peer Review Expert meeting report TC 80 on mammalian toxicology (published in the 'Peer Review Report' under Open EFSA, Supporting documents section of EFSA Q -2020-00140, refer to Part 3, Peer Review Report_Glyphosate_expert meeting report Annexes_TC80, Annex 9, electronic pages 213-214). Overall, the study was considered not to add relevant elements to the risk assessment of glyphosate. This study is also referred to in Volume 1 of the RAR (cf Table 2.6.8.2-3: Summary table of other studies on microbiome which are not considered further, electronic page 636 of 1405), with the study summary and the AGG assessment given in RAR Vol 3 CA B6.8.2 (electronic pages 143-149 of 439) – published in the Final RAR under Open EFSA, Supporting documents section of EFSA Q -2020-00140, (refer to 'Renewal Assessment Report (final)' – Vol 14c). For Ren et al. 2018, see "RAR_01_Volume_1_2023-04-21_public", page 673.

([68]) For an explanation of the terms used to categorise literature studies see pages 84-85 of Volume 1 of the RAR - "Table 2.0.5.2-3. Clarifications on the terminology and how toxicology studies are used in the revised RAR".

([69]) See page 16 of the RAR: "RAR_14c_Volume_3CA_B.6.8.2_toxicology and metabolism_2023_02_14_public".

([70]) See "RAR_01_2023-04-21_public", page 673: "*Summary provided, details can be found under RAR Vol. 3 B.6.8.2.17 Glyphosate purity not reported. Only one dose level for glyphosate was tested (0.5% solution added to drinking water), it is unclear what actual dose was administered per day. The number of animals used per dose level was too low (5 animals) and only one dose level was considered with no justification for the selection. Insufficient information is given on the biochemical methods used. Glyphosate not sufficiently characterised (purity). Daily dose administered through drinking water not calculated/provided. This publication is considered unreliable. The exact composition of the Roundup formulation tested is not stated in the paper (a.i. content, source, surfactant system / co-formulants). It is therefore not possible to confirm whether the product used is the representative glyphosate formulation MON 52276 relevant for the glyphosate EU renewal. Furthermore, in the absence of a concurrent control for each to the component of the formulation, it is not possible to conclude whether the observed effects claimed to be secondary to exposure to glyphosate are due to glyphosate exposure or of one of the other components. The uncertainty associated with whether the product contains polyethoxylated tallow amine (also polyoxyethyleneamine, POEA) or not, suggests that the findings in this paper should be treated with high level of caution.*".

request clarifications from any authors of scientific studies. And those authors are under no obligation to provide information, nor can this information be verified.

70. In paragraph 19 of the IRR, the Requestors state that a study carried out by the Ramazzini Institute (known as the 'Global Glyphosate Study') would demonstrate that MON 52276 was carcinogenic.

71. The Commission, along with EFSA and ECHA, is aware of the public announcement by the Ramazzini Institute concerning a study carried out on glyphosate and products containing it ([71]). However, the full study results have still not yet been disclosed, nor have they undergone Peer Review or been published in any scientific journal. The Commission asked EFSA and ECHA to write to the Ramazzini Institute to request the data on which its studies were based, for evaluation by the agencies. Despite repeated requests, the Ramazzini Institute has not submitted the requested information.

72. As explained in Section II.2.b above, the assessments carried out by EFSA and ECHA concluded that glyphosate should not be classified as carcinogenic and therefore a mere announcement from the Ramazzini Institute without making available of the full study results and data for scrutiny cannot invalidate the rigorous assessment that took into account a very large body of evidence, including animal studies and epidemiological data. However, should ECHA or EFSA confirm, based on data from the Ramazzini Institute, if and when this is made available, that glyphosate no longer meets the approval criteria, the Commission may review the approval in accordance with Article 21 of the PPP Regulation.

73. In paragraph 20 of the IRR, the Requestors argue that the tests conducted on MON 52276 by the applicant for toxicity other than acute toxicity are not sensitive and limited to certain aspects of genotoxicity and therefore cannot negate the results of the published scientific literature.

74. However, the three studies provided ([72]) cover the three endpoints for genotoxicity (namely, gene mutation, clastogenicity and aneugenicity) and according to the Scientific Committee of EFSA ([73]), an Ames test and in vitro micronucleus test are sufficient to examine genotoxicity (if negative then no concern is raised), as these two tests fulfil the basic requirement to cover the three genetic endpoints with the minimum number of tests. Contrary to the claim, in paragraph 14 of the IRR, that the tests were affected by methodological errors, the AGG and EFSA found two out of the three tests fully reliable and one reliable with restrictions (as correctly stated in paragraph 20 of the IRR), which did not impact the validity of the study. Therefore, the studies on the MON 52276 were fully adequate to assess genotoxicity. Furthermore, negative genotoxicity tests are relevant in the assessment of long-term toxicity, since genotoxicity is implicated in long-term degenerative diseases ([74]).

75. The Commission also notes that the argument raised by the Requestors that the results of these studies could not negate the findings in published scientific literature studies appears rather selective: on the one hand, they claim that applicants must submit tests on the product for representative uses, but when the appropriate tests are submitted on the product for representative uses, ruling out genotoxicity, they claim based on literature on other PPP

([71]) https://glyphosatestudy.org/press-release/global-glyphosate-study-reveals-glyphosate-based-herbicides-cause-leukemia-in-early-life/

([72]) MON 52276: Bacterial Reverse Mutation Assay, 2016 (OECD 471), MON 52276: Micronucleus Test in Human Lymphocytes in vitro, 2020 (OECD 487) and In Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL), 2016 (OECD 471)

([73]) Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment, page 2 https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2011.2379.

([74]) See Section 2.1 of the Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment.

formulations that concerns for genotoxicity cannot be excluded. In other words, while on one hand the Requestors advocate for specific tests on PPPs to be conducted (as appropriately done in the assessment of glyphosate), on the other hand, when such tests do not have outcome they desire, they reject the outcome of such tests by citing the results from literature studies that are not related or were not found relevant.

76. The Requestors also criticise the allegedly limited number of studies conducted with MON 52276 compared to the total number of studies conducted with glyphosate. However, the sufficiency of the studies on a representative product has to be assessed on the basis of the merits of those studies and cannot be established by simple numerical comparison to the number of studies conducted on the active substance, in particular in the case of an active substance as extensively studied as glyphosate. Furthermore, the inclusion of the three *in vitro* genotoxicity tests on MON 52276 in the renewal dossier by the GRG provided additional information even beyond what is required by the data requirements for PPPs (testing PPPs for genotoxicity is not a requirement laid down in Commission Regulation (EU) No 284/2013). Finally, it must be recalled that the assessment carried out in the renewal procedure for the approval of an active substance is not the same as the assessment carried out for the authorisation of a PPP (or renewal thereof).

77. In paragraph 21 of the IRR, the Requestors refer to formaldehyde and N-nitroso-N-phosphonomethylglycine as impurities of MON 52276 and claim that "*Many data gaps were identified in the EFSA Conclusion on these impurities, while the identity of other impurities remains unknown, even though their identification and toxicological profile had in principle to be provided by applicants for re-approval under Regulation 283/2013*". In order to substantiate this claim, the Requestors refer (in footnotes 32 and 33) to three statements on page 37 of the EFSA Conclusion.

78. The Commission notes, first, that the substances referred to are not impurities in the product for representative uses MON 52276 but are impurities in the active substance glyphosate as manufactured ([75]), hence why EFSA refers to the specific issues as being relevant for all representative uses.

79. However, the first two statements in the EFSA Conclusion referred to by the Requestors (footnote 32) relate to data gaps for one source of glyphosate from one of the producers that is part of the GRG (Industrias Afrasa) but is not applicable to all. Therefore, it does not affect the possibility to conclude, based on all relevant information produced in relation to all other sources of glyphosate, whether PPPs containing glyphosate can be expected to fulfil the approval criteria, including point 3.4 of Annex II to the PPP Regulation. These data gaps were not critical for the decision to renew the approval of glyphosate, as during authorisation of PPPs gaps can be closed through additional data if this production source was requested to be used in PPPs.

80. The third statement in the EFSA Conclusion referred to by the Requestors (footnote 33) pertains to a data gap identified by EFSA that is unrelated to the specification of glyphosate as manufactured, but rather concerns the need to clarify certain information on impurities present in batches used in toxicity tests ([76]). This data gap is not of a nature to raise such uncertainties that it was reflected as a concern, and it only concerns some batches used in some toxicity tests but not all. Therefore, it does not affect the possibility to conclude that

([75]) See page 9 of the EFSA Conclusion: "N-nitroso-glyphosate (NNG), formaldehyde, triethylamine and formic acid were considered relevant impurities at levels of<1 mg/kg,<1 g/kg,≤2 g/kg and≤4 g/kg, respectively".

([76]) Applicant **to clarify** the identity (CAS, name, structure) of some of the impurities listed in the composition of the batches used in toxicological studies and to clarify whether these impurities are the ones in the reference specification (emphasis added)

PPPs containing glyphosate can be expected to fulfil the approval criteria laid down in the PPP Regulation The Requestors claim that there was a breach of the requirements laid down in Commission Regulation (EU) No 283/2013 to identify impurities is incorrect as the impurities referred to by EFSA (namely, in the batches used for testing) are not those concerned by the data requirements ([77]), which relate to impurities in the technical material produced for inclusion into plant protection products. For the same reason, the claim that the identity of some impurities in the technical material is unknown is also incorrect.

81. In fact, at the levels set by EFSA for those impurities, along with another three relevant impurities (all five are listed in the renewed approval with maximum limits), no concerns were raised during the Peer Review ([78]) and those levels were accordingly laid down in the Reviewed Regulation. Therefore, the claim that the assessment of impurities would confirm the "manifestly incomplete and biased character" of the assessment is unfounded.

1.b Lack of data concerning certain co-formulants (paragraphs 22 to 25 of the IRR)

82. In paragraphs 22 and 23 of the IRR, the Requestors contend, with reference to the judgment of the Court in case C-616/17 ([79]) (the "Blaise case") and to an opinion of the Legal Service of the European Parliament, that "*the lack of assessment of the long-term toxicity of the representative formulation as a whole renders the risk assessment itself inconsistent with the requirements of Regulation (EC) No 1107/2009*" and that such an assessment cannot be replaced by an analysis of the toxicity of each component taken in isolation.

83. First, regarding the judgment of the Court in the Blaise case the Commission notes that, in the paragraphs cited by the Requestors, the Court does not develop any requirement for "long-term testing of a representative product as a whole" but reiterates the requirement of Article 4(1) and (5) of the PPP Regulation to demonstrate, at approval level, compliance of one or more representative uses of at least one PPP with the approval criteria of Article 4(2) and (3) of the PPP Regulation as the identification of at least one "safe use" by at least one PPP allows the conclusion, required for the approval of an active substance, that PPPs containing the active substance concerned can be expected to fulfil the approval criteria. According to Article 4(2), point (a), and Article 4(3), point (b), of the PPP Regulation, the assessment carried out for the approval of an active substance (or the renewal thereof) therefore also needs to take "into account known cumulative and synergistic effects" of the active substance concerned, on the one hand, and other components of the products with that active substance, on the other hand – albeit only "where the scientific methods accepted by the Authority to assess such effects are available" ([80]).

84. Second, it is recalled that Article 4(3), point (b), of the PPP Regulation requires that PPPs do not have immediate or delayed harmful effect on human health, "*taking into account*

([77]) The Requestors also do not specify which data requirement would be breached but the Commission assumes that they may refer to Part 1, Point 1.10.2 and 1.10.3 of the Annex to Commission Regulation (EU) No 283/2013.

([78]) See page 10 of the EFSA conclusion: "*Regarding the proposed reference specification, the impurities N-nitroso-glyphosate (NNG), formaldehyde, triethylamine and formic acid are identified as relevant (see Section1) based on their hazard properties, as classified according to Annex VI of Regulation (EC) No 1272/20087(CLP Regulation). Regarding the other impurities occurring in batches from the different manufacturing sources, none were found to be relevant, except for one impurity, which showed a potential for clastogenicity in an in vitro chromosome aberration test that was not appropriately followed up in vivo. Therefore, the toxicological relevance for this impurity is inconclusive (data gap, see Section9.1). This impurity was present in some of the batches used in toxicity studies at levels representative of the proposed reference specification, however its maximum level in any of the specifications cannot be established while its genotoxicity profile has not been clarified. Accordingly, the assessment of any reference specification cannot be finalised (see Section9.1)*.".

([79]) Judgment of the Court of 1 October 2019, *Blaise and Others*, C-616/17, EU:C:2019:800.

([80]) Judgment of the Court of 1 October 2019, *Blaise and Others*, C-616/17, EU:C:2019:800, paras. 67-68.

known *cumulative and synergistic effects* ***where the scientific methods accepted by the Authority*** *to assess such effects are available*" (emphasis added). In the case of glyphosate, no known risks or concerns for cocktail effects from exposure to MON 52276 were identified ([81]) and, in any case, relevant scientific methods accepted by EFSA are not yet available.

85. Third, in any event, for the product for representative uses examined during the renewal procedure of the active substance (MON 52276), a number of studies on the physical and chemical properties were provided as well as a package of acute toxicity tests (oral, dermal, inhalation, skin irritation, eye irritation and skin sensitisation) and an *in vitro* genotoxicity test battery. Furthermore, tests with MON 52276 on non-target species including aquatic organisms, non-target arthropods including bees and soil organisms were provided. Accordingly, the renewal assessment took into account data and information related to the product for representative uses MON 52276, which included an examination of studies carried out with MON 52276 directly as well as a full consideration of studies and information on its constituent co-formulants.

86. Fourth, the Requestors' claim that long-term toxicity testing of the product for representative uses cannot be replaced by an analysis of the toxicity of its components in isolation is unfounded. Concerning the long-term health effects from exposure to PPPs (in the case of glyphosate, MON 52276), specific studies on the formulated PPP are not required. Instead, a component-based approach is used to evaluate such long-term health effects, based on the hazard properties of the substances contained in the PPP (which is a mixture). Scientific guidance documents (e.g. EFSA, ECHA, OECD ([82])), recommend the component-based approach and outline how to assess hazards of mixtures without the need to perform the full range of tests on each product individually. In addition, such an approach is set out in Article 6(3) of the CLP Regulation as a method to evaluate the hazards of mixtures. Therefore, it is not necessary to carry out long-term toxicity tests on all PPPs since the products contain well-defined components, for which data is available separately and which allows an assessment of the hazards of the product in its entirety. Furthermore, ECHA has explained ([83]) why performing long-term toxicity studies on mixtures is not scientifically robust to detect effects since they lack statistical power and therefore are not meaningful for testing carcinogenic, mutagenic, and reprotoxic hazards.

87. In the case of MON 52276, a large database of toxicological information is available either on the PPP itself or on each component. A comprehensive assessment of all co-formulants

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([81]) See EFSA Conclusion, page 14: "MS experts and the RMS considered that the available toxicological information is sufficient to conclude on the safety of 'MON 52276'."

([82]) European Food Safety Authority (EFSA) Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2019.5634, and EFSA Genotoxicity assessment of chemical mixtures https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2019.5519.
European Chemicals Agency (ECHA) *Guidance on the Application of the CLP Criteria (*(1.1.6.2. Information relevant for the classification of mixtures))
https://echa.europa.eu/documents/10162/2324906/clp_en.pdf/58b5dc6d-ac2a-4910-9702-e9e1f5051cc5
https://echa.europa.eu/support/mixture-classification
Organisation for Economic Co-operation and Development (OECD) GD on mixtures https://www.oecd.org/chemicalsafety/risk-assessment/considerations-for-assessing-the-risks-of-combined-exposure-to-multiple-chemicals.pdf;

([83]) See presentation by ECHA at the Workshop on the assessment of plant protection products and co-formulants (23 May 2023, Brussels): see link on page 7
https://food.ec.europa.eu/document/download/0035541c-d171-48ec-b206-34aff93135a3_en?filename=pl_pesticides_auth-ppp_report.pdf

contained in MON 52276 was conducted by the AGG and deliberated upon by experts during the evaluation of MON 52276. This assessment is outlined in the Volume 4 of the RAR ([84]) (confidential section - not publicly available – accessible only to EFSA, Member States, and the Commission) and the expert meeting reports ([85]) (confidential version of the PRR – not publicly available – accessible only to EFSA, Member States, and the Commission).

88. Various studies performed on products containing glyphosate as active substance other than MON 52276 were also considered during the assessment of glyphosate since they can potentially provide information as regards the toxicity of the active substance itself or information on potential higher toxicity of a particular product compared to MON 52276 ([86]). For this reason, EFSA requested the GRG to disclose information regarding the composition of commercial plant protection products. This was part of the additional information requested during the Peer Review to assess equivalence with the declared composition of MON 52276. It also aimed to facilitate interpretation of toxicological and ecotoxicological studies from publicly available scientific literature conducted on glyphosate-containing products.

89. This was considered sufficient by the AGG and experts in the Peer Review (as noted on page 14 of the EFSA Conclusion "*MS experts and the RMS considered that the available toxicological information is sufficient to conclude on the safety of 'MON 52276'*"). Risk managers considered that information and determined that "*as there are representative uses for which no risk was identified, the renewal of approval is not precluded*", as explained in the Renewal Report.

90. Fifth, it is also noted that extensive epidemiological information, taking into account exposure to PPPs containing glyphosate, was assessed by both EFSA and ECHA and harmful effects on human health were not found [(87)].

([84]) Glyphosate Volume 4 Confidential Information Conclusion on the specifications of active substance from all sources, February 2023.

([85]) Experts consultation point 2.36 in Peer Review Report on Glyphosate (AIR V) Part 3 of 6 - Pesticides peer review meeting reports.

([86]) For example, see EFSA Conclusion page 15: "Evidence provided from the peer reviewed scientific literature (Jianmeiet al., 2005; Satchivi et al., 2000) showed that no differences - neither in the rate nor the amount of glyphosate absorbed – were observed when compared with diammonium and isopropylammonium salt formulations. Therefore, all studies, regardless of the salt formulation, can be used to assess the metabolism of glyphosate in plants." See EFSA Conclusion page 17: "Where the test material used in an investigation was a formulated product, this information coming from different formulations was assessed equally, independently of whether the material was 'MON 52276' or another formulation.".

([87]) For example, the RAC Opinion states:

Page 75: "*In the epidemiological studies described below, the data relate to exposure to glyphosate-based herbicide, not specifically to glyphosate*".

Page 92: "*Epidemiological data: "No association between exposure to glyphosate-based herbicide and non-Hodgkin's Lymphoma was found in the AHS cohort, which is the only prospective cohort study available. Weak positive associations have been observed in some case-control studies, and in meta-analyses of glyphosate-based herbicide exposure and non-Hodgkin's Lymphoma, as concluded in the meta-analyses by Chang and Delzell (2016), Schinasi and Leon (2014), Zhang et al. (2019), and also in IARC Monograph 112 (2015). However, Kabat et al. (2021) concluded that results of meta-analyses of glyphosate-based herbicide exposure and non-Hodgkin's Lymphoma risk depend on assumptions made about both exposure level and latency period. RAC notes that the increased risk of non-Hodgkin's Lymphoma observed in some case-control studies was not consistently observed in all case-control studies nor in the only cohort study available. For cancers other than non- Hodgkin's Lymphoma, there are less studies available and no consistent indication of an increased risk. In the AHS cohort an association between acute myeloid leukaemia and exposure to glyphosate was reported for the highest*

91. Finally, the Commission notes that, according to the data requirements for PPPs ([88]), a number of studies or information on the formulated PPP must be provided to the Member States in applications for authorisations of PPPs, which would thus reflect any potential cocktail effects of the components contained therein.

92. Hence, MON 52276 was assessed as thoroughly as required in order to determine whether glyphosate, the active substance contained therein, fulfils the approval criteria under Article 4 of the PPP Regulation. The assessment resulted in the conclusion that PPPs with glyphosate can be expected to fulfil the approval criteria in Article 4(3) of the PPP Regulation, including as regards any known cumulative or synergistic effects of glyphosate with other components of such PPPs.

93. In paragraphs 24 and 25 of the IRR, the Requestors note that EFSA set a data gap for one co-formulant of MON 52276 as there was no information available and claim that, in the Renewal Report, the Commission considered this data gap not to be an obstacle to the renewal of approval because the particular co-formulant is a polymer, which is contained in other pesticides authorised by several Member States. However, in the Requestors' view, co-formulants are subject to the same safety requirements as active substances, safeners and synergists, and that it would follow from the applicable data requirements in Regulations (EU) No 283/2013 and (EU) No 284/2013 that it is necessary to obtain data on long-term toxicity and carcinogenicity of co-formulants. They therefore consider that the absence of the required data (i.e. the data gap set by EFSA) for one of the co-formulants precluded the AGG and EFSA from concluding that the conditions for renewing the approval of glyphosate were met.

94. First, the Requestors' claim that points 1.2 and 1.11 of the Introduction of the Annex to Regulation (EU) No 284/2013 and point 1.11 of the Introduction of the Annex to Regulation (EU) No 283/2013 require "*all data on long-term toxicity and carcinogenicity of co-formulants*" is incorrect. Besides it being unclear what is meant by "all data on long-term toxicity and carcinogenicity", the specified points do not require such data on co-formulants to be provided. Point 1.11 of the Introduction to Regulation (EU) No 283/2013 requires that the information on the active substance, taken together with the information concerning one or more plant protection products containing the active substance and together, if appropriate, with the information concerning safeners and synergists and other components of the plant protection product, is sufficient to enable a full risk assessment (the point then details specific elements that should be assessed). None of these refers to long-term and carcinogenicity data of co-formulants. Similarly, points 1.2 and 1.11 of the Introduction to

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quartile of exposure when a 20-year lag period was taken into account, however, a low number of cases was found in this exposure group. RAC notes that this tumour type should be followed in future updates of the AHS. A causal relationship could not be established by RAC because chance, bias, and confounding factors could not be ruled out, and the evidence from epidemiological studies was considered insufficient to demonstrate carcinogenicity in humans".

Page 94: "*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*".

Page 123: "*Epidemiological studies show no convincing evidence of developmental effects following in utero exposure to glyphosate*".

For further comments, see the reply to EP question 001499/2022 https://www.europarl.europa.eu/doceo/document/P-9-2022-001499-ASW_EN.html and to the Commission's observations to Petition No 1324/2021 on behalf of the French NGO "Secrets toxiques" where the Commission has provided extensive input and responses.

([88]) Commission Regulation (EU) No 284/2013 of 1 March 2013 setting out the data requirements for plant protection products, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, OJ L 93, 3.4.2013, p. 85.

the Annex to Regulation (EU) No 284/2013 do not specify that long-term and carcinogenicity data must be submitted by applicants. Point 1.11 only provides the possibility for competent authorities to request such data if found necessary and after having assessed all information available from other Union legislation ([89]). As explained in the Renewal Report, neither the AGG nor EFSA saw the need to request further data on the particular co-formulant referred to by the Requestors.

95. Second, as to the claim by the Requestors that the identification of a data gap in relation to one of the co-formulants in the product for representative uses would have prevented the renewal of approval, it must first be borne in mind that "data gap" does not equal "concern". Data gaps refer to missing information that could enhance understanding but the absence of which does not necessarily compromise the approval of an active substance when uncertainties (and associated risks if any) can be managed appropriately. The identification of data gaps as part of the assessment process is common across almost all active substances. As risk managers, the Commission and Member States are tasked with evaluating these gaps alongside any uncertainties and, in light of the overall outcome of the risk assessment, with determining safety and setting appropriate risk mitigation measures, conditions, and restrictions. Accordingly, the identification of data gaps during the assessment and peer review of an active substance does not imply by default the non-compliance with the criteria outlined in Article 4 of the PPP Regulation ([90]). Each data gap must be evaluated individually, with due consideration given to the totality of available evidence, any uncertainties and the application of sound scientific principles in decision-making processes.

96. Third, contrary to what is inferred by the Requestors in paragraph 24 of the IRR, the Commission did not base its conclusion that the data gap in relation to one of the co-formulants in MON 52276 did not prevent renewal solely on the consideration that it is a polymer that is contained in other pesticides authorised in several Member States. As set out in pages 6-7 of the Renewal Report (to which the Requestors refer in footnote 36), the Commission's conclusion that overall there is no indication of concern for the particular co-formulant is based on a number of other considerations clearly explained in the first two paragraphs of page 7 of the Renewal Report.

97. Finally, the Commission recalls that, in any event, under the PPP Regulation, the co-formulants of a PPP will be assessed by the national authorities as part of the authorisation of the relevant PPP. Article 29(1), point (c), of the PPP Regulation requires a PPP's co-formulants not to be included in the negative list under Article 27 of the PPP Regulation. In addition, Article 29(1), points (e) and (f), of the PPP Regulation require that a PPP as a whole complies with the approval criteria of Article 4(3) and that the nature of and quantity of the co-formulants can be determined by appropriate methods. In that context of this assessment, the Member States will also ensure that sufficient data on co-formulants is provided.

98. Consequently, none of the arguments brought forward by the Requestors in relation to the lack of data concerning certain co-formulants contained in MON 52276 is able to demonstrate that the Reviewed Regulation renewing the approval of glyphosate subject to conditions and restrictions would be in breach of environmental provisions of Union law.

([89]) *"Information as provided for in Commission Regulation (EU) No 283/2013 may be required by the competent authorities on co-formulants. Before requiring additional studies to be performed, the competent authorities shall assess all available information provided in accordance with other Union legislation."*.

([90]) Judgment of the General Court of 21 February 2024, *PAN Europe v Commission*, T-536/22, EU:T:2024:98, paras 272, 309 and 314.

1.c Absence of evaluation of ecotoxicity on birds, mammals and amphibians (paragraphs 26 to 29 of the IRR)

99. In paragraphs 26 and 27 of the IRR, the Requestors argue that the environmental impact of MON 52276 was assessed incorrectly because studies carried out with MON 52276 to assess the effects on certain non-target organisms (birds, mammals, amphibians, fish, invertebrate aquatic organisms, and sediment dwelling organisms) were not submitted and no justification is given to why the studies available with glyphosate were sufficient to predict the toxicity of the PPP.

100. However, as the Requestors admit, according to Point 1 of the introduction to section 10 of Part A of the Annex to Regulation 284/2013 setting out the data requirements on PPPs, certain studies must be carried out using the PPP only where its toxicity cannot be predicted on the basis of data on the active substance ([91]). It is clear from the EFSA Conclusion and the RAR that it was concluded that such toxicity could be predicted on the basis of the data for glyphosate.

101. In the EFSA Conclusion ([92]) the risk assessors clarified that: "*The experts at the meeting agreed with the RMS that the risk to birds and mammals from the formulation for representative uses ('MON 52267') was sufficiently addressed by the risk assessment carried out for the active substance given that the available acute toxicity data for mammals did not indicate increased toxicity*" and that "*Unpublished regulatory dossier studies provided by the applicants were available to address the effects of exposure via surface water to glyphosate and the formulation for representative uses 'MON 52276' to fish, aquatic invertebrates, algae and macrophytes. The formulation for representative uses 'MON 52276' was shown to be less toxic than glyphosate. Therefore, the current risk assessment covers the formulation for representative uses*".

102. This is also in line with the RAR ([93]) which states with regard to birds and mammals "*Risk assessment for the representative formulation: An acute oral mammalian study is available with the formulation which is presented in the toxicological section of Volume 3CA. This study shows that the acute toxicity of the formulation (> 5000 mg/kg bw) is not more elevated than the toxicity of the active substance alone (> 2000 mg/kg bw). Assuming a similar pattern for birds as for mammals, the avian risk assessment for the representative formulation is considered to be covered by the avian risk assessment presented for the active substance glyphosate*" and "*An acute oral mammalian study is available with the formulation which is presented in the toxicological section (Volume 3CP, section 6). The data shows, that the acute toxicity of the formulation (> 5000 mg/kg bw) is not higher than the toxicity of the active substance alone (> 2000 mg/kg bw). Therefore, the mammalian risk assessment for the representative formulation is considered to be covered by the mammalian risk assessment presented for the active substance glyphosate*".

103. In paragraph 28 of the IRR, the Requestors state that harmful effects on tadpoles were observed in the metamorphosis assay on amphibians submitted on glyphosate. However,

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([91]) "*Testing of the plant protection product shall be necessary where its toxicity cannot be predicted on the basis of data on the active substance. Where testing is necessary, the aim shall be to demonstrate whether the plant protection product, taking account of content of active substance, is more toxic than the active substance. Thus bridging studies or a limit test may be sufficient. However, where a plant protection product is more toxic than the active substance (expressed in comparable units), definitive testing shall be required*.".

([92]) See page 22 of the EFSA conclusion https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2023.8164.

([93]) See "RAR_29_Volume_3CP_MON 52276_B-9_ecotoxicology_2023-04-21_public", page 11 and 12.

according to the RAR ([94]) this is not the case. Moreover, the various published studies cited by the Requestors to demonstrate harmful effects were considered and/or taken into account during the Peer Review ([95]). With regards to amphibians, the EFSA Conclusion states that "*The effects of glyphosate (either as active substance or formulated) to the aquatic stage of amphibians were investigated in several studies retrieved from the open literature. A comparison of the hazard data with fish was carried out and discussed at the Pesticides Peer Review Experts' TC82*" ([96]). The studies evaluated and the approach taken for the assessment are explained in the RAR ([97]).

104. Finally, the claim made in paragraph 29 of the IRR that it was impossible to carry out the risk assessment for insects due to issues with two first-tier regulatory studies on ecotoxicity of the representative formulation, is addressed in Section III.1 - Subsection 7.b below.

105. Based on the above, the Commission concludes that this ground is unfounded.

1.d. Conclusion (paragraph 30 of the IRR)

106. It follows from the above that the Requestors do not succeed in demonstrating manifest errors in the toxicity assessment of the product for representative uses MON 52276 or a lack of compliance with the approval criteria laid down in Article 4 of the PPP Regulation.

107. Contrary to the alleged "manifest errors of assessment" on which the Reviewed Regulation is based, which the Requestors have put forward in paragraph 30 of the IRR with regard to the toxicity of the product for representative uses, the preceding paragraphs in this Section III.1.1 have demonstrated that:

- The assessment carried out by the AGG and EFSA took into account the cited independent literature on long-term toxicity and carcinogenicity for MON 52276 and did not raise any concerns;
- Impurities in the representative product were considered and did not raise any concerns;
- The studies provided by the GRG on the long-term toxicity of the product for representative uses comply with the data requirements and a component-based approach demonstrated the safety of the product, including for long-term effects;
- The information available for the co-formulants was sufficient to carry out an assessment to conclude that the approval criteria are met;
- A robust assessment was conducted on ecotoxicological effects on birds, mammals and amphibians, which was also predictive for the product for representative uses.

([94]) See page 185 of the "RAR_29_Volume_3CP_MON 52276_B-9_ecotoxicology_2023-04-21_public": "The study was conducted at water concentrations up to 90 mg a.e./L, and although a slight increase was observed in the wet weight of Xenopus laevis tadpoles at 90 mg a.e./L, there were no other effects observed in the study, with no effects on growth and development, no mortality and no effects on the thyroid, following a 21-day exposure period."

([95]) L. Almeida (2020), Güngördu (2013), Relyea (2012), available in Glyphosate_RAR_19_Volume_3CA_B-9_ecotoxicology_2023-04-21_public.pdf;
Edge *et al.* (2014), available in Glyphosate_RAR_29_Volume_3CP_MON 52276_B-9_ecotoxicology_2023-04-21_public.pdf;
Wagner *et al*. (2013), Bach *et al*. (2016), available in Glyphosate_RAR_20_Volume_3CA_B-9_ecotoxicology_appendix literature search_2023-04-21_public.pdf
Baier *et* al. (2016) - this study was screened but not considered relevant for the EU assessment.

([96]) Pages 22-23 of the EFSA Conclusion.

([97]) See Section B 9.2.3 of the "RAR_29_Volume_3CP_MON 52276_B-9_ecotoxicology_2023-04-21_public".

2. Alleged illegalities and manifest errors in the assessment of the genotoxicity of glyphosate (paragraphs 31 to 65 of the IRR)

2.a. Alleged serious indications of genotoxic potential from independent scientific literature systematically questioned or ignored (paragraphs 34 to 41 of the IRR)

108. In paragraph 34 of the IRR, the Requestors claim that the "vast majority of independent peer-reviewed scientific studies on the subject" would have concluded that glyphosate has a genotoxic potential. They raise concerns regarding the evaluation process of the studies by the AGG, inferring that only a small fraction of relevant studies from the published literature was considered during the re-approval process, with many older studies not reviewed. They also refer to a publication by INSERM and INSERM's contribution to the public consultation in the context of the renewal procedure for glyphosate according to which '*studies showing that glyphosate has genotoxic effects are more important in terms of quality and quantity than those suggesting an absence of effect*'.

109. The Commission recalls that the AGG, ECHA and EFSA assessed the genotoxic potential of glyphosate, as explained in Section II.2.a above. These assessments led to the same conclusion, namely that glyphosate is not genotoxic. This conclusion is underpinned by a vast range of data, underscoring the robustness of the process and its adherence to stringent standards.

110. In paragraph 35 of the IRR, the Requestors claim that the GRG would have provided only a fraction of the relevant literature studies and criticise that the AGG did not ask for more studies, including those older than 10 years. They claim that because the older literature studies would not have been correctly evaluated during the last renewal procedure, they were never properly examined. These claims are unfounded. In fact, EFSA requested further clarification from both the applicant and the AGG regarding the literature search conducted ([98]). This included seeking clarity on the approach used for assessing the relevance and reliability of studies, as well as considering studies conducted outside the specified timeframe and those included in previous assessments like the RAR addenda from Germany in 2015, which covered the International Agency for Research on Cancer (IARC) monograph. These actions demonstrate that EFSA thoroughly evaluated a wide range of literature studies and addressed potential gaps in the evidence examined.

111. In paragraphs 36 to 39 of the IRR, the Requestors point out that none of the literature studies have been categorised as '*pertinent and reliable'* or '*pertinent and reliable with restrictions'* so that none has been used as a direct support for the evaluation and most have been found only supplementary and hence of limited validity. They also recall INSERM's perspective that EFSA's conclusion on genotoxicity overlooked essential data from non-standardised test models and formulations, which would offer a more realistic assessment of human exposure. Additionally, the Requestors claim that the studies provided by the GRG did not adhere to current testing guidelines. They argue that these guidelines, developed in consultation with industry, may not adequately reflect study sensitivity or incorporate the latest scientific knowledge. The Requestors underline the importance of studies with formulated products, which provide insights into both formulation toxicity and real-world exposure effects. They express concern that the competent authorities did not assess formulation composition before disregarding relevant studies, highlighting a significant oversight.

([98]) See EFSA conclusion on data requirements (general) 2.62 and 2.63 and related action points for the RMS in Part 4_Peer Review Report_evaluation tables_July 2023, available in the Peer review Report in Open EFSA, Supporting documents section under EFSA-Q-2020-00140 (Part 4_Peer Review Report_Glyphosate_evaluation tables_public, refer to section 2, electronic page 282-288 of 1093).

112. The Commission considers that none of these claims casts doubt on the outcome of the assessment conducted by the AGG, EFSA and ECHA. The assessment of genotoxicity followed a WoE approach (EFSA Scientific Committee, 2011 ([99]), incorporating over 70 studies, both regulatory guideline studies carried out to internationally agreed and accepted protocols and studies from public literature, assessed as acceptable, supplementary or supportive ([100]). The reasons for considering studies not to be relevant and/or reliable are set out in the RAR ([101]). Studies on mammalian species were given higher relevance than non-mammalian species (such as fish), as were those conducted according to agreed international protocols, which is not the case for fish genotoxicity studies ([102]). The criticism of the Requestors that the agreed test guidelines were developed in 'concertation with industry' does not prove in any way that these guidelines are inappropriate: international test guidelines are developed by experts from governments, industry and academia and are validated according to strict procedures in the context of the OECD ([103]). Their final adoption is subject to approval by all governments who are members of the OECD.

113. The Commission also recalls that during the Peer Review, the views and conclusions expressed in the report of INSERM in 2021 and the comments submitted during the public consultation on the draft RAR were fully taken into account ([104]).

114. As regards the composition of the tested formulations, where available, the applicants provided information on the composition of the formulations (different to the product for representative uses, MON 52276) used in published and non-published studies. Considerations on whether these formulations were comparable to the formulation for the representative uses were also included in the RAR Volume 4. Depending on the availability of the evidence for the different toxicological endpoints, e.g. developmental neurotoxicity (DNT) studies conducted with different salts and/or formulations other than the one for representative uses, were considered for their reliability and relevance and discussed as part of the WoE in the risk assessment ([105]).

115. As to the contribution of studies performed with formulations containing glyphosate, including the formulation for representative uses, it should be noted that studies with formulations may inform on the genotoxicity of glyphosate and therefore were considered for the assessment of glyphosate. However, to assess the genotoxicity of glyphosate, lower weight was given to studies with formulations, given the high uncertainties regarding potential different components of the formulation, not only glyphosate ([106]). In any case, as evident from page 14 of the EFSA Conclusion, the product for representative uses, MON

([99]) EFSA Scientific Committee, 2011. Scientific Opinion on genotoxicity testing strategies applicable to food and feed safety assessment. EFSA Journal 2011;9(9):2379, 69 pp. https://doi.org/10.2903/j.efsa.2011.2379.

([100]) Available in the Open EFSA, 'Supporting documents' section under EFSA Question number EFSA-Q-2020-00140: https://open.efsa.europa.eu/study-inventory/EFSA-Q-2020-00140 (refer to Glyphosate_Final RAR_public.zip).

([101]) See Volume 1 of the RAR as well as Volume B3 Section B.6.4 (genotoxicity).

([102]) Available in the Peer Review Report in Open EFSA, Supporting documents section under EFSA-Q-2020-00140 (Part 2_Peer Review Report_Glyphosate_reporting tables_public, electronic page 2383 of 2930).

([103]) https://www.oecd.org/chemicalsafety/testing/oecd-guidelines-testing-chemicals-related-documents.htm

([104]) Available in the Peer review Report in Open EFSA, Supporting documents section under EFSA-Q-2020-00140 (see data requirement 2(51) in Part 2_Peer Review Report_Glyphosate_reporting tables_public, electronic page 2417 of 2930).

([105]) See Data requirement (general) 2.62 in Part 4_Peer review report_evaluation table (section 2).

([106]) Available in the Peer review Report in Open EFSA, Supporting documents section under EFSA-Q-2020-00140 (Part 3_Peer Review Report_Glyphosate_Annexes: Peer Review Report_Glyphosate_Annexes_TC80_public.pdf

52276, is unlikely to be genotoxic or mutagenic, based on a WoE approach and considering the studies performed with MON 52276 itself.

116. In paragraphs 40 and 41 of the IRR, the Requestors claim that there is a clear contradiction in the reasoning "*developed to diminish the importance of positive results from in vitro Comet assays reported in independent literature*". The Requestors state that results from Comet assays are qualified because of the existence of a '*negative result for induction of DNA repair (UDS)*' and state that it appears that the results of UDS studies were used to minimise the relevance of the results from an *in vivo comet study*, together with another wrong argument.

117. This statement is unclear since negative results in UDS tests were not relied on to discount positive results in Comet assays. The RAC Opinion 2022 actually states that "*Two negative Unscheduled DNS Synthesis (UDS) assays using primary hepatocytes was presented in the CLH dossier (CA 5.4.1/033, 1994; CA 5.4.1/034, 1984). The studies were considered to be not acceptable by the DS due to deviations from the OECD TG 482. RAC notes that the UDS assay is no longer a standard method and that the OECD TG482 has been deleted*". Moreover, the AGG did not rely on the UDS studies for its assessment of genotoxicity ([107]) and it is clear from the RAR that UDS tests were not used to minimise results from Comet assay tests ([108]). Therefore, this claim is unfounded.

2.b. Alleged deficient regulatory studies (paragraphs 42 to 56 of the IRR)

118. In paragraphs 42 to 46 of the IRR, the Requestors argue that the methodology employed by the AGG and EFSA demonstrates a bias, as it would have "nearly absolute" confidence in unpublished tests commissioned by producers while dismissing studies conducted in independent academic institutes and published in peer-reviewed journals. They consider this contrary to the principles of completeness, excellence and independence.

119. In order to demonstrate the alleged bias, the Requestors compare, on the one hand, two studies deemed acceptable and reliable with restrictions (such as CA 5.4.1/027 and CA 5.4.2/009), which in their view have incomplete historical control data and errors in cell evaluation, and two studies that were considered less relevant and reliable (such as De Aleida *et al.*, 2018 I*n vitro Comet assay (supplemental: less relevant and reliable with restrictions)*, Mladinic *et al*., 2009b *In vitro MN test (supplemental: less relevant and reliable with restrictions*, Mladinic *et al*., *2009 in vitro comet and MN test (supplemental: less relevant and reliable with restrictions)*).

120. The Commission notes that the data requirements for active substances and PPP as set out in Regulations (EU) No 283/2013 and No 284/2013, respectively, require certain studies to be submitted and in most cases these must be conducted (or mandated to specialised test laboratories) by applicants according to agreed international guidelines and in accordance

([107]) See Volume 1 of the RAR, page 313: "Several studies investigating glyphosate in in vitro DNA damage assays are available. These include in vitro unscheduled DNA synthesis (UDS) and sister chromatid exchange (SCE) studies, and DNA repair studies. It is noted that most of these studies were considered not acceptable and therefore are not included into Vol.1 and are not taken into account into the overall weight of evidence assessment. One study was considered supplementary (IET 94-0141). This DNA repair test (Rec-assay) showed no relevant DNA damaging activity of glyphosate either in the absence or presence of metabolic activation."
See also Experts' consultation 2.4 identified following comments by public (Part 3 of 6 of the Peer Review Report) UDS, SCE and DNA repair. Most studies considered not acceptable and thus not considered further. One DNA repair study (Rec-assay) was considered supplementary and showed no relevant DNA damaging activity of glyphosate.

([108]) See Volume 1 of the RAR, page 313:
"Several in vitro indicator tests gave positive results for induction of SCE and DNA strand breaks (comet assay) mainly at cytotoxic concentrations but a negative result for induction of DNA repair (UDS). However, for all these studies several methodological shortcomings were identified."

with the quality assurance system Good Laboratory Practice. All studies submitted by the GRG in the renewal dossier underwent thorough scrutiny. The acceptance of most of these studies does not inherently indicate bias but rather reflects the outcome of the comprehensive evaluation of available evidence according to agreed methodological guidance. Some guideline studies carried out/submitted by the GRG were also not accepted ([109]).

121. Moreover, as already discussed in the preceding subsection, publicly accessible literature studies form an integral part of the body of evidence that applicants must submit and that EFSA and the RMS must assess All these studies, i.e. both those conducted by (or for) applicants and those from public literature are assessed for scientific relevance and reliability by the RMS and subsequently in the Peer Review, aligning with EFSA Guidance documents such as those from 2011 and its 2019 Appendix ([110]), along with the EFSA Scientific Committee's guidelines from 2017 ([111]). According to the EFSA Scientific Committee's definition, *"the reliability is defined as the extent to which the information comprising a piece or line of evidence is correct. The reliability of a study may be assessed by considering the uncertainty of the evidence and everything that contributes to that uncertainty should be included when assessing reliability"*. Consequently, deviations from OECD Test Guidelines are considered in the overall reliability assessment to ddetermine if these deviations might affect the reliability of a study by applicants. Similarly, published literature is also assessed for relevance and reliability according to the applicable guidance.

122. The Commission also notes that the two studies referred to in paragraph 44 of the IRR as examples of studies that would have been considered "relevant, acceptable and reliable" (CA 5.4.1/027 and CA 5.4.2/009) were considered reliable with restrictions (emphasis added). The deviations from the test guidelines are clearly documented in the RAR, and contrary to the claim by the Requestors that they showed major deviations, in both cases the AGG considered that *"The deviations were not expected to significantly impact the study outcome"* ([112]). Furthermore, these guideline studies (an *in vitro* micronucleus study and an *in vivo* micronucleus study) were part of a large body of evidence, including other studies of the same type and were taken into account in the WoE assessment.

123. The three studies from public literature referred to in paragraphs 45 and 46 of the IRR as examples of studies considered less relevant, were indeed considered as less relevant and reliable with restrictions by the AGG and EFSA, which clearly shows that they were considered in the assessment. Two of them report on the outcome of Comet assays, which measure DNA damage, which is not considered an apical endpoint as DNA damage can be repaired. Therefore, although the *in vivo* Comet assay can a be suitable follow-up for substances positive *in vitro* in gene mutation or clastogenicity assays (EFSA Scientific Committee, 2011), its endpoint nature (i.e. DNA damage) is considered in the overall WoE approach. The other test reported in two of the studies mentioned by the Requestors as being considered less reliable is an *in vitro* micronucleus test, which is a guideline test that is used to assess clastogenicity and aneugenicity. The argument that two of the three studies mentioned were considered less relevant only because they use a type of test that is not subject to a test guideline is not correct. As mentioned in the passages quoted from the RAR

([109]) For example, the study "LX1146-02 (Glyphosate techn.) Tier II Non-Target plant hazard evaluation – Terrestrial vegetative vigor" was not accepted despite being GLP compliant. See Glyphosate_RAR_19_Volume_3CA_B-9_ecotoxicology_2023-04-21_public.pdf

([110]) EFSA (European Food Safety Authority), 2011. Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009. EFSA Journal 2011;9(2):2092, 49 pp. doi:10.2903/j.efsa.2011.2092

([111]) EFSA Scientific Committee, 2017. Scientific Opinion on the guidance on the use of the weight of evidence approach in scientific assessments. EFSA Journal 2017;15(8):4971, 69 pp. https://doi.org/10.2903/j.efsa.2017.4971

([112]) See pages 138- 45 and 255-260 of Volume 3 – B.6.4 (AS) of the RAR.

by the Requestors themselves, there were various reasons why the studies were considered less reliable. Therefore, all tests, whether subject to a regulatory test guideline or not, were considered objectively for their relevance and reliability.

124. In paragraphs 47 and 48 of the IRR, the Requestors raise a concern that applicants may not submit all studies that they carry out, citing the example of a DNT study on glyphosate-trimesium, and that there is no control of whether all studies were submitted. In addition, the Requestors insinuate that guideline regulatory studies carried out by applicants to meet the data requirements cannot be trusted due to inherent bias of applicants. In response, it is recalled that all raw data from the studies conducted must be submitted and are evaluated by the RMS and EFSA, any bias in the summary and interpretation of the data by the applicants is thus detected. Furthermore, test facilities that conduct regulatory studies according to good laboratory practice ('GLP') are regularly inspected by national monitoring authorities and, in case of doubts, specific audits can be carried out by such authorities ([113]). In the case of the DNT study referred to, it is first noted that the GRG did not submit the study as they considered it not relevant since glyphosate-trimesium is a different substance that was not part of the renewal dossier ([114]). The study was identified during the Peer Review and was requested by EFSA and then taken into account in the assessments by both ECHA and EFSA. If anything, this shows that the Peer Reviewis robust, and that all relevant information is taken into account.

125. In paragraph 49 of the IRR, the Requestors state that, even though the RMS and EFSA should have carried out a thorough assessment, no additional studies were requested from the applicants or commissioned by the European authorities. However, this is incorrect. EFSA requested additional information, including various additional studies on the basis of Regulation (EC) No 844/2012 ([115]). Furthermore, the Requestors do not substantiate what additional studies should have been requested or should have been commissioned by EFSA.

126. Contrary to the claim by the Requestors in paragraph 50 of the IRR that the risk assessment was only based on studies provided by the applicant, the assessment conducted by the AGG and EFSA included a rigorous evaluation of both industry studies submitted by the applicants and studies found in public literature (some which were identified during the Peer Review and requested by EFSA), which were equally assessed for their relevance and reliability for the risk assessment and were taken into account the WoE approach**.** The claim that the assessment only took into account studies submitted by the GRG is therefore unfounded.

127. In paragraphs 51 and 52 of the IRR, the Requestors submit that the studies provided by the applicants were "affected by numerous defects". The Commission notes that, to allow a transparent assessment of all the submitted studies, including the regulatory studies from the applicants, the AGG was asked to transparently report both the assessment of the reliability of the studies and the relevance of the study results to conclude on the overall WoE and, following the categorisation of toxicology standard studies as acceptable, supplementary, supportive and not acceptable ([116]), as already mentioned, more than 70 studies (regulatory and public literature studies) to assess genotoxicity were deemed acceptable, supplementary or supportive ([117]). This is an unprecedented number of studies to assess genotoxicity

([113]) Directive 2004/9/EC of the European Parliament and of the Council of 11 February 2004 on the inspection and verification of good laboratory practice (GLP) (OJ L 50, 20.2.2004, p. 28).

([114]) See section B.6.7.1.4 in Vol.3 CA B.6.7 of the RAR (Developmental neurotoxicity study with glyphosate-trimesium salt)

([115]) See the request letter sent on 14 March 2022: "Glyphosate_additional information request" at https://open.efsa.europa.eu/questions/EFSA-Q-2020-00140

([116]) See RAR, volume 1, level 2.

([117]) See Renewal Assessment Report at Table 2.0.5.2-3 and Table 2.0.5.2-4 (RAR, Volume 1, 2023).

compared to other active substances, therefore providing a rich data basis for the assessment. Overall, all available studies, both from the applicants and from publications, have been duly considered and assessed for their relevance and reliability following a rigorous approach as detailed in the RAR.

128. With regard to the genotoxicity assessment EFSA did identify the need for additional data to be provided by the applicants, as shown in the Peer Review Report ([118]).

129. In addition, a dedicated expert consultation on all relevant endpoints took place, including specific discussion on the impact of the identified deviations of the genotoxicity studies on glyphosate (considerations of major vs minor deviations) as referred to by the Requestors in paragraphs 51 and 52 of the IRR. The experts' consultation resulted in the collegial agreement by the experts on the relevance and reliability of the studies, taking into account deviations from the applicable test guidelines (TGs) ([119]).

130. EFSA applied, as recommended in the guidance from the EFSA Scientific Committee, 2011, a WoE approach for genotoxicity on glyphosate during the Peer Review. It included more than 70 studies, both regulatory and from public scientific literature, which assessed as acceptable, supplementary or supportive. The studies that were considered not acceptable were not taken into account for the overall WoE assessment on genotoxicity of glyphosate. Specifically, the issue of interpretation of the results of the Comet assay was discussed during the Pesticides Peer Review Experts' meeting TC 80 (see below). In addition, it should be noted that although the majority of studies were not considered as 'reliable without restrictions' this was mostly due to minor deviations which still permitted the studies to be used in the assessment. Overall, the genotoxicity data package on glyphosate was considered extensive and sufficiently robust to permit proper conclusions to be drawn on genotoxicity without the need for requesting further studies.

131. In paragraph 52 of the IRR, the Requestors submit that the "*15 bacterial genetic mutation tests are negative is of very limited interest and does not contradict positive results from independent scientific literature indicating clastogenic effect (ability to produce breaks in DNA molecules, i.e. chromosomal aberrations*".

132. The rationale behind this statement is hard to understand since bacterial gene mutation tests are designed to detect gene mutations, and therefore those tests are not suitable and were not used to assess clastogenicity potential. In fact, a range of *in vitro* and *in vivo* tests were available to assess clastogenicity ([120]).

133. In paragraph 53 of the IRR, the Requestors state that "so*me studies from published literature document a clastogenic effect in other tissues such as liver and kidney, breast gland or uterus (Mañas et al. (2013), De Almeida et al. (2018[7]). In view of those results, the authorities should have required applicants for re-approval to carry out further tests on those tissues, in particular a Comet Assay (OECD 489, 2016) or a transgenic rodent somatic and germ cell gene mutation test (OECD 488, 2011)."*

134. The Commission notes that the transgenic rodent assay can detect point mutations and small deletions but is not a test used to assess clastogenic potential and therefore suggesting using such a test to assess alleged clastogenic effects does not seem to be scientifically justified. Accordingly, the EFSA Scientific Committee recommends the *in vitro* micronucleus test to assess clastogenicity and in case of positive results, follow up with the *in vivo* micronucleus

([118]) See Part 2 of 6 of the Peer Review Report on Glyphosate (AIR V) Reporting table (section 2) points 2(149), 2(151), 2(152), 2(153), 2(154), 2(155), 2(158), 2(161), 2(165), 2(169), 2(201), 2(202), 2(203), 2(204) and Reporting table identified following public comments (section 2) points 2(43), 2(44), 2(51).

([119]) See Experts' consultation point 2.3 in Part 3 of 6 of the Peer Review Report on Glyphosate (AIR V).

([120]) As summarised on pages 35-40 of the RAC Opinion,

test, not the Comet assay, which is an indicator test ([121]). A number of *in vitro* and *in vivo* micronucleus tests were available and assessed as part of the WoE assessment ([122]).

135. In paragraphs 54 to 56 of the IRR, in order to reinforce the idea of an incomplete genotoxicity testing, the Requestors criticise the competent authorities' refusal to run additional tissue tests, citing both independent scientific research and EFSA's own recommendations (in its "Scientific Opinion on genotoxicity testing strategies"). In the mentioned opinions, the Requestors underline that EFSA emphasises the importance of testing multiple tissues for genotoxicity and highlights the value of the Comet Assay test.

136. However, the EFSA Scientific Opinion on genotoxicity testing strategies ([123]), recommending the WoE approach, considered that indicator tests (such as the Comet assay) detect pre-mutagenic lesions, which may not result in mutations, e.g. repairable DNA damage measured by the Comet assay ([124]).

137. This consideration was part of the discussion during the Pesticides Peer Review Experts' meeting TC 80 ([125]) where it has been stated that *"In the overall WoE for genotoxicity, more weight is given to apical endpoints, gene mutation and chromosome aberrations (i.e. permanent DNA lesions), than to primary DNA damage (may be transient or reversible). This is also in line with the European Union data requirements where the data package should address the three apical genotoxicity endpoints: gene mutation, clastogenicity and aneugenicity. Primary DNA damage, as measured by Comet assay, is not an apical endpoint as DNA damage may be transient or reversible. Although the in vivo Comet assay can be a suitable follow up for substances positive in vitro in the gene mutation or clastogenicity assays (EFSA SC, 2011), the nature of the endpoint, primary DNA damage, is also considered in the overall WoE".*

138. Moreover, all pertinent studies were also part of the hazard assessment undertaken in the context of the formal assessment of the proposal for harmonised classification and labelling in accordance with Regulation (EC) No 1272/2008 conducted by ECHA in parallel to the Peer Review.

139. ECHA dealt with the same topic raised by the Requestors in its letter ([126]) to the Vice-Chair of the Committee on the Environment, Public Health and Food Safety of the European Parliament. After clarifying that the RAC must classify substances using all available information according to the CLP Regulation and that positive results from specific tests are required for a Category 2 classification, the letter underlines that the data reviewed showed negative results in key tests. The opinion mentions that even though certain tests (i.e. Comet assay and Transgenic Rodent) were not part of the data package, their absence was not critical due to the equivocal biological relevance of DNA damage for assessing

([121]) See EFSA Scientific Committee; Scientific Opinion on genotoxicity testing strategies applicable to food and feed safety assessment. EFSA Journal 2011;9(9):2379. [69 pp.] doi:10.2903/j.efsa.2011.2379. Available online: www.efsa.europa.eu/efsajournal. See page 28: "As a follow-up for in vitro positives for clastogenicity or aneugenicity, the in vivo mammalian erythrocyte micronucleus test is suitable. As a follow-up for in vitro gene mutation positives, both the transgenic rodent gene mutation assay and the Comet assay are suitable. It should be noted, however, that the transgenic rodent assay is a test that measures gene mutations directly, whereas the Comet assay is an indicator test for DNA lesions that may or may not result in mutations."

([122]) See in particular Experts' consultation 2.1 identified following comments by public in Part 3 of the 6 of the Peer Review Report on Glyphosate (AIR V).

([123]) EFSA Scientific Committee, 2011.

([124]) See chapter 4.1.

([125]) See experts' consultation point 2.1 identified following comments by public in https://open.efsa.europa.eu/study-inventory/EFSA-Q-2020-00140.

([126]) https://echa.europa.eu/documents/10162/11395738/Response_MEP_Eickhout.pdf/6bb175d0-e101-7243-e187-bb00ea74cd6c?t=1668160382964.

mutagenicity. More in detail, the latter reads"*Firstly, RAC is obliged under CLP to classify on the basis of the available information and evaluations are always carried to a conclusion in the categories specified by the regulation.*

Having said this, and as noted in the opinion, according to the criteria in the CLP Regulation, classification as Category 2, is largely based on positive evidence obtained from somatic cell mutagenicity tests in mammals or other in vivo somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays. The gene mutation assays in the data assessed were all negative and bone marrow mutagenicity was considered negative in a weight of evidence assessment of the available oral micronucleus assays and intraperitoneal micronucleus assays.

The statement quoted from the opinion related to the Comet assay and Transgenic rodent (TGR) somatic and germ cell gene mutation assays which are two particular assays among many other lines of evidence potentially informing a classification. The opinion noted the absence of these assays/studies in relevant tissues, but also noted that the biological importance of such DNA lesions (i.e., as identified from these assays) in relation to mutagenicity is equivocal, therefore the fact that some studies of this type were not included is not crucial for the conclusion.

More specifically, the data available for evaluation of germ cell mutagenicity is extensive and includes studies covering bacterial and mammalian cell in vitro mutagenicity assays as well as in vivo mammalian mutagenicity assays and even some human data. Furthermore, according to the opinion, the data includes studies of sufficient reliability and relevance to allow a robust evaluation, especially in the perspective of the requirements of the CLP Regulation. In RAC's view, the data were sufficient to arrive at a robust conclusion without these assays/studies".

140. Consequently, the opinion concluded that there was enough reliable and relevant data from other tests to make a solid conclusion without those tests.

141. Therefore, the claim made in paragraph 56 of the IRR that the *in vivo* genotoxicity studies submitted by applicants are the least capable of revealing genotoxic potential is unfounded. In particular, the Requestors do not take into account the fact that the assessment was based on all available information, including that from scientific literature, and using a WoE approach.

2.c. Alleged genotoxic potential of one impurity (paragraphs 57 and 58 of the IRR)

142. In paragraphs 57 and 58 of the IRR, the Requestors refer to one of the impurities resulting from the glyphosate production process, namely glyphosine, which EFSA found to have potential for clastogenicity based on an in *vitro chromosomal aberration assay.* They argue that it should have been followed up by an *in vivo* test and classified - as allegedly done in other dossiers such as cypermetrin, isoflcypram and benfluralin – as a "critical area of concern" and not as a "data gap".

143. First, EFSA indeed noted that the impurity glyphosine showed a potential for clastogenicity in an *in vitro* chromosomal aberration assay that was not appropriately followed up *in vivo*. Both the assessment of toxicological relevance and its maximum content of this impurity were identified as a data gap. However, this impurity was present in some of the batches used in toxicity studies at a higher level than the one proposed in the reference specification. Therefore, EFSA identified this as an issue that could not be finalised and not as a critical area of concern.

144. Furthermore, it must be recalled that glyphosine has not been confirmed to have clastogenic properties, rather, based on the available studies carried out and submitted on glyphosine, a clastogenic potential could not be excluded. The implications of the data gap (related to the

genotoxic potential, specifically for clastogenicity) set by EFSA for glyphosine were carefully considered by risk managers as set out l on pages 4-5 of the Renewal Report. As noted in the Renewal Report, glyphosine was present in the batches of glyphosate tested in two in vivo micronucleus tests (an appropriate test to investigate clastogenicity) at levels of ~10 g/kg and of ~21 g/kg, respectively. Results of both in vivo micronucleus tests were negative, i.e. there was no evidence of genotoxicity. It should be noted that presence of a toxicologically relevant impurity is not an absolute ground for non-renewal of an active substance, if its content can be restricted to levels where it is demonstrated to be safe. Therefore, in order to address the uncertainty raised by EFSA, the Commission took a prudent approach to set a maximum limit of 3 g/kg for glyphosine in glyphosate as manufactured (as proposed by the AGG), which was considered as sufficiently protective by risk managers.

145. The Requestors also state, in paragraph 57 of the IRR, that the positive *in vitro* chromosomal aberration assay test should have been followed up by an *in vivo* test. The GRG and the AGG considered that the studies available on glyphosate that contained glyphosine were sufficient to address any concern ([127]). Moreover, the statement by the Requestors that an *in vivo* study would be needed is not supported since the experts concluded *"The majority of MS considered that this could be addressed by better in vitro chromosomal aberration studies (e.g. appropriate dose spacing for dose-response assessment, use of human lymphocytes). If this test would provide positive or inconclusive results, an in vivo study should be considered. It was noted that this impurity is not present in all the technical materials; however, since one reference specification is proposed for all technical materials, this data gap on the toxicological relevance will apply to all of them."* ([128]). In fact, the experts also acknowledged that some technical materials do not contain glyphosine, further supporting the conclusion by risk managers that the issue did not prevent renewal of approval of glyphosate.

146. Concerning the comparison made by the Requestors in paragraph 58 of the IRR with other active substances (cypermethrin, isoflucypram and benfluralin), it should be noted that each substance has its own characteristics and specificities that can thus lead to different assessments and conclusions. In those three cases the relevance of the impurity has been identified, but it was not possible to conclude on its maximum content. A detailed explanation of the differences is provided in EFSA and ECHA's "Technical and scientific assistance on the internal review" (as requested by the Commission) ([129]).

2.d. Conclusion (paragraphs 59 to 65 of the IRR)

147. In the overall conclusion to this sub-section, the Requestors summarise the claims raised in the preceding paragraphs and contend that the assessment conducted was not complete and not founded on the most reliable scientific data available, on the results of the most recent international research and on the principles of excellence, transparency and independence. They also point to a different approach taken in the assessment of genotoxicity for another active substance, chlopyriphos-methyl.

([127]) See page 246 of the Pesticide Peer Review TC 80 (14 – 25 November 2022), found in Part 3 of 6 of the Peer Review Report on Glyphosate (AIRV).
"Based on the available information, including the in vivo micronucleus studies with glyphosate containing (up to 21.2 g/kg), overall, the RMS considered not to induce chromosomal aberration in mammalian cells (in the presence or in the absence of metabolic activation). Based on the available information, the RMS considers that the impurity is not toxicologically relevant".

([128]) See pages 246-247 of the Pesticide Peer Review TC 80 (14 – 25 November 2022), found in Part 3 of 6 of the Peer Review Report on Glyphosate (AIRV).

([129]) See pages 59 and 60,
Available at: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2024.EN-8737.

148. However, as set out throughout this Section III.1.2, none of the arguments brought forward by the Requestors demonstrated a failure in the work of EFSA, ECHA or the Commission in reaching the conclusion that a concern for genotoxic potential could not be identified.

149. First, all pertinent studies on genotoxicity were evaluated as part of the hazard assessment undertaken in the context of the formal assessment of the proposal for harmonised classification and labelling in accordance with Regulation (EC) No 1272/2008 carried out by ECHA in parallel to the Peer Review, leading to the conclusions as delivered in the RAC Opinion 2022.

150. In the Peer Review, all available studies, both from the applicants and from publications, were duly considered and assessed for their relevance and reliability following a rigorous approach as detailed in the RAR; where needed additional information has been requested ([130]) and a dedicated expert consultation on all relevant endpoints (including the impact the identified deviations of the genotoxicity studies on glyphosate) took place (for further details please refer to Section III.1.2.b above).

151. Therefore, overall, the genotoxicity data package on glyphosate was considered extensive and sufficiently robust to reach proper conclusions on genotoxicity without the need for requesting further vertebrate studies and the WoE assessment conducted in the Peer Review was in line with the ECHA RAC Opinion 2022.

152. Second, the comparison with the assessment made for chlorpyrifos-methyl, made in paragraph 64 of the IRR, is not relevant. That assessment considered studies carried out by the applicants as well as from literature publications in the same way as done for glyphosate. However, the genotoxicity assessment for chlorpyrifos-methyl was itself related closely to that of chlorpyrifos for which the data package provided by the applicant was not as sufficiently extensive or robust as for glyphosate: *"the genotoxicity potential remained unclarified (positive findings from an in vitro chromosome aberration study and two in vitro unscheduled DNA synthesis assays; in vivo positive findings from open literature on chromosome aberration and on DNA damage caused through oxidative stress or by topoisomerase II inhibition which was considered a MIE for infant leukaemia* (EFSA statement on chlorpyrifos, 2019 ([131]). As regards chlorpyrifos-methyl, "*the available regulatory genotoxicity data set submitted for chlorpyrifos-methyl did not show any concern. The experts highlighted that very limited literature data were retrieved specifically for chlorpyrifos-methyl. Considering also the read-across discussion, most experts decided to precautionary apply to chlorpyrifos-methyl the same conclusions as for chlorpyrifos. Therefore, the experts concluded that the genotoxicity potential of chlorpyrifos-methyl remains as unclear as that of chlorpyrifos"* (EFSA statement on chlorpyrifos-methyl, 2019[132]). Therefore, comparing glyphosate to chlorpyrifos-methyl is misleading as the available database and findings are substantially different.

153. Third, with regards to the alleged breach of the precautionary principle due to an alleged failure to recognise the genotoxicity of glyphosate, the Commission recalls that the outcome of the assessment conducted by the AGG, ECHA and EFSA is clear, i.e. *"Glyphosate is unlikely to be genotoxic based on a WoE approach; this is in line with ECHA RAC*

([130]) See Reporting table (section 2) points 2(149), 2(151), 2(152), 2(153), 2(154), 2(155), 2(158), 2(161), 2(165), 2(169), 2(201), 2(202), 2(203), 2(204) and Reporting table identified following public comments (section 2) points 2(43), 2(44), 2(51).

([131]) EFSA (European Food Safety Authority), 2019. Statement on the available outcomes of the human health assessment in the context of the pesticides peer review of the active substance chlorpyrifos. EFSA Journal 2019;17(8):5809, 23 pp. https://doi.org/10.2903/j.efsa.2019.5809.

([132]) EFSA (European Food Safety Authority), 2019. Updated statement on the available outcomes of the human health assessment in the context of the pesticides peer review of the active substance chlorpyrifos-methyl. doi: 10.2903/j.efsa.2019.5908

assessment (ECHA, 2022)" ([133]) and there is no remaining scientific uncertainty that would justify recourse to the precautionary principle.

154. Furthermore, the ground is based on an erroneous interpretation of the precautionary principle. Even if there would have been scientific uncertainty as to the potential genotoxicity of glyphosate, that would not necessarily mean that the precautionary principle would have precluded the renewal of the approval of glyphosate.

155. The precautionary principle means that where there is uncertainty as to the existence or extent of risks, including risks to the environment, protective measures may be taken without having to wait until the reality and seriousness of those risks become fully apparent. Where it proves to be impossible to determine with certainty the existence or extent of the alleged risk, because the results of studies conducted are inconclusive, but the likelihood of real harm to the environment persists should the risk materialise, the precautionary principle justifies the adoption of restrictive measures ([134]).

156. The PPP Regulation is underpinned by the precautionary principle in order to ensure that active substances or products placed on the market do not adversely affect human or animal health or the environment ([135]). This includes in particular the approval and authorisation procedures put in place by the PPP Regulation for active substances and PPPs, which constitute an expression of the precautionary principle ([136]).

157. That being said, the precautionary principle only justifies the adoption of restrictive measures on the condition that they are not only non-discriminatory and objective, but also proportionate: this necessitates a careful, evidence-based examination of the identified (potential) risks and uncertainties and the formulation of a response that is proportionate to the level of such risks ([137]). Furthermore, from a scientific point of view "zero-risk" does not exist in practice and preventive measures cannot solely be based on hypothetical risks, based on simple assumptions that have not been scientifically verified ([138]). A preventive measure can only be taken if the risk, without its existence and scope having been fully demonstrated by conclusive scientific data, nevertheless appears sufficiently documented on the basis of the scientific data available at the time the decision was taken ([139]).

158. Under the PPP Regulation, this means that the precautionary principle does not imply an automatic or default stance against the approval of active substances (or the renewal thereof) in the face of scientific uncertainty. By contrast, it means that, following risk assessment, the Commission must assess how any identified risks or uncertainties can be managed effectively through the imposition of appropriate conditions and restrictions, ensuring these measures are sufficient to ensure that use of the active substance will fulfil the criteria set out in Article 4 of the PPP Regulation.

([133]) See page 11 of the EFSA Conclusion.

([134]) Judgment of the Court of 6 May 2021, *Bayer CropScience et Bayer v Commission*, C-499/18 P, EU:C:2021:367, para. 80.

([135]) Recital 8 and Article 1(4) of the PPP Regulation.

([136]) Judgment of the Court of 17 May 2018, *Bayer CropScience and Others v Commission*, T-429/13 et T-451/13, EU:T:2018:280, para. 108

([137]) Judgment of the General Court of 21 February 2024, *PAN Europe v Commission*, T-536/22, EU:T:2024:98, paras. 72-73, judgment of the General Court of 4 April 2019, *ClientEarth v Commission*, T-108/17, EU:T:2019:215, paras. 282 and 284.

([138]) Judgment of the General Court of 21 February 2024, *PAN Europe v Commission*, T-536/22, EU:T:2024:98, para 80.

([139]) Judgment of the General Court of 21 February 2024, *PAN Europe v Commission*, T-536/22, EU:T:2024:98, para. 82, judgment of the General Court of 17 March 2021, *FMC v Commission*, T-719/17, EU:T:2021:143, para. 73.

159. In conclusion, the AGG, ECHA and EFSA conducted a thorough assessment that found glyphosate not to be genotoxic (see Section II.2. a. above). While the Requestors disagree with the outcome of that assessment, none of the arguments brought forward cast doubt on the correctness of the assessment conducted. Therefore, the Reviewed Regulation fully complies with the procedural and substantive requirements of the PPP Regulation.

3. Alleged illegalities and manifest errors in the assessment of the carcinogenicity of glyphosate (paragraphs 66 to 100 of the IRR)

160. With this ground, the Requestors argue that the conclusion that glyphosate is not carcinogenic, as reported in the EFSA Conclusion which takes into account the RAC Opinion 2022, would be affected by manifest errors or assessment. The Requestors consider that the EFSA Conclusion relies on biased analyses diverging from OECD guidelines and ECHA's own guidance documents, minimising carcinogenicity findings in the studies provided for the renewal. As part of this claim, the Requestors provide in Annex 4 to the IRR an analysis of two experts that would further develop these points.

161. According to the Requestors, these alleged errors and shortcomings in the methodology of the assessment can be seen in the way ECHA dismissed evidence concerning a) keratoacanthomes (epidermis tumours), b) renal tumours, c) maline lymphoma and d) indications from human epidemiological studies. In the view of the Requestors, if these erros and shortcomings would have been avoided, the results of the of the assessment would have been that there is sufficient proof of the carcinogenicity of glyphosate ([140]).

162. Before going into these specific areas, the Commission makes two general points.

163. First, the Requestors' argument ignores the obligation from the CLP Regulation to weigh all of the available evidence in each case when assessing proposals for harmonsied classification and labelling for substances (including for active substances used in PPP as was the case for glyphosate) ([141]). A WoE assessment means that data is given different weight depending on factors such as the quality and consistency of the results. Also, the statement in the CLP Regulation that "*both positive and negative results shall be assembled together in a single weight of evidence determination*" (emphasis added) does not imply the need for a majority of studies supporting one or the other outcome. RAC is obliged to make an overall WoE analysis of the complete data set. In the case of glyphosate, some studies were awarded no weight, and were not included in the analysis ([142]). In addition to multiple animal studies, data from the epidemiology studies and genotoxicity studies were also considered in the WoE assessment. RAC concluded in its Opinion in 2022 that, despite some indications of carcinogenicity seen in some studies mainly in mice, the criteria for classification are not met when all the studies and findings are considered together. Thus, RAC reached the unequivocal conclusion that no classification for carcinogenicity is warranted.

164. Second, concerning the additional claims raised in Annex 4 to the IRR, the Commission notes that the Commission is only obliged to respond to points made in the body of the IRR.

([140]) Please note that this argument has already been addressed by ECHA in their responses to a report from HEAL, which has been published on its website in July 2022 https://echa.europa.eu/documents/10162/2082415/reply_glyphosate_heal_report_en.pdf/40ee075a-8b57-f524-9a82-b492a77a53f1?t=1656935695273.

([141]) See recital 33 and Article 9(3) of the CLP Regulation and Section 1.2 of Annex XI to the REACH Regulation and CLP Annex I (section 1.1.1.3) (both referred to in Art 9(3) of the CLP Regulation).

([142]) For example, two studies in mice which were negative for carcinogenicity were considered to be conducted with too low doses and "*did not comply with current standards*" (CA 5.5/022, 1988 and Report no. 80 10; CA 5.5/024, 1982 original report, revised 1992) and, therefore, were considered as unacceptable.

The annexes have a purely evidential and instrumental function and the Commission cannot be obliged to seek out and identify, in the annexes, possible additional grounds for internal review. Nonetheless, the additional claims raised in Annex 4 to the IRR have been addressed by EFSA and ECHA in their technical and scientific input provided at the request of the Commission to respond to the IRR ([143]).

A. Keratoacanthomes (paragraphs 70 to 82 of the IRR)

165. In paragraph 70 of the IRR, the Requestors claim that trend analyses (on groups of rats subjected to low, medium or high doses of glyphosate compared to the control group), allegedly demonstrating the capacity of glyphosate to increase the incidence of keratoacanthomes, were disregarded by ECHA.

166. However, ECHA assessed all available evidence and all statistical analyses, including trend analyses, were presented transparently in the RAC Opinion 2022 for each tumour type examined as part of the assessment process. These analyses were essential components of the thorough review of the findings.

167. In fact, some of the outcomes arising from the statistical analyses depend on the test used i.e. pairwise comparison (where incidences in the control group are compared with those of an individual treatment group) or trend tests (which evaluate statistical significance by integrating the incidences in the control and all treated group) and whether those tests are one-sided (clear expectation of the direction of the effect) ([144]) or two-sided (if the direction of the effect is not specified or could be in either direction) ([145]).

168. With regards to statistical analyses on glyphosate it was found that:

- None of the tumours referred to in the IRR were statistically significant using pairwise comparison with two-sided testing;
- Some were statistically significant following two-sided testing using the trend test;
- Additional findings were also statistically significant when one-sided pairwise comparisons or trend tests were employed.

These considerations were included in the assessment.

169. In paragraphs 71 and 72 of the IRR, the Requestors assert that ECHA used a strategy to dismiss the conclusions that result from a trend analysis, namely by considering trend studies as not necessarily corroborated by pair comparisons, which in the Requestors' view is in contradiction with OECD guidelines. In their view, the guidelines state that trend studies and pair comparisons, according to the United States Environment Protection Agency ('EPA'), serve as alternative methods for establishing statistical significance. They also claim that the way in which ECHA did pairwise comparisons was not in line with correct statistical methods.

([143]) See pages 32 to 42 of the document available at https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2024.EN-8737

([144]) For example, in pairwise comparisons, it can be tested whether one group is significantly higher than another (e.g., Group A > Group B), without considering the possibility of Group B being higher than Group A. In trend tests, it checks if there is a directional trend across ordered groups or time points (e.g., increasing trend).

([145]) This approach tests for differences or trends in both directions. In pairwise comparisons, it assesses if there is any significant difference between groups A and B, without assuming a specific direction (e.g., Group A ≠ Group B). In trend tests, it evaluates whether there is any trend, regardless of its direction (e.g., any monotonic trend, whether increasing or decreasing).

170. It is correct that both types of tests (trend and pair-wise testing) are described in OECD Guidance Document 116 ([146]), including some of the benefits and disadvantages of each approach.

171. The CLH Report ([147]), as well as the RAC Opinion 2022, includes the results for both one- and two-sided testing from both trend as well as pairwise comparisons of the incidences of tumours. In the CLH, the data from the Portier (2020) paper ([148]) for the one-sided testing from both types of tests was included alongside the two-sided data in the tables describing each tumour type. The fact that (according to OECD 116) a trend test is more powerful was taken into account in the analysis.

172. Crump et al. (2020) explained that there are many studies on glyphosate's potential to cause cancer, with each study looking at numerous tumour types in both male and female rodents. This large number of tests increases the likelihood of finding significant results by chance. Crump et al. used a statistical method to show that some of the significant tumour findings could be random and stressed the need to carefully assess these findings for real biological significance. Portier (2020) also analysed the same data but did not account for the chance of false positives due to multiple testing, as Crump did. Portier's analysis used a different statistical approach, which RAC considered, but it was noted that ignoring the multiple testing issue could lead to misleading conclusions.

173. OECD guidelines emphasise that statistical significance alone does not determine the biological importance of findings. In the CLH Report and RAC Opinion 2022, the significant trends found by Portier were included, but it was recognised that Portier's methods differed from those used in the original studies and the analysis done by the data submitter.

174. Overall, the point is that while there are statistically significant tumour findings in studies on glyphosate, these need to be interpreted with caution. The Requestors' claim that these findings should be considered in regulatory assessments, and the response highlights that these assessments have indeed considered the potential for chance findings and differences in statistical methods.

175. The opinion states that "*RAC notes that the analysis made by Crump et al. (2020, B.6.5.18.1) shows that statistically significant effects on tumour incidences should be carefully evaluated for biological relevance due to the high number of studies assessed, as chance findings may occur*" ([149]). The point was elaborated in detail in the CLH report, and summarised in the opinion as follows: "*Due to the IARC conclusion, experts have investigated why there are different conclusions from different investigating bodies (Crump et al., 2020, B.6.5.18.1; Portier, 2020, B.6.5.18.2).*

Crump et al. (2020, B.6.5.18.1) pointed out that the animal carcinogenicity data on glyphosate are extensive (≥ 15 long term rodent oral bioassays of glyphosate identified by US EPA (2016), EFSA (2016) and IARC (2015). Each bioassay was conducted in both sexes, with each sex potentially having 40-60 unique tumour types, resulting in over 1000 potential statistical tests, which could result in many statistically significant ($p \leq 0.05$) tumours by chance alone – approximately 5%. Crump et al. (2020, B.6.5.18.1) further assessed the probability of false positives using a modification of the permutation approach of Farrar

([146]) Guidance Document 116 on the Conduct and Design of Chronic Toxicity and Carcinogenicity Studies, Supporting Test Guidelines 451, 452 and 453 https://doi.org/10.1787/9789264221475-en

([147]) https://echa.europa.eu/registry-of-clh-intentions-until-outcome/-/dislist/details/0b0236e185e41a77.

([148]) The author has disclosed that he has been paid to provide expert testimony for litigation on the carcinogenicity of glyphosate.

(149) See pages 65, 72 of the RAC Opinion.

and Crump (1988 and 1990). The analysis made by Crump et al. (2020, B.6.5.18.1) showed that statistically significant effects on tumour incidences should be carefully evaluated for biological relevance as chance findings may occur.

Portier (2020, B.6.5.18.2) also provided an additional revised statistical evaluation and trend test analyses of relevant tumour types reported in the carcinogenicity studies but did not take into account the chance effect due to multiple testing as pointed out by Crump et al. (2020, B.6.5.18.1). Furthermore, as indicated in the OECD Guidance document 116, statistical significance is only part of the interpretation of the biological importance of a particular finding. In the CLH dossier, as well as in the current RAC assessment, the tumour types showing statistically significant trends in the analysis by Portier (2020, B.6.5.18.2) were taken into consideration in the assessment of cancer types. One of the differences between the study by Portier (2020, B.6.5.18.2) and the analysis by the DS was that Portier used 1-sided testing with a significance level of 0.05, whereas in the original study reports and the DS analysis 2-sided testing was applied with a significance level of 0.05 (which is equivalent to 1-sided testing using a significance level of 0.025)" ([150]).

176. Therefore, the analysis of the statistical testing was part of the thorough analysis of the data conducted by RAC for its opinion in 2022, Statistical analyses formed one part of the RAC assessment for biological significance.

177. RAC has also noted that when using trend tests, significant trends are in some cases related to smaller increases in tumours only reported in the high dose group with no or low incidences in the control group. In these cases, provided the findings were not significant in pairwise testing, the strength of the evidence was considered to be weak.

178. There is no indication in OECD Guidance Document 116 that only one or the other type of statistical analysis should exclusively be used (as further explained below). An objective analysis should not favour using a methodology which drives towards a pre-determined conclusion but should consider all the relevant factors. Hence although RAC considered the results from trend tests in their analysis, RAC did not exclusively rely on these results. The analyses conducted were consistent with the requirement in CLP in relation to applying a WoE approach (Annex I, 1.1.1.3 and Article 9(3)), as well as OECD Guidance Document 116.

179. The text from the paragraph from OECD Guidance Document 116, quoted at the end of paragraph 72 of the IRR, continues as follows: "*A statistically significant response may or may not be biologically significant and vice versa. The selection of a significance level is a policy choice based on a trade-off between the risks of false positives and false negatives. A significance level of greater or less than 5% (the most common significance level) is examined to see if it confirms other scientific information. When the assessment departs from a simple 5% level, this should be highlighted in the risk characterization. A two-tailed test or a one-tailed test may be used. In either case a rationale is provided*.". The focus of the assessment carried out by RAC was on determining whether each finding was biologically significant.

180. In paragraphs 73 to 77 of the IRR, the Requestors delve into the distinction between unilateral pair comparison tests (aiming at testing one scenario: i.e. the increase in cancer cases) and bilateral tests (aiming at testing two scenarios: i.e. increase or decrease in cancer cases), emphasising the marginal pertinence of the latter in the context of carcinogenicity. In fact, in order to contest the use of bilateral tests made in the assessment for glyphosate, they assert that bilateral tests 1) render the detection of statistically significant association,

(150) See pages 48-49 of the RAC Opinion.

twice as difficult and 2) are devoid of any practical value, given the absence in glyphosate of a protective effect against cancer (i.e. no decrease cases).

181. However, according to OECD Guidance Document 116 ([151]) "*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. Regulatory authorities may have specific opinions. For instance, the US EPA (2005) notes that either "a two tailed test or a one-tailed test may be used*" (emphasis added). Therefore, in accordance with OECD Guidance Document 116, it is also acceptable to conduct either one or two tailed tests.

182. As quoted by the Requestors themselves, OECD Guidance Document 116 states that "*The statistical methods most appropriate for the analysis of results, given the experimental design and objectives, should be established before starting the study*". The starting point for the analyses is thus the method chosen by the parties compiling the original study report.

183. The approach to the statistical analyses by the dossier submitter (i.e. Sweden on behalf of the AGG) is explained on page 257 of the CLH Report ([152]), as follows: "*The statistical analyses provided by AGG 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 AGG own statistical analysis. However, both one- or two-sided significance can be calculated, depending on the hypothesis to test. OECD Guidance Document 116 stipulates "The choice of whether to use a one- or two-sided test should be made at the design rather than the analysis stage. A two-sided statistical hypothesis test tests for a difference from the negative control (in a pairwise comparison) in either direction. A one-sided comparison tests for a difference in only one pre-specified direction, but as a consequence has more power. 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*". In the AGG overall analysis on the tumour relevance, two-sided testing was applied as this is in line with how the statistical analysis was established in the study protocols of the available carcinogenicity studies".

184. The RAC Opinion in 2022 also transparently summarised the approach to statistical analyses used "*The main statistical methods used in the animal studies were the Fisher's exact test for pairwise comparisons and the Cochran-Armitage trend test, and in this opinion these two methods are referred to unless stated otherwise. In their detailed assessment of findings, the DS repeated both the pairwise and trend test statistical calculations for the findings from relevant studies (eight studies in rats and five studies in mice; for details, see below). In addition, for one study in mice (CA 5.5/016, 2001), a Peto-analysis was performed for the induction of malignant lymphomas*." ([153]).

185. Therefore, contrary to the Requestors' claim, the dossier submitter and RAC did not merely consider the statistical analyses conducted in the study report, but as already explained above, transparently compiled and took into account the various alternative approaches to statistical analysis for each tumour type, including those indicated in the publication by Portier (2020). This clearly does not reflect "blind confidence" of authorities in the choice of statistical methods used by the applicants, as claimed by the Requestors.

([151]) § 384, p 133.
([152]) https://echa.europa.eu/registry-of-clh-intentions-until-outcome/-/dislist/details/0b0236e185e41a77.
([153]) Page 48 of the RAC Opinion, under "Summary of the Dossier Submitters Proposal".

186. The specific tests used are those described in OECD Guidance Document 116 under the heading 4.15 "*Standard (simple) statistical analysis of qualitative data*", which include the Fisher exact test and the Cochran-Armitage trend test. The Peto test was used in one (2001) study in mice. As explained above, the dossier submitter and RAC went beyond what was included in the original study reports by also providing results from additional testing of the data (including from one- and two-sided testing using the standard trend tests and pairwise testing referred to above).

187. The primary information used in developing a RAC Opinion stems from the CLH Report on the respective substance as well as the comments received during the consultation of the CLH report. From the comments received during the consultation, it is clear that not all statisticians agree with the assertion that, since glyphosate is not expected to be a protective treatment against cancer, the use of the two-sided statistical test is incomprehensible.

188. According to some comments provided by statisticians on the CLH Report ([154]) ("Response to comments document" or "RCOM"), some concerns on the use of one-sided significance levels were raised as "*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*".

189. The comments on the CLH Report also pointed to the findings of Crump et al. (2020), in which it is stated, after analysing ten of the rodent carcinogenicity studies for positive and negative dose-response trends using the same statistical trend test, that more evidence for negative dose-response trends rather than positive were found (marginally) ([155]). The focus of the analyses in the CLH report as well as RAC was on the findings indicating increased tumours, and these were analysed in detail. Taking into account whether there are increasing or decreasing trends in tumour incidences is also part of this analysis, to ensure that potential false positive as well as false negative findings are appropriately addressed, and their biological relevance is established.

190. In paragraph 78 of the IRR, the Requestors claim that ECHA made a third methodological error in deciding not to take into account results from the highest dose group of rats. The Requestors believe the approach was biased and contrary to OECD Guidance Document 116, which they consider requires substances to be tested at three doses, including a high dose, and that the results related to the highest dose must be taken into account.

191. However, RAC considered the results of all studies and concluded that the findings are insufficient for classification, in particular since the increased incidences above controls were only observed at very high doses (>= 940 mg/kg/d) ([156]) except in one study (out of six) where increases were seen at intermediate doses. In two studies no increases were seen at any dose, despite the use of a high highest dose. The RAC Opinion clearly sets out the reasoning for the approach taken and the conclusion reached ([157]). It is thus clear that the results at high doses were not dismissed, but rather the findings in the studies were considered in a WoE approach "*Based on the weight of the evidence, RAC considers that the increase in skin keratoacanthomas only reported in male rats is not of sufficient relevance for classification for carcinogenicity" ([158]).*

192. In paragraphs 79-82 of the IRR, the Requestors claim that ECHA went against its own guidance by diminishing the importance of keratoacanthomas in male rats, based on a single

([154]) See page 17, comment 21 to the CLH report https://echa.europa.eu/documents/10162/8f8b6a87-8bd8-3cdd-0f70-587fbfb41beb

([155]) See page 18, comment 21 to the CLH report: "*more tumor types showing significant decreases in tumor rates with increasing glyphosate levels than there were showing significant increases*".

([156]) Equivalent to over 65 g/d for an average human.

([157]) See page 64 of the RAC Opinion.

([158]) See page 62 of the RAC Opinion.

study that supposedly provided a reliable historical monitoring database, arguing that these were not observed in female rats nor in mice and that such tumours are common in this rat species.

193. However, the skin keratoacanthoma observations in the studies referred to by Portier (2020) were not statistically significant by either pairwise comparison or by trend test (two-sided testing), but Portier (2020) found a statistically significant trend following one-sided trend testing. No skin keratoacanthoma findings were seen in two studies. RAC noted in its Opinion ([159]) that skin keratoacanthoma is a benign tumour which is shown to be rather common in aged male rats and in fact were only reported in male rats (and not in female rats nor in male or female mice). Furthermore, no malignant squamous cell carcinomas were reported. In humans, this type of benign skin tumour is associated with multiple exposure to sunlight, whereas in rats, which are most likely only exposed to artificial light, the cause of skin keratoacanthomas is unknown. RAC concluded that the increase in skin keratoacanthomas only reported in male rats is not of sufficient relevance for classification for carcinogenicity. A more detailed analysis of the skin keratoacanthoma findings from this and other studies where this was observed is in the RAC Opinion in 2022 ([160]).

194. Moreover, the single study referred to by the Requestors (Zwicker et al, 1992) is not cited as historical control data (HCD) for the tumour type, as claimed (the actual incidences in the study were not referred to either in the RAC Opinion 2022 or in the CLH report). Rather, the published paper by Zwicker et al. provides evidence that the tumour type is rather common in aged male rats. The paper itself notes that (in terms of skin neoplasms in aged Sprague Dawley rats, the topic of the article) "*Keratoacanthoma was the most frequent epithelial neoplasm in males*". This is an additional factor appropriately taken into account by RAC in the assessment and consideration of the timing of tumour appearance was part of assessing this consideration. The differences in the incidences in the studies assessed between male and female rats reflect the differences seen in the article by Zwicker et al (1992).

195. Indeed, as stated by the Requestors, the relevant OECD guidelines emphasise that data from the concurrent control group (i.e. the study itself) should always be preferred to HCD. In the RAC Opinion in 2022, for each finding, RAC notes the historical control data, but the emphasis was placed on comparisons with the concurrent control. Therefore, the argument of the Requestors is unfounded since the study by Zwicker at al. was not, as they claim, used to provide HCD.

B. <u>Kidney tumours (paragraphs 83 to 88 of the IRR)</u>

196. In paragraphs 83 and 84 of the IRR, the Requestors argue that ECHA dismissed the results of three mice studies (out of a total of five) indicating a statistically significant rise in kidney tumours in males, on the basis of alleged inaccurate assertions, namely that the findings are not supported by historical control data (HCD) on mice for two of those studies and that the historical monitoring data are not sufficient to draw conclusions for the third one.

197. The claim is inaccurate: the RAC Opinion in 2022 did not state that HCD did not support the findings. That Opinion notes ([161]) that HCD were not available for one study, in one study the findings were slightly above the HCD and in a third study the findings were within the HCD range.

198. The ambiguity and lack of clarity in the Requestors' statement appear to be centred around the study involving Swiss mice. However, the RAC Opinion in 2022 at page 67 states that

([159]) See page 64, https://echa.europa.eu/documents/10162/5702e99d-d503-f154-226f-d8ab070ac47a.
([160]) See page 64 of the RAC Opinion.
([161]) See page 67 of the RAC Opinion.

"*Spontaneous control incidences for Swiss male mice included for the CA 5.5/016 (2001) study were based on eight studies performed between 1996 and 2002, with a mean of 2.0% and a range of 0 – 6%. The increased incidence of renal tubular adenomas in the CA 5.5/016 (2001) study was within the HCD and is therefore considered incidental and not related to glyphosate exposure.*".

199. In paragraph 85 of the IRR, the Requestors contest the statement in the RAC Opinion in 2022 concerning the absence of evidence for a progression to malignancy. They claim that this statement not only is contrary to the OECD Guidelines (which simply require indications, not evidence) and that the potential for progression of this type of tumour from adenoma to carcinoma stage would be well known. Additionally, they contest the short duration of the studies not allowing to draw conclusions on the absence of such progression.

200. In this regard, the Commission notes that page 67 of the RAC Opinion in 2022 states that "*differentiation between tubular cell adenoma and tubular cell carcinoma is not always clearly apparent and both lesions are derived from the same cell type. Accordingly, it is the combined incidences that have been used in the statistical analysis.*". The findings were thus thoroughly considered by RAC and the study durations were all within those prescribed in the OECD Guidelines for mice (18 or 24 months).

201. In paragraph 86 of the IRR, the Requestors claim that ECHA excluded results related to high dose administration on the grounds that these doses are too high and exceed the limit dose of 1 g/kg. However, RAC did not dismiss the tumour findings at doses above 1000 mg/kg bw/day, but the findings at the very high doses (above 4000 mg/kg bw/d) ([162]) were given lower weight, for the reasons explained in the Opinion. In particular, RAC notes on page 67 (in relation to the kidney tumours) that in two studies, kidney tumors in mice were only seen at very high doses of glyphosate (over 4000 mg/kg bw/d – which would correspond to over 300 g of glyphosate per day ingested by humans), which also caused significant weight loss. According to the relevant guideline, the highest dose in carcinogenicity studies should identify toxic effects without causing severe harm. Therefore, RAC gave less importance to these findings due to the excessive dosage and considers the relevance of these high-dose results to humans to be low.

202. In the same vein, the dossier submitted already noted in the RCOM ([163]) that the OECD TG 453 states 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*". Furthermore, paragraph 117 of OECD Guidance Document 116 states that "*As indicated in the Test Guidelines, a top dose not exceeding 1000 mg/kg body weight/day may apply except when human exposure indicates the need for a higher dose level to be used*". Thus, giving less weight to doses at or greater than 1000 mg/kg bw/day for glyphosate is consistent with the guideline as the exposure to humans is far below this level as it cannot reasonably be expected that an average human would consume over 70 g of glyphosate per day for prolonged periods. In addition, this value exceeds the acceptable daily intake (ADI) set as a result of the assessment by more than three orders of magnitude, which also indicates that such high doses are clearly not safe and are expected to produce significant (unspecific) adverse effects.

203. In paragraph 87 of the IRR, the Requestors assert, against ECHA's statement on the absence of plausible explanation for the occurrence of such tumours, that the genotoxic potential of glyphosate and its ability to produce oxidative stress would be the evidence of emerging

([162]) Equivalent to above 280 g/d for an average human.
([163]) See page 38 of the response to comments document (RCOM) https://echa.europa.eu/documents/10162/8f8b6a87-8bd8-3cdd-0f70-587fbfb41beb

tumours, as demonstrated in studies such as Gao et al. (2019) which showed glyphosate causing oxidative stress in kidneys of male mice.

204. However, in the context of the CLP criteria, the primary source of evidence to inform on classification is enumeration of tumours in animal studies and determination of their level of statistical significance. Many other factors can be taken into consideration including mode of action/mechanistic considerations. Oxidative stress is a mechanism that can lead to tumour formation and therefore falls into the latter category as a factor that can be taken into consideration when assessing tumour incidences. RAC's assessment is based on a large number of scientific studies designed to examine the hazardous properties of glyphosate, including whether it causes cancer. Every piece of available evidence underwent careful scrutiny to reach a conclusion. No significant findings were disregarded. Tumour occurrences in the accessible studies were thoroughly analysed, leading to the determination that there was insufficient evidence to substantiate the claim that glyphosate induces tumours ([164]).

205. In the absence of clear evidence of tumours linked to glyphosate, evidence that glyphosate causes oxidative stress is not relevant for the conclusion. Findings of oxidative stress in one single study are not on their own sufficient for classification. In particular, basing conclusions solely on the potential mechanisms from one study is not reliable without solid evidence of cancer-causing effects from other studies. In any case, the mechanistic data from the Gao et al (2019) study was included in the CLH Report[165] and considered in the RAC Opinion 2022 ([166]).

206. In paragraph 88 of the IRR, the Requestors state that ECHA noted that differences in gender impact remain unexplained but consider that such lack of explanation is not such as to diminish the relevance of positive results, even if differentiated between the sexes.

207. However, RAC did not diminish kidney findings based on differences between sexes, rather RAC explained that *"Furthermore, the apparent sex differences in response remain unexplained and this lowers the consistency of the reported findings in mice as well as increasing the inconsistency in tumour incidences between the mouse carcinogenicity studies. The increased tumour incidences observed are therefore considered to be of equivocal biological relevance*."

C. Malignant lymphoma (paragraphs 89 to 95 of the IRR)

208. The Requestors claim that ECHA wrongly dismissed positive findings of malignant lymphomas in mice, although these were statistically significant.

209. In paragraph 91 of the IRR, the Requestors criticise the methods of statistical analyses used, referring to paragraph 71 of the IRR, to which the Commission has already responded above.

210. In paragraph 92 of the IRR, the Requestors contend that ECHA's statement that the HCD do not corroborate the results on the incidence of cases of malignant lymphoma due to glyphosate exposure is not correct and refer to Annex 4 of the IRR as evidence that HCD for two studies (Sugimoto, K., 1997 and Kumar D.P.S., 2001 reported under CA 5.5/018-019 and CA 5.5/016 in the RAC Opinion in 2022) do corroborate the findings, while none exist for a third (Wood, E., et al., 2009 reported under CA 5.5/012-015 in the RAC Opinion in 2022).

([164]) This issue has been addressed and published on the ECHA website https://echa.europa.eu/documents/10162/11035849/ECHA_EFSA_reply_NGOs.pdf/7e7b03bc-b2f1-8949-b6f6-da9feb1f7292?t=1696573111452

([165]) https://echa.europa.eu/registry-of-clh-intentions-until-outcome/-/dislist/details/0b0236e185e41a77

([166]) See pages 43-44 and 74-75 of the RAC Opinion.

211. It is not clear on what basis the Requestors make this statement since it is not stated in the RAC Opinion in 2022 that the HCD data do not support the findings. That Opinion states that "*the maximum incidences in the majority of the studies were considered to be within the historical control range for the CD-1 mice, although adequate HCD were not available for all studies*". The opinion clearly sets out the view with regards to HCD and the findings in those studies. It is noted in the RAC Opinion in 2022 that *"the tumour incidence of 12% at the high dose of 4348 mg/kg bw/d (a very high dose) in the study by CA 5.5/018-019 (1997) was within the historical control range for Crj:CD-1 male mice obtained from seven studies, since the range was 3.8% to 19.2% with a mean of 7%".* The opinion also noted, however, that "*six of the seven studies had a control incidence ≤ 6% leading to a range of 3.8% to 6% with a mean of 4.92%. Therefore, when taking into account HCD from the six studies the incidences of malignant lymphoma in male mice exceeded the HCD*" ([167]).

212. Furthermore, it is reported that *"the 10% incidence in the study CA 5.5/012-015 (2009) was borderline significant in the pairwise Fisher's exact test. However, the incidence of lymphomas in controls was very low and there were limited HCD available from the laboratory. In a trend test (1- and 2-sided), a statistically significant increase was reported for both."*

213. This is also the case for Swiss albino mice, where it is stated in the opinion that "*In Swiss albino mice (CA 5.5/016, 2001), the incidence of malignant lymphoma in male and female mice at the top dose was 38% and 50%, respectively. However, the high background incidence in this strain must be taken into consideration. The HCD in males had a mean of 15.8% with a range of 6 – 30% and in females a mean of 33% with a range of 14 – 58%. Thus, the incidences of malignant lymphomas were above the upper range of the HCD for the male mice*." (see page 71 of the RAC Opinion 2022).

214. Therefore, the historical control data are clearly and accurately reported in the RAC Opinion 2022.

215. In paragraph 93 of the IRR, the Requestors criticise the assessment by RAC that the increases were limited to high doses. According to the Requestors, apart from being irrelevant, this statement would also be incorrect since in two studies effects were observed at other doses.

216. Even though it is unclear which statement in which RAC Opinion 2022 the Requestors are referring to, it is assumed that the statement refers to the findings in study CA 5.5/012-015 (2009) and CA 5.5/016 (2001), where the incidences at the intermediate doses were intermediate between those in the controls and the high dose groups. The findings in the 2009 study at the intermediate doses were low (1/51 = 2% at the low dose and 2/51 = 4% at the mid-dose). In the 2001 study, the findings at the low dose and mid-dose were 15/50 = 30% and 16/50 = 32%, respectively, and were observed against a high background in the male controls (10/20 = 50%).

217. The statistical significance of malignant lymphomas observed in these studies were noted by the dossier submitter to be very much dependent on the statistical method used for analysing the data. In the 2009 study, the findings were statistically significant when the trend test was applied (either one- and two-sided). They were also not statistically significant at the high dose when a pairwise comparison was performed (but were statistically significant with a one-sided pairwise test (Portier, 2020)). The increased incidence in the 2001 study was not confirmed either by the trend test (one- or two-sided) or by a two-sided pairwise test but only when using a one-sided pairwise test and one-sided Peto-analysis. The increased incidence in the 2001 was against a high background incidence.

(167) See page 71 of the RAC Opinion.

218. Therefore, contrary to the claim by the Requestors, RAC has reviewed all of the data and in a WoE assessment concludes that the reported incidences of malignant lymphoma in CD-1 mice and Swiss mice is not considered related to glyphosate exposure. A more detailed analysis of the malignant lymphoma findings from these and other studies where this tumour type was observed is in the RAC Opinion ([168]).

219. In paragraph 94 of the IRR, the Requestors argue that "*ECHA observes that lymphoma increases are not consistent from one sex to another. However, as explained above (see paragraph 81 above), it is apparent from ECHA's own guidance document that this cannot preclude a finding of carcinogenicity*".

220. It is indeed correct that findings in the two different sexes were not consistent. The incidences of the findings in control females were equivalent to those at the highest dose in males in two studies and more than two-fold those at the highest dose in the remaining three studies. There were no significant findings lymphoma findings in females in any of the studies.

221. The Commission understands that the Requestors refer to ECHA's Guidance on the application of the CLP Regulation ([169]). However, in the version available (2017) at the time of the assessment and also in the latest version (2024) the relevant section also states that *"Effects seen only in one sex in a test species may be less convincing than effects seen in both sexes, unless there is a clear patho-physiological difference consistent with the mode of action to explain the single sex response. However, there is no requirement for a mechanistic understanding of tumour induction in order to use these findings to support classification* ([170]). Therefore, the claim by the Requestors is not substantiated since the analysis conducted by RAC was completely consistent with the applicable CLP Guidance.

222. In paragraph 95 of the IRR, the Requestors claim that "*ECHA considers that the possible role of oncogenic viruses cannot be ignored. For the reasons set out in detail in the experts' analysis, this claim is unfounded and is based on the abusive extrapolation of a single article*". However, the quote is from the summary of the proposal of the dossier submitter. RAC does not refer to the role of oncogenic viruses in its assessment.

D. <u>Human epidemiological studies (paragraphs 96 and 97 of the IRR)</u>

223. In paragraphs 96 and 97 of the IRR, the Requestors quote a part of the RAC Opinion 2022 mentioning that "*a weak association can be seen for persons with a relatively high exposure (third tertile) and acute myeloid leukaemia and non-Hodgkin's Lymphoma (p. 54)*" and "*Overall, available epidemiological case-control studies, reviews, re-analyses and meta-analyses show weak statistically significant associations between exposure to glyphosate-based herbicide and findings of cancer, especially non-Hodgkin's Lymphoma (p. 91)*". The Requestors argue that these reflect the definition of "*limited evidence of carcinogenicity*" and therefore should have led to at least classification as carcinogenic category 2.

224. However, the quote from the RAC Opinion 2022 is from the summary of the dossier submitter's proposal and it is taken out of context. The relevant paragraph in page 54 of the RAC Opinion 2022 states: "*Andreotti et al. (2018) showed that, based on the data from the AHS cohort, no overall association between exposure to glyphosate-based herbicides and cancer was reported. However, a weak association can be seen for persons with a relatively*

([168]) Under the heading "Malignant lymphoma" at page 69 of the opinion, https://echa.europa.eu/documents/10162/5702e99d-d503-f154-226f-d8ab070ac47a

([169]) Guidance on the Application of Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures https://echa.europa.eu/documents/10162/2324906/clp_en.pdf/58b5dc6d-ac2a-4910-9702-e9e1f5051cc5

([170]) See pages 385-386 of the Guidance.

high exposure (third tertile) and acute myeloid leukaemia and non-Hodgkin's Lymphoma after a 20-year lag time (time between exposure and tumour development). These data also concern a very small research population of n=15 and n=8 cases, respectively, and therefore the DS considered these findings to be of questionable value. However, the DS noted the finding of a possible association with acute myeloid leukaemia should be looked at carefully in future updates on the AHS data. The DS, however, noted that a high number of cancer sites were analysed so there was the possibility of statistical findings by chance and that acute myeloid leukaemia was not observed in any of the other epidemiological studies with glyphosate". Therefore, the RAC Opinion reflects that the dossier submitter reported a weak association with acute myeloid leukaemia and non-Hodgkin's lymphoma at high exposure levels but that these findings involved a very small sample size and are of questionable value, and that the dossier submitter suggests future updates of the AHS data should examine carefully the possible association with acute myeloid leukaemia, but acknowledges the potential for statistical anomalies and notes this association was not seen in other studies.

225. However, following their own assessment, RAC concluded that "*A causal relationship with exposure to glyphosate-based herbicide can thus not be confirmed by RAC. More specifically, this is due to a number of factors – i.a. the weak associations which were only significant when certain statistical tests were applied, small studies with low number of exposed cases, the probability of recall bias for previous exposure (duration and dose) especially in the case-control studies, selection bias, the lack of biomonitoring data, frequently not adjusting for confounding factors such as co-exposure to other pesticides and risk estimates often getting lower when more comprehensive adjustment was applied, the presence of a toxic co-formulant (POE-tallowamine), and the changes in the definitions of non-Hodgkin's Lymphoma/other cancers over the years*" ([171]). The reasons justifying these conclusions are described in considerable detail in the opinion (and by the dossier submitter in the CLH Dossier). It was only after careful consideration of all the information that RAC concluded at page 91 of the Opinion 2022 that "*No association between exposure to glyphosate-based herbicides and incidences of non-Hodgkin's Lymphoma was observed in the only robust cohort study available*".

226. In addition, RAC indicated in the Opinion 2022 that "*The findings from the epidemiology studies are used in a weight of evidence approach together with the findings in animal studies*".

E. Conclusions (paragraphs 98 to 100 of the IRR)

227. In paragraph 98 of the IRR, the Requestors criticise the assessment by the AGG and ECHA (RAC) as being biased and incorrect. They recall, firstly, their earlier claims of an alleged arbitrary and unjustifiable exclusion of high dose results and the use of inappropriate statistical analysis methods; secondly, the alleged absence of any reliable study to assess the carcinogenicity of glyphosate found "reliable without restriction", thirdly, the allegedly biased assessment of epidemiological studies which should have led to a classification as carcinogenic category 2, fourthly, the allegedly systematic dismissal of literature studies, and finally, claim that ECHA itself would have expressed doubts as to the absence of genotoxicity due to the absence of in vivo comet tests and the examination of tissues other than spinal cord.

228. The Commission has already responded to all of these claims in the preceding Secntion III1. - Subsection 3, except for two additional claims related to the absence of a carcinogenicity study recognised as "reliable without restriction" and the alleged doubts expressed by ECHA

([171]) See page 91 of the RAC Opinion.

in relation to genotoxicity due to the absence of in vivo comet tests and the examination of tissues other than spinal cord.

229. As to the first new claim, it is indeed correct that the AGG, ECHA and EFSA found none of the 11 acceptable ([172]) carcinogenicity studies (6 in rats and 5 in mice) as 'reliable without restriction'. However, all 11 studies were evaluated and were considered to have only minor deviations from the test guidelines (hence reliable with restrictions) and were considered sufficiently robust for the assessment. Moreover, an approach requiring only studies considered as 'reliable without restriction' to be decisive, would significantly limit the available information for the assessment of toxicity and would substantially weaken the regulatory process concerning chemical substances and mixtures within the European Union and beyond, because the vast majority of the available body of evidence would then not contribute to the overall WoE underpinning the outcome of the risk assessment.

230. As regards the second new claim, it should be noted that the process established by the CLP Regulation relies on the assessment of available data – *i.e.* there is no mechanism to generate additional information. In addition, the statements quoted from the RAC Opinion relate to the Comet assay and Transgenic rodent (TGR) somatic and germ cell gene mutation assays, which are two particular assays among many other lines of evidence potentially informing a classification. The RAC Opinion 2022 notes the absence of these assays/studies in relevant tissues, but also noted that the biological importance of such DNA lesions (i.e., as identified from these assays) in relation to mutagenicity is equivocal. Therefore, the absence of certain studies of this nature does not significantly impact the conclusion. Furthermore, the data available for evaluation of germ cell mutagenicity was extensive and includes studies covering bacterial and mammalian cell *in vitro* mutagenicity assays as well as *in vivo* mammalian mutagenicity assays and even some human data. According to the RAC Opinion 2022, the data include studies of sufficient reliability and relevance to allow a robust evaluation, especially in the perspective of the requirements of the CLP Regulation. In RAC's view, the data were sufficient to arrive at a robust conclusion without these assays/studies ([173]). Further information is provided in Section III.1 - Subsection 2.b above, in response to paragraphs 53-56 of the IRR.

231. The claim in paragraph 99 of the IRR that the study by the Ramazzini Institute would have reinforced the evidence of the carcinogenicity of glyphosate and should have been taken into account is addressed in Section III.1 - Subsection 1.a above.

4. Alleged illegalities and manifest errors in the assessment of the effect of glyphosate on microbiome (paragraphs 101 to 119 of the IRR)

232. In paragraphs 101 to 119 of the IRR, the Requestors claim that the assessment of glyphosate did not adequately take into account the possible effects on the gut microbiome of humans and animals (and possible health consequences) due to the lack of guidelines/standardised methods, without an adequate search and evaluation of independent, relevant scientific and technical information. This claim is equally applied to the active substance, its metabolites and impurities. This approach would allegedly have led to contradictory conclusions, to a breach of the legal requirements in the PPP Regulation and in the General Food Law

([172]) It is noted that there were 9 long term studies in rats and 7 in mice available to RAC, however, 3 studies in rats and 2 in mice were not considered acceptable due to significant limitations – see RAC Opinion, in particular page 57 "Therefore, seven rat and five mice carcinogenicity bioassays form the major basis of the current RAC evaluation of carcinogenicity in animals, as was the case in RAC's 2017 assessment."

([173]) See pages 46-48 of the RAC Opinion.

Regulation ([174]) regarding excellence and independence which would imply a more cautious approach as regards conclusions on safety. Additionally, the Requestors consider that some studies should have been followed up by additional investigations.

233. The microbiome is defined ([175]) as a characteristic microbial community occupying a reasonable well-defined habitat; as such it refers to the microorganisms involved but also encompass their theatre of activity, resulting in the formation of specific ecological niches. The field of microbiome research has evolved rapidly over the past few decades, and it could play an important role in various areas of EFSA's scientific assessments. In particular, the gut microbiome can be seen as a biological component directly and indirectly involved in the metabolism of food/feed components and chemicals and in the protection of the host against adverse environmental exposure; as such it could have potential relevance for all risk assessments of (oral) exposure to chemicals.

234. As noted by EFSA, there are currently no specific regulatory requirements, methods or guidance documents in place to specifically investigate possible effects of substances on microbiomes or effects by microbiomes on human and animal health; this is common to all (food) regulatory areas. Standardised protocols and guidance would facilitate the consistent and reliable assessment of the effects of active substances used in PPP on the microbiome. Nevertheless, despite the absence of standardised protocols, as part of the assessment a literature search was carried out for glyphosate and its metabolites, with search strings including keywords relevant for investigating impacts on the microbiome.

235. During the Peer Review, additional studies were identified during the public consultation on the draft RAR. Publicly available studies on the gut microbiome, its perturbations and possible consequence for the health of humans and animals (livestock and pets) included primary research studies, reviews, commentaries, editorials and EFSA outputs, was considered potentially relevant and duly assessed by a dedicated working group. All the studies indicated by the Requestors in paragraph 101 of the IRR were assessed in the Peer Review, except Chen et al 2021, Puigbo et al 2022 and Walsh et al 2023. The Requestors also cite a passage from a report by INSERM to demonstrate the importance of the issue and need for it to be considered in regulatory assessments. The passage does not refer to specific studies but, in any case, EFSA already responded to criticism that findings from INSERM were not fully considered in the assessment and confirmed that all studies had been taken into account ([176]).

236. The information retrieved during the Peer Review provided an up-to-date overview of activities conducted to explore the possible effects of glyphosate on gut microbiomes in humans and domestic animals and possible consequent effects on health at the time of the assessment. Overall, EFSA concluded that *"the available mammalian toxicity dataset supports a sufficiently protective assessment for any health impact possibly mediated by the microbiome on humans, livestock and pet animals."* ([177]).

237. The retrieved information was considered by experts from EFSA and the Member States to be of unclear relevance and overall not adequate to derive definitive conclusions on the effects of glyphosate on the gut microbiota for a series of reasons, which include the following: studies were conducted according to variable, not standardised approaches using

([174]) Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety, OJ L 31, 1.2.2002, p. 1.

([175]) See Experts' consultation 5.1 identified following comments by public in Part 3 of 6 of the Peer Review Report on Glyphosate (AIR V).

([176]) See the joint statement from ECHA and EFSA; dea0ca45-5bd9-61b3-4b8b-07d2912f4b80 (europa.eu), pages 9-11.

([177]) See page 13 of the EFSA Conclusion.

a variety of tools and methodologies, thus making the comparability and repeatability of results difficult; studies were often aimed at investigating specific microbiota populations and/or specific hypothesis, not the whole gut microbiome and/or organisms' response; the causal links between the microbiome (and its dysfunctions) and humans/animals pathological conditions need further consolidation, as indicated by most authors; finally, various weaknesses were identified, hampering reliability. The full information on the identified studies and methodology for their appraisal is reported in the supporting published documentation of the Pesticides Peer Review Experts' Meeting TC 80 ([178]). These considerations are in line with the recent publication by Moreno et al, 2024 (see below).

238. Regarding the new publications mentioned in paragraph 101 of the IRR by the Requestors, the study by Puigbo et al., 2022 reports *in silico* studies on potential targets for glyphosate on the human microbiome, the authors admit that this necessitates support by empirical studies and epidemiological investigations to clarify the effect of glyphosate on the healthy human microbiome. Chen et al 2021 and Walsh et al 2023 are reviews about respectively possible effect that glyphosate has on the human body with a specific focus on the gut microbiome and the potential consequences for human health, and on the regulatory mechanisms of the intestinal microbiome and its metabolites (mainly neurotransmitters and their precursors) on cognitive functions and the pathogeneses of neurodegenerative diseases such as Alzheimer and Parkinson disease. Overall, EFSA confirmed in its input requested by the Commission to respond to the IRR ([179]) that these studies do not add evidence that change the current conclusions on glyphosate.

239. In absence of definitive information from the open literature, it should be reiterated that the derived toxicological reference values are considered protective towards all the observed adverse effects, including those that could be secondary to gut microbiome perturbation, under the current state of knowledge ([180]). The references made in paragraph 105 of the IRR (footnotes 120 and 121 of the IRR) are not related to glyphosate or active substances used in PPPs, but rather to the link between the microbiome and the immune system. Therefore, they do not provide any information relevant for the specific assessment of glyphosate.

240. In paragraphs 106 to 109 of the IRR, the Requestors state that the reasons underpinning the assessment of impacts on the microbiome provided fails to comply with the requirements of the PPP Regulation and that this should have led to the non-renewal of approval of glyphosate and that the "absence of *ad hoc* guidelines or guidance documents cannot be used as a pretext for competent authorities to dispense with the assessment of a health effect that is extensively documented in independent literature". The Requestors also state that it cannot be inferred from any provision of the PPP Regulation that an EFSA scientific opinion must necessarily be based on prior standardised guidelines or methods. However, as mentioned above, an assessment of the available information, according to the latest scientific knowledge was undertaken therefore there was no failure to assess the particular issue. The outcome of that assessment was that the reference values established are protective of health. Therefore, the claim that non-renewal should have been proposed is unfounded.

([178]) Available in the Peer Review Report in the Open EFSA under 'Supporting documents' under EFSA Question number EFSA-Q-2020-00140: (https://open.efsa.europa.eu/study-inventory/EFSA-Q-2020-00140); refer to Part 3 – TC 80_Peer Review Report_Glyphosate_Annexes. Refer to Annex 9.

([179]) See pages 66-67 of the "Technical and scientific assistance on the internal review" available at the following link https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2024.EN-8737: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2024.EN-8737

([180]) See page 13 of the EFSA Conclusion and page 67 of 42 of "Technical and scientific assistance on the internal review" available at the following link https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2024.EN-8737

241. As regards the need for proactivity by EFSA as referred to in paragraph 108 of the IRR, EFSA has acknowledged that the field of microbiome research has evolved rapidly over the last years and could play an important role in various areas of EFSA's scientific assessments. In June 2020, EFSA published an editorial (Merten et al, 2020) ([181]), highlighting that gut microbiome research is expected to play a relevant role in regulatory science and that further research is needed to enhance the understanding of the toxicological significance of microbiome-mediated metabolism of chemicals. To start building this capacity, EFSA launched a thematic grant in March 2020 (GP/EFSA/ENCO/2020/02) on this topic to collaborate with EU Member States and to identify indications for future EU research agendas with a focus on specific needs from a risk assessment perspective; reports have been published in February 2024 (Moreno et al, 2024 ([182]) and Debode et al, 2024 ([183]).

242. As regards the mammalian gut microbiome (Moreno et al, 2024), the outcome of the work converges with EFSA's conclusions on glyphosate, indicating a lack of consistency and standardisation in methodologies necessary for robust comparison both in humans and animals, and a major lack of understanding of the underlying molecular mechanisms mediated by the gut microbiome and their link to host phenotypes, as well as dose-dependent effects. This applies to glyphosate and its metabolite AMPA, also investigated in the literature search run by Moreno et al, 2024. This work proposes a roadmap for future activities of relevance for incorporating the assessment of microbiomes in risk assessment, as well as multidisciplinary research strategy to provide key information to fill knowledge and methodology gaps and eventually developing policy actions aimed at the elaboration of decision frameworks for the future incorporation of gut microbiome data into specific guidelines and, ultimately, into regulatory programmes.

243. In paragraphs 110 to 116 of the IRR, the Requestors refer to alleged serious lacuna in the supplementary dossiers submitted by the GRG, considering that these did not comply with the legal requirements for providing data in relation to effects of glyphosate on the microbiome and as a consequence, the AGG should have declared the application inadmissible. They criticise the insufficient provision of scientific literature studies, that no additional tests have been conducted in light of the concerns available from literature and that the AGG has not found it necessary to request such a study, while also not evaluating the available literature studies.

244. Furthermore, there are indeed currently no specific regulatory requirements or guidance documents established for active substances or PPPs to specifically investigate possible effects on microbiomes and/or effects on human and animal health; this is common to other regulatory areas, and principally derives from a scientific backbone currently still insufficient for purpose. Certainly, standardised protocols would facilitate the consistent and reliable assessment of the microbiome in the pesticide area, nevertheless the lack of

([181]) Merten C, Schoonjans R, Di Gioia D, Pelaez C, Sanz Y, Maurici D, Robinson T, 2020. Editorial: Exploring the need to include microbiomes into EFSA's scientific assessments. EFSA Journal 2020;18(6):e18061, 7 pp. https://doi.org/10.2903/j.efsa.2020.e18061

([182]) Moreno, Francisco Javier; Florencio Pazos, Manuel Garrido-Romero, Cyrielle Payen, Gonzalo Borrego-Yaniz, Mónica Chagoyen, Nieves Corzo, Martine Denis, Christelle Fablet, María Fernández, Adela Granja, Maryse Guinebretière, Muriel Guyard, Rodrigo Jiménez-Saiz, Alassane Keita, Annaëlle Kerouanton, Ana Márquez, Javier Martín, Antonia Montilla, Ana Muñoz-Labrador, Jorge Novoa, Frédéric Paboeuf, Marta G. Rivera-Ferre, Patricia Ruas-Madiedo, Lorena Ruiz, Amandine Thépault, Mar Villamiel, Carlos Benito and Marianne Chemaly, 2024. Roadmap for the integration of gastro-intestinal (GI) tract microbiomes (human and domestic animal) in risk assessments under EFSA's remit. EFSA supporting publication 2024:EN-8597. 238 pp. doi:10.2903/sp.efsa.2024.EN-8597.

([183]) Debode F, Caulier S, Demeter S, Dubois B, Gelhay V, HulinJ, Muhovski Y, Ninane V, Rousseau G, and Bragard C, 2024. Roadmap for the integration of environmental microbiomes in risk assessments under EFSA's remit. EFSA supporting publication 2024:EN-8602.93pp. doi:10.2903/sp.efsa.2024.EN-8602.

standardised protocol is not a sufficient argument to dismiss possible effects on the gut microbiome and hence an assessment was undertaken.

245. As explained by EFSA ([184]), a literature search was carried out for glyphosate and its metabolites, with search strings including keywords relevant for investigating microbiome. During the Peer Review, additional studies were identified. The set of publicly available studies on the gut microbiome, its perturbations and consequence for the health of humans and animals (livestock and pets) included primary research studies, reviews, commentaries, editorials and EFSA outputs, was considered potentially relevant and duly assessed by the Working Group on glyphosate (57 studies). Therefore, regardless of a lack of data provided by the GRG, or an assessment by the AGG, the renewal process ensured that an assessment was carried out on the basis of sufficient scientific and technical information, and the claim made by the Requestors does not affect the legality of the Reviewed Regulation.

246. In paragraphs 117 and 118 of the IRR, the Requestors claim that the EFSA assessment of glyphosate on microbiota was limited to the potential effects on gut microbiome of bees and some publications for other non-target organisms are quoted in order to demonstrate that this information would have been available for a more comprehensive assessment.

247. Contrary to this allegation, a significant amount of literature was taken into consideration to assess potential effects on different non-target organisms. Only the studies assessed as relevant and reliable were further used (the criteria for evaluating relevance and reliability were agreed at the Pesticides Peer Review Experts' TC 82) ([185]).

248. With regards to the literature allegedly showing an effect on the microbiota of non-target species (such as earthworms) mentioned in paragraph 117 of the IRR, the quoted studies by Owagboriaye, 2021 and Ruuskanen, 2020 were included in the assessment ([186]), Bellot, 2023 and DeBeer *et al*. 2023 were published after the time frame for which the assessment of the literature was performed.

249. As regards Anderson 2017 and Rayman & Moran 2018, they are not primary research studies and they do not focus on pesticides (glyphosate is not even mentioned in these papers). It should be noted that the EFSA Conclusion does not claim that a link between dysbiosis of individual bees and effects on population does not exist; EFSA's Conclusion only flags that the relevance of such effects is not known. The Requestors claim that an attempt should have been made to quantify the effects on the population (in order to assess whether a reduction of more than 10 % in colony strength may happen). The applicant was not requested to make such an attempt, since it was clear to EFSA that a method does not exist to do so and, in general, this scientific topic needs further research and development. Although the quoted publications that investigated the importance of such effects (Anderson 2017 and Rayman & Moran 2018, DeBeer *et al*. 2023) were not assessed, they seem to only reiterate that effects on individual level may escalate to higher organisation level.

250. In paragraph 118 of the IRR, the Requestors claim that the risk assessment of a possible alteration of the microbiome was not carried out. The Requestors also claim that the alleged body of evidence from independent scientific literature demonstrating that the health impact on the microbiome should have led to the conclusion that unacceptable effects were demonstrated.

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(184) See page 65 of Technical and scientific assistance on the internal review under Regulation (EC) No 1367/2006 of Commission Implementing Regulation (EU) 2023/2660 renewing the approval of the active substance glyphosate in accordance with Regulation (EC) No 1107/2009
Available at: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2024.EN-8737

([185]) See Experts' consultation 5.1 identified following comments by public in Part 3 of 6 of the Peer Review Report on Glyphosate (AIR V).

([186]) See section B.9.15. MICROBIOTA of the RAR (Volume 3 – B.9 (PPP) – MON 52276).

251. However, EFSA disagrees that the available evidence from scientific literature demonstrating that the health impact on honeybees should have led to a conclusion that there would be unacceptable effects at population level, as such effects would need to be demonstrated for the colony ([187]). Furthermore, the Requestors fail to acknowledge that a risk assessment for bees was carried out by EFSA, based on both a guidance document ([188]) endorsed and accepted by Member States in 2002 as well as an updated guidance for conducting the risk assessment for bees that it adopted in 2013 ([189]), although this guidance has never been endorsed and accepted by the Member States. Additionally, scientific literature was thoroughly evaluated. As a result, EFSA did not identify risks to bees for any representative use of glyphosate ([190]). Although the Requestors claim that the effects should have been followed up, they do not provide any concrete information on what they consider should have been done and, therefore it remains unclear what else could or should have been done. Therefore, the assertion that the effects caused by glyphosate on the microbiome in bees were not assessed is unfounded.

252. At the end of paragraph 118 of the IRR, the Requestors quote the judgment of the General Court of 4 October 2023 in case T-77/20, where the General Court ruled that *in order for an application to be rejected, it is sufficient for a mere uncertainty as to the presence of a risk concerning that substance to be identified* ([191]). However, this judgment confirms that the precautionary principle empowers the Commission to take measures in light of uncertain risks, but it does not relate to any obligation to do so. In any event, this judgment also has to be read together with the case law on the application of the precautionary principle in the implementation of the PPP Regulation more generally, as referred to in Section III.2 - Subsection 2.d above, in which the Court has considered that "zero-risk" does not exist in practice and that preventive measures cannot solely be based on hypothetical risks, based on simple assumptions that have not been scientifically verified ([192]), with the consequence that recognising a risk or an uncertainty does not automatically lead to non-renewal of an active substance.

253. Finally, in paragraph 119 of the IRR, the Requestors put forward that EFSA would have concluded that the assessment of the effects of glyphosate on the microbiome would be conditional on the drafting of guidelines and their subsequent adoption by the Commission and Member States. The Requestors argue that making the assessment conditional to the drafting of guidelines and their subsequent adoption by political bodies would amount to a reversal of the burden of proof.

254. This argument is clearly unfounded given that an assessment was carried out and that a conclusion was reached. Although EFSA noted that *"Further developments are needed to understand the importance of the microbiome in risk assessment and identify dedicated strategies and methodologies accordingly"* ([193]), EFSA did not leave the assessment of

([187]) See page 70 of annex "Technical and scientific assistance on the internal review" attached to this reply and also available at the following link https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2024.EN-8737

([188]) European Commission, 2002. Guidance Document on Terrestrial Ecotoxicology Under Council Directive 91/414/EEC. SANCO/10329/2002-rev. 2 final, 17 October 2002.

([189]) European Food Safety Authority, 2013. EFSA Guidance Document on the risk assessment of plant protection products on bees (Apis mellifera, Bombus spp. and solitary bees). EFSA Journal 2013;11(7):3295, 268 pp.,doi:10.2903/j.efsa.2013.3295 https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2013.3295

([190]) See page 23 of the EFSA Conclusion.

([191]) Judgment of the General Court of 4 October 2023, *Ascenza Agro v Commission*, T-77/20, EU:T:2023:602, para. 413.

([192]) Judgment of the General Court of 21 February 2024, *PAN Europe v Commission*, T-536/22, EU:T:2024:98, para. 80.

([193]) See page 13 of the EFSA Conclusion.

effects on the microbiome open due to absence of guidance, as clearly explained in the paragraphs above.

255. Based on the above, the Commission concludes that this ground for review is unfounded.

5. Alleged illegalities and manifest errors in the assessment of the neurotoxicity and the reproductive toxicity of glyphosate (paragraphs 120 to 160 of the IRR)

256. In this ground, the Requestors claim that that "illegalities and manifest errors" of assessment would have been made in the assessment of the neurotoxicological effects of glyphosate. More specifically, the Requestors argue that:

a. neurotoxic effects from independent scientific literature were not properly identified and examined;
b. the only developmental neurotoxicity study carried out on a glyphosate salt, which proved to be positive, was not submitted by the applicants for re-approval, and was excluded without serious scientific reasoning;
c. the studies submitted by the applicants for re-approval are insufficient to establish the absence of developmental neurotoxicity;
d. the EFSA Conclusion does not properly reflect the concerns that emerged from the review of the dossier.

257. The Commission will discuss each of these claims in turn below.

(a) Neurotoxic effects from independent scientific literature (paragraphs 123 to 131 of the IRR)

258. Contrary to the Requestors' claim in paragraph 122 of the IRR, studies on the neurotoxicological effects of glyphosate were thoroughly examined. The set of studies considered in the renewal assessment of glyphosate included a package of neurotoxicity studies performed in rodents (one acute and two sub-chronic neurotoxicity studies in rats) and a delayed polyneuropathy study (one delayed neurotoxicity study in domestic hens), in agreement with the data requirement as set out in Commission Regulation (EU) No 283/2013. As indicated in the EFSA Conclusion, no indication of neurotoxicity potential of glyphosate can be found from the above-mentioned studies[194].

259. Contrary to the claim in paragraph 129 of the IRR, the GRG submitted a literature review of the last 10 years preceding the dossier submission ([195]) in line with the legal requirements. During the public consultation, further studies from the literature were identified and subsequently requested by EFSA and submitted by the GRG. All public literature submitted to the AGG and EFSA throughout the regulatory process for the renewal of glyphosate (i.e. included in the supplementary dossier or requested following the public consultation phase) was considered as potentially relevant and included in the assessment. Public literature available to EFSA included primary research studies (*in vivo*, *in vitro* and mechanistic), epidemiological studies, and reviews.

260. To assess the available literature on neurotoxicity, EFSA, with the support of a Working Group, followed a multistep and structured approach as described in Annexes 7 (neurotoxicity studies) and 4 (epidemiological studies, including neurotoxicity) of the

([194]) See page 12 of the EFSA Conclusion

([195]) See page 54 of Volume 1 of the RAR:
"The literature search was conducted accessing 11 bibliographic databases (AGRICOLA, BIOSIS, CABA, CAPLUS, EMBASE, ESBIOBASE, MEDLINE, TOXCENTER, FSTA, PQSCITECH, SCISEARCH) in order to identify scientific peer-reviewed open literature published within the 10 years prior to the renewal dossier submission (2010- 2020). Top-up literature search was conducted to cover the period directly before the dossier submission, e.g. between January 2020 and June 2020."

Pesticides Peer Review Experts' Meeting Report TC 80 ([196]). Moreover, following the work of the Working Group, experts from Member States extensively discussed the potential for neurotoxicity ([197]).

261. The scope of the Working Group activity was to assess the available information and provide a WoE evaluation of the possible effects of glyphosate on human health. Individual studies commented during the public consultation phase were grouped in different sub-sections (e.g., autism, Parkinson's disease, neurotransmitters, developmental neurotoxicity and other neurotoxicity studies).

262. Overall, the evidence made available to the EFSA Working Group on neurotoxicity (epidemiological studies included) was limited and quite heterogeneous regarding exposure (most studies used glyphosate-based PPPs rather than glyphosate and at a very wide dose range) as well as the endpoints assessed.

263. In general, the reliability of the studies was considered too low to infer causal associations, which limited their utility for risk assessment as no robust conclusion could be drawn. The additional papers identified after public consultation and considered appropriate to support the assessment were further assessed and the outcome included in Annex 4 and 7 of the Pesticides Peer Review Experts' Meeting Report TC 80. Regarding literature on neurotoxic effects in humans and other species, it is noted that the study by Martinez et al., (2019) was taken into account ([198]). They review by Costas-Ferreira (2022) was published outside of the period required by the legislation but nevertheless screened by EFSA who concluded that since it is a review it is considered not relevant and not having an impact in the current risk assessment ([199]). The report by INSERM was also considered by EFSA and ECHA who provided a Statement on it in 2023 ([200]).

264. Regarding literature on developmental neurotoxicity, the studies cited in paragraph 124 of the IRR were all taken into account in the assessment ([201]). Based on the body of evidence assessed by the EFSA Working Group (see Annex 7 of the Annexes to Peer Review Meeting Report TC 80), although some effects were reported for glyphosate-based PPPs (commercial formulations) ([202]) (Ait Bali et al., 2020) and various types of glyphosate salts (monoisopropylamine in the case of the study by Luna et al., 2021 and Coullery et al., 2020; and trimesium for the 2001 study), EFSA concluded that there was no clear pattern of effects suggesting DNT liabilities for glyphosate acid. The potential for developmental

([196]) Available in the Peer Review Report in the Open EFSA under 'Supporting documents' under EFSA Question number EFSA-Q-2020-00140: https://open.efsa.europa.eu/study-inventory/EFSA-Q-2020-00140); refer to Part 3_Peer Review Report_Glyphosate_Annexes. TC 80. Refer to Annexes 4 and 7.

([197]) See experts' consultation point 2.27 in Part 3 of 6 of the Peer Review Report on Glyphosate (AIR V).

([198]) See section B.6.7.3. Publications on neurotoxicity of Volume 3 – B.6.7 (AS) of the RAR

([199]) See "Consolidated list of newly available publications on glyphosate brought to the attention of EFSA and AGG after the public consultation phase until the time point of drafting the EFSA conclusion" available at https://open.efsa.europa.eu/questions/EFSA-Q-2020-00140
"*The paper was screened for potential impact on risk assessment. This is a systematic review investigating the effects of glyphosate or its commercial formulations on the nervous system of humans and various animal species. Glyphosate seems to impair neurotransmission as well as behavioral and locomotor changes. However, a number of limitations were identified and including: inconsistencies of results across studies, the use of different formulations of glyphosate (therefore it was not possible to determine precisely which component(s) of the formulation was (or were) responsible of the neurotoxic effects), the use of concentrations higher to the ones the general populations are commonly exposed to. Finally, considering the paper is a review, it is considered not relevant and not having an impact in the current risk assessment.*"

([200]) https://echa.europa.eu/documents/10162/11035849/ECHA_EFSA_Gen_Futures_reply.pdf/dea0ca45-5bd9-61b3-4b8b-07d2912f4b80?t=1696593222943

([201]) See Experts' consultation 2.27 in Part 3 of 6 of the Peer Review Report.

([202]) See Ait Bali et al., 2020.

neurotoxicity was discussed by experts from Member States and EFSA who concluded that "*based on the available data on glyphosate acid and GBH and on the fact that it is not possible to identify a pattern of effects suggesting DNT liabilities for glyphosate acid using the available dataset, it is considered that the current toxicological reference values (TRVs) are protective"* ([203]).

265. From the 7 epidemiological studies available ([204]), including reviews, and investigating the possible relationship between exposure to glyphosate and autism, only one found significant associations with glyphosate exposure (von Ehrenstein et al., 2019). However, it was not possible to assume unambiguous levels of exposure to single pesticides considering concomitant co-exposures, and the EFSA Working Group considered that no conclusion could be drawn on the possible correlation between exposure to glyphosate and autism since this unique study had limitations regarding exposure assessment ([205]). Concerning the assessment of the studies mentioned in paragraph 125 of the IRR, it is noted that the one by Ongono et al., 2020 (systematic review of epidemiological data in children and in vivo studies in rodents) was not considered reliable for the risk assessment whereas the one by Pu et al., 2020a was considered of low reliability ([206]). The paper by Pu et al., 2021 was not considered by the Working Group, since it was outside of the time frame used for the literature review and not identified after public consultation.

266. Regarding the epidemiological studies on Parkinson's disease referred to in paragraph 126 of the IRR, 8 studies were made available to the EFSA Working Group and only Caballero et al., 2018 was considered acceptable with restrictions. This study found a significant association with glyphosate exposure, but the limitations inherent to GIS-based exposure assessment ([207]) prevented from drawing robust conclusions. The remaining studies were case reports (Barbosa et al. 2001; Zheng et al. 2018; Wang et al., 2011), reviews or assessed exposure using an ecological approach (at the group level rather than at individual level). The case report by Eriguchi et al., 2019 was not part of the studies assessed in the RAR, neither was it highlighted during the public consultation. It should be noted that it is a case report of a 38-year-old man who developed parkinsonism 4 years after ingesting unknown amounts of glyphosate as part of unknown liquid formulations. The published data do not allow any causal link to be established between the exposure to glyphosate and observed pathology. The study by Pu et al., 2020b was not considered since it was not part of the literature review and not identified after public consultation.

267. Regarding amyotrophic lateral sclerosis (ALS), mentioned in paragraph 127 of the IRR, only two studies were made available with inconsistent results. While the AHS agriculture cohort found no association between glyphosate and ALS (Kamel et al., 2012), a case-control study (Andrew et al., 2021) reported a significant increased risk based on glyphosate exposure using GIS data (an indirect estimate of actual exposure that pose risk of misclassification). The study by Anderson et al., 2023 was not considered by the Working Group since it was out of the time frame used for the literature review and not identified after public consultation.

([203]) See Experts' consultation 2.27 in Part 3 of 6 of the Peer Review Report on Glyphosate (AIR V).

([204]) Available in the Peer Review Report in the Open EFSA under 'Supporting documents' under EFSA Question number EFSA-Q-2020-00140: https://open.efsa.europa.eu/study-inventory/EFSA-Q-2020-00140); refer to Part 3_Peer Review Report_Glyphosate_Annexes. TC 80. Refer to Annex 4.

([205]) See Annex 4 of the Annexes to Peer Review Meeting Report TC 80; Evaluation of the epidemiological studies on possible effects of Glyphosate on human health.

([206]) See Annex 4 and Annex 7 of the Annexes to Peer Review Meeting Report TC 80 - available in the Peer Review Report in the Open EFSA under 'Supporting documents' under EFSA Question number EFSA-Q-2020-00140: https://open.efsa.europa.eu/study-inventory/EFSA-Q-2020-00140); refer to Part 3_Peer Review Report_Glyphosate_Annexes. TC 80.

([207]) Geographic Information Systems.

268. Regarding the potential effects of glyphosate on the human and animal gut microbiome, cited in paragraph 128 of the IRR, the Commission refers to its response in section 3, subsection III.4 above and to the outcome of the Pesticides Peer Review Experts' Meeting Report TC 80 ([208]), according to which "*studies on potential effects of glyphosate on the human and animal gut microbiome are not expected to impact the risk assessment, based on the current state of knowledge; the available data for the mammalian toxicity assessment were sufficiently protective for any health impact for livestock and pet animals (in line with the conclusions of the EFSA scientific report, 201846)*". Concerning the three papers cited, it is noted that Kulcsarova K et al., (2023) was published in November 2023, i.e. after the publication of the EFSA Conclusion. It is also noted that this is a review article that is not specific to glyphosate and does not provide any original new data. The paper by Rueda-Ruzafa L et al., (2019) was evaluated ([209]) and, as mentioned above, the report by INSERM was also considered by EFSA and ECHA who provided a Statement on it in 2023 ([210]).

269. In response to paragraph 129 of the IRR, it must be noted that the study by Kamel et al., 2012 was assessed by the EFSA Working Group and not Kamel et al., 2007, as the latter was outside the 10-year period before submission of the dossier (as required by Article 8(5) of the PPP Regulation and Article 7(1)(m) of Implementing Regulation (EU) No 844/2012). Studies by Luna et al., 2021 and Coullery et al., 2020 referred to in paragraph 124 of the IRR were assessed (see Annex 7 of the Peer Review Experts' Meeting Report TC 80) and discussed during the Experts' meeting TC 80 ([211]). The paper by Pu et al., 2021 was not considered by the Working Group since it was published outside of the time frame required for the literature review and not identified after public consultation. The studies by Martinez et al., 2018 and Martinez et al., 2019 were considered by the EFSA Working Group: Martinez et al., 2019 showed effects of glyphosate on the integrity of the blood brain barrier (BBB) at high doses in an *in vitro* study; Martinez et al., 2018 showed changes in dopaminergic neurotransmitters, particularly dopamine, but these effects were not observed at doses below 35 mg/kg bw per day for 6 days in this *in vivo* study in rats, and humans are highly unlikely to be exposed to higher dose ([212]).

270. Finally, the claim made in paragraph 130 of the IRR that *"it appears from the experts' meeting that some key studies were not even assessed by them at all, as they were not brought to their attention until the last minute"* is incorrect and seems to stem from a misreading of the expert meeting report. The sentence quoted in footnote 174 of the IRR, referring to the studies by Luna et al., (2021) and Coullery et al., (2020) does not provide the full picture. As mentioned above in response to paragraph 124 of the IRR, those studies were assessed (see Annex 7 of the Peer Review Experts' Meeting Report TC 80) and considered during the experts' meeting TC 80. The evaluation of those studies can be found in the RAR ([213]).

(b) <u>Failure to take into account the only developmental neurotoxicity (DNT) study on glyphosate (paragraphs 132 to 145 of the IRR)</u>

271. In this section of the IRR, the Requestors criticise that the GRG did not submit a DNT study conducted on a salt of glyphosate although that study would have shown adverse effects and

([208]) available in the Peer Review Report in the Open EFSA under 'Supporting documents' under EFSA Question number EFSA-Q-2020-00140: https://open.efsa.europa.eu/study-inventory/EFSA-Q-2020-00140); also refer to Part 3_Peer Review Report_Glyphosate_Annexes. TC 80

([209]) See Experts' consultation 2.27 in Part 3 of 6 of the Peer Review Report on Glyphosate (AIR V).

([210]) https://echa.europa.eu/documents/10162/11035849/ECHA_EFSA_Gen_Futures_reply.pdf/dea0ca45-5bd9-61b3-4b8b-07d2912f4b80?t=1696593222943

([211]) Regarding the potential effects of glyphosate on the human and animal gut microbiome, please see the outcome of the EFSA Working Group dealing with this topic and included in Annex 9 of the Peer Review Experts' Meeting Report TC 80.

([212]) See Annex 7 of the Pesticide Peer Review Experts' TC 80.

([213]) Luna et al., see B.6.7.3.24 of Volume 3 – B.6.7 (AS) of the RAR.

therefore should have been submitted in line with the data requirements set in Regulation (EU) No 283/2013 (paragraph 135 of the IRR).

272. The DNT study in question was conducted in 2001 with glyphosate-trimesium (a salt of glyphosate which has a different toxicological profile than glyphosate acid). Contrary to the claim by the Requestors, its inclusion in the supplementary dossier was not required because, as reported in the minutes of the Pesticides Peer Review Experts meeting TC 80 and its Annex 7, glyphosate-trimesium is not considered a structural analogue of glyphosate acid, but a substance with evidence of neurotoxicity likely triggered by the trimesium ion (see US EPA assessment 2005) ([214]). Glyphosate-trimesium has not been approved in the EU since the approval of glyphosate was renewed in 2017 (and according to the GRG, Syngenta, the original producer of glyphsoate-trimesium has not placed any PPPs containing it on the market since 2004 ([215])), and it was not part of the application submitted by the GRG in 2019, as also noted in paragraph 133 of the IRR by the Requestors.

273. Nevertheless, during the process for the renewal, the author of the DNT study informed EFSA about the study, and EFSA requested the GRG to submit it. The study was subsequently made available to both EFSA and ECHA as well as the AGG to allow consideration of all available evidence in the evaluations. During the Pesticides Peer Review Experts' Meeting TC 80, a specific action point was set for the AGG to include the assessment of the study performed with glyphosate-trimesium in the RAR.

274. In response to the claim made in paragraphs 137-138 of the IRR that a lower Acceptable Daily Intake (ADI) value should have been established due to concerns for DNT, it is recalled that during the Pesticides Peer Review Experts' Meeting TC 80 it was discussed if an additional uncertainty factor was needed in the derivation of reference values to cover the uncertainties related to the fact that no DNT study with glyphosate acid was available. However, no neurotoxic effects were observed in the available test guideline studies on glyphosate acid that would have triggered the need for an *in vivo* DNT study. Some evidence of DNT effects was present in studies conducted with different salts, different formulated products and non-appropriate routes of administration. Further assessment of the study by Ojiro et al., 2023 and the data from US EPA ToxCast/Tox21 Dashboard highlighted during the Pesticides Peer Review Experts' TC 80 allowed experts to conclude that the reference values proposed are sufficiently conservative to cover the uncertainty related to the missing in vivo DNT study with glyphosate acid ([216]).

275. In paragraph 139 of the IRR, the Requestors claim that neurotoxic effects could have led to classification of glyphosate as toxic for reproduction category 1B or 2. However, this claim is unfounded given that RAC fully considered all available information, including the DNT study on glyphosate-trimesium and concluded that *"Overall, in a weight of evidence assessment RAC concludes that no classification for adverse effects on development is warranted" ([217])*. In relation to the DNT study specifically, RAC concluded that "*due to the*

([214]) U.S. EPA. Data evaluation Record. Glyphosate Trimesium. Study type: developmental neurotoxicity study - rat; MRID 45539801. 2005 Accessed from: https://www.regulations.gov/document/EPA-HQ-OPP-2016-0093-0183

([215]) See Volume 1 of the RAR.

([216]) See minutes of the Pesticides Peer Review Experts' TC 80 containing also a post meeting note discussing the assessment of the Ojiro et al., 2023 study and US EPA ToxCast/Tox21 Dashboard data, available in the Peer Review Report in the Open EFSA under 'Supporting documents' under EFSA Question number EFSA-Q-2020-00140: https://open.efsa.europa.eu/study-inventory/EFSA-Q-2020-00140); refer to Part 3_Peer Review Report_Glyphosate_expert meeting reports_public.pdf (TC 80, Expert consultation point 2.27).

([217]) See page 123 of the RAC Opinion.

limitations in the study, it has no major impact on the classification of glyphosate for developmental toxicity" ([218]).

276. In paragraphs 142 to 143 of the IRR, the Requestors infer that glyphosate-trimesium should have been assessed and should not have been treated as a distinct substance from the active substance glyphosate to which the application for renewal relates. The Requestors also submit that this would have required evidence that the adverse effects reported in the DNT study are due to trimesium ion and not glyphosate itself, for which further and different studies should have been submitted/requested/assessed. The Requestors also argue that independent literature would clearly indicate that glyphosate and different products based on it have neurological effects on children or young animals (Pu *et al*., 2021, Ojiro *et al*., 2023, Costas Ferreira *et al. 2022, Madani and* Carpenter 2022, von Ehrenstein e*t al*., (2019), Ongono *et al*., 2020)

277. However, the Commission shares the view of the AGG and EFSA set out above that glyphosate-trimesium is different from glyphosate-acid and was not part of the renewal application. During the Peer Review Expert Meeting TC 80, a data gap was identified to further investigate the cause of the observed effects from studies conducted with both glyphosate-based PPPs and trimesium. As previously indicated, the paper by Pu et al., 2021 was not considered by the EFSA Working Group, since it was published outside of the time frame used for the literature review and not identified after the public consultation. The same applies to the study by Madani and Carpenter, 2022. Regarding Ojiro et al., 2023, the Commission has already responded in relation to paragraph 137 of the IRR above. The studies by Costas Ferreira et al., 2022, von Ehrenstein et al., 2019 and Ongono et al., 2020, were considered as part of overall assessment ([219]).

278. In paragraph 144 of the IRR, the Requestors assert that the rejection of the only DNT study carried out on a glyphosate salt would contrast with the way in which, conversely, EFSA and Member State experts used data on chlorpyrifos to conclude on the toxicity of a structural analogue, namely chlorpyrifos-methyl and in that case a DNT study was carried out on chlorpyrifos-methyl, but had some flaws. However, differently from the case of chlorpyrifos and chlorpyrifos-methyl (where chlorpyrifos-methyl was considered a structural analogue of chlorpyrifos), glyphosate-trimesium salt is not considered a structural analogue of glyphosate and glyphosate-trimesium per se has a specific toxicological profile (as confirmed by US EPA 2005 and also as evidenced in Annex II of the Review Report from the first approval of glyphosate ([220])).

279. In paragraph 145 of the IRR, the Requestors speculate that, due to "shortcomings" in the dossier, the competent authorities would not have had sufficient time to carry out a thorough developmental neurotoxicity assessment of glyphosate, citing the comment made by the AGG that "*the RMS and Member States had limited time to review these data for discussion during the meeting"*.

280. However, this claim is not underpinned by the facts. First, the fact that the RMS indicated limited time does not mean that an assessment to the necessary standard was not carried out. An assessment of all available data was undertaken. In addition to the assessment by the AGG, this includes also an in-depth evaluation of the neurotoxicity data performed by the EFSA Working Group on glyphosate which was subsequently subject to an extensive scrutiny by experts during the Pesticides Peer Review Experts' Meeting TC 80 before arriving to the final conclusions. As preparatory work to facilitate subsequent discussions in

([218]) See pages 110-111 of the RAC Opinion.
([219]) See Annex 7 and Annex 4 of the Pesticides Peer Review Experts' Meeting TC 80.
([220]) https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/start/screen/active-substances/details/811

the expert meeting, the EFSA Working Group provided a thorough assessment of all the available information including appraisal of the published literature data, and a weight-of-evidence evaluation of the possible effects of glyphosate on human health as described in the Annexes of the Peer Review Expert Meeting Report TC 80. This included also a rigorous assessment following a multistep and structured approach regarding neurotoxicity ([221]).

281. In conclusion, contrary to the claim by the Requestors in this section, the DNT study was taken into account in the assessment conducted by the AGG, EFSA and ECHA. Furthermore, contrary to what is advocated by the Requestors, its consideration did not result in the conclusion that glyphosate is considered to be toxic for reproduction.

(c) Allegedly insufficient regulatory studies (paragraphs 146 to 149 of the IRR)

282. In paragraph 146 of the IRR, the Requestors note that in their view, only particularly robust regulatory data would have been able to negate 'serious and consistent concerns' about the developmental neurotoxicity of glyphosate. However, they are of the opinion that the renewal dossier contains only acute and subchronic toxicity studies, which are proven not to be adequate for the assessment of developmental neurotoxicity.

283. Against this claim, it should be noted that EFSA and Member States did not make use of information from acute and subchronic toxicity studies to conclude on the developmental neurotoxicity potential of glyphosate but noted that the absence of signs of neurotoxicity in regulatory studies does not trigger the requirement to perform a developmental toxicity study with glyphosate. The assessment was based on all available information, including information from the published literature as well as ToxCast/Tox 21 data. The experts from the Member States and EFSA did not consider that the database was insufficient to reach a conclusion ([222]) and instead concluded that there was no clear pattern of effects suggesting a DNT effect for glyphosate, and the toxicological reference values established were considered as sufficiently protective. Concerning the ToxCast/Tox 21 data, EFSA transparently highlighted that the data are not fully covering the current DNT in vitro test battery, but this uncertainty was not deemed to impact the overall conclusion reached ([223]). The availability of additional data was however highlighted during the Peer Review and included an *in vivo* study in rats on glyphosate-trimesium, where DNT-related endpoints were assessed and considered as not affected by the high doses administered to dams, and ToxCast/Tox 21 data, where glyphosate was not showing any activity in all tested *in vitro* assays, except for one parameter at high concentrations. Further data, including public literature studies on glyphosate-based PPPs and studies on other glyphosate salts (including the one on glyphosate-trimesium), showing some DNT effects, were also assessed during the Peer Review.

284. In paragraph 147 of the IRR, the Requestors go on to argue that the alleged deficiencies in the data package for developmental neurotoxicity are not filled by data on reproductive toxicity, in particular noting that the dossier on glyphosate does not contain an extended one-generation reproductive toxicity study (TG 443). However, as noted above, the experts from Member States and EFSA were able to reach a conclusion that the toxicological

([221]) See Annex 7 of the Expert Meeting report TC 80.

([222]) See Experts' consultation 2.27 in Part 3 of 6 of the Peer Review Report on Glyphosate (AIRV)

([223]) See See Experts' consultation 2.27 in Part 3 of 6 of the Peer Review Report on Glyphosate (AIRV) "There is a remaining uncertainty because the assays included in Tox21 are not fully covering the current DNT in vitro test battery (Blum et al., 2023) and some processes were not tested. In conclusion, although the DNT potential of glyphosate acid cannot be concluded (data gap), when considering the additional evidence from the Ojiro et al. 2023 and ToxCast/Tox21 data, the approach taken by the RMS and the proposed reference values thereof, is sufficiently conservative to cover the uncertainty related to the missing in vivo DNT study with glyphosate acid (see also experts' consultation in 2.34)."

reference values established were considered as sufficiently protective. Neither Member States nor EFSA indicated that an extended one-generation study was required.

285. Contrary to the view of the Requestors in paragraph 148 of the IRR, no study was discarded; all of the available information was integrated in a WoE approach. EFSA explicitly referenced this WoE approach and identified a data gap concerning the cause of the DNT effects observed in public literature studies with glyphosate-based PPPs and the study with glyphosate-trimesium.

286. Therefore, while the Requestors have a different view on the point and consider that serious concerns exist, EFSA's comprehensive integration of all available data and its unequivocal conclusion on DNT, including the recognition of a data gap, provided risk managers with a clear and detailed foundation for decision-making.

(d) Alleged wrong and unlawful risk communication (paragraphs 149 to 155 of the IRR)

287. In this section of the IRR, the Requestors argue that the wording in the EFSA Conclusion would not reflect the outcome of the assessment in relation to developmental neurotoxicity. In their view, instead of identifying a data gap in relation to developmental neurotoxicity, EFSA should have concluded that this is a critical area of concern.

288. In paragraphs 149 to 152 of the IRR, the Requestors refer to the Pesticides Peer Review Experts' Meeting TC 80 and to the "genuine concern" amongst national experts concerning the developmental neurotoxicity of glyphosate as a basis for their argument that EFSA should have identified a critical area of concern instead of a data gap.

289. However, as explained in detail in the preceding subsections, the available data package on glyphosate (acid) did not indicate concerns triggering requests for additional studies (namely a DNT study). In addition, it remains unclear why a data gap on developmental neurotoxicity based on studies that do not concern the active substance being assessed should necessarily have resulted in the identification of a critical area of concern (as defined by EFSA).

290. Furthermore, EFSA found it appropriate to report under section 10 of its Conclusion, amongst several other aspects, the need to obtain further clarification on the effects reported in the DNT study with glyphosate-trimesium and with glyphosate-based PPPs. This section lists information that is not considered critical for the assessment but may present some uncertainties and therefore be of relevance to Member States in the national process of authorisation of plant protection products. Nevertheless, the Commission as risk manager considered the gaps and uncertainties as part of the decision-making. With specific regard to the data gap set for DNT findings, the Commission clarified the reason why this did not preclude the renewal of approval: as explained in the Renewal Report ([224]), the studies on glyphosate available for the Peer Review did not show any neurotoxicity effects, and the experts concluded that a specific study for developmental neurotoxicity (DNT) on glyphosate is therefore not needed. In addition, EFSA concluded that the toxicological reference values set for glyphosate ensure adequate protection for potential DNT effects. Therefore, no specific requirement needed to be set as a condition for the approval.

291. With regards to the alleged flaws in terms of risk communication referred to in paragraph 153 and 154 of the IRR, the conclusions of the Peer Review referenced by the Requestors in fact support the conclusions reached by EFSA. Indeed, the reported conclusion of the Peer Review reflects the view of all experts except one, whose opinion has been clearly reported in accordance with the far-reaching transparency standards characterising EFSA's work. In

([224]) See page 6 of the Renewal Report.

this regard, ample evidence of EFSA's proactive and reactive transparency policies is available on its website ([225]).

292. In paragraph 155 of the IRR, the Requestors argue that the finding of a simple data gap would violate the *patere legem quam ipse fecisti* principle. This principle is better known in Union administrative law as the principle whereby, in the absence of legislative standards, and therefore in the presence of a considerable technical discretion, any Union Institution, body or agency is bound by its own determinations, and its discretion, where present, is limited by self-imposed constraints. In this scenario, the competent Union administration must ensure not to infringe legitimate expectations that may have been created by these policies or guidelines, as well as compliance with the principle of equal treatment or non-discrimination.

293. In the EFSA Conclusion, EFSA opted for applying the concept of critical areas of concerns as per the standard definition set out in the first paragraph of section 9.2 at page 32 of the EFSA Conclusion. Therefore, EFSA did not exceed the limits of the self-imposed constraints set out in this definition by not identifying any critical area of concern.

(e) *Conclusion (paragraphs 156 to 160 of the IRR)*

294. In paragraphs 156 and 157 of the IRR, as an overall conclusion on the neurotoxicity assessment process, the Requestors recall their claim of manifest errors of assessment and irregularities in the assessment and a breach of the principles of excellence and independence and refer to alleged breaches of the legal requirements in Article 8(5) of the PPP Regulation and Article 7(1)(m) of Regulation (EU) No 844/2012, which should have resulted in the AGG declaring the dossier inadmissible, as well as of the ruling in the Blaise case.

295. Concerning the claim that there was a breach of legal requirements concerning the submission of literature laid down in Article 8(5) of the PPP Regulation and Article 7(1)(m) of Regulation (EU) No 844/2012, it is recalled that the applicant provided a literature search which was then supplemented based on identification of further studies either during the public consultation and even thereafter (in the interests of completeness). There was no breach of the PPP Regulation as interpreted in the Blaise judgment since all available information was considered in a WoE approach and no "systematically preponderant weight" was given to studies submitted by the applicants. Moreover, as further detailed in Sub-section 8, point a, below, the Requestors erroneously equate the two different concepts of admissibility and data gaps: while admissibility concerns the initial eligibility of an application by the RMS, data gaps relate to uncertainties or further need for information identified during the Peer Review of the renewal application.

296. It should also be underlined as explained in detail above, that a robust assessment of all available data has been undertaken in the context of the Peer Review process. In addition to the AGG assessment, this included also an in-depth evaluation of the neurotoxicity data performed by the EFSA Working Group on glyphosate which was subsequently subject to an extensive scrutiny by Member States during the Pesticides Peer Review Experts' Meeting TC 80 before arriving to the final conclusions. Indeed, as preparatory work to facilitate subsequent discussions in the expert meeting, the EFSA Working Group provided a thorough assessment of all the available information including appraisal of the published literature data, and a weight-of-evidence evaluation of the possible effects of glyphosate on human health as described in the Annexes of the Peer Review Expert Meeting Report TC 80. This included also a rigorous assessment following a multistep and structured approach regarding neurotoxicity (cf Annex 7 of the Expert Meeting Report TC 80).

([225]) See https://www.efsa.europa.eu/en/about/transparency

297. Finally, in paragraphs 158 to 160 of the IRR, the Requestors recall their claim that the applicants' failure to submit the study on glyphosate-trimesium in the renewal dossier would have violated multiple provisions of Commission Regulation (EU) No 283/2013, while EFSA and the AGG would have failed to exercise due diligence, as per Article 11(3) of Implementing Regulation (EU) No 844/2012, by not recognising this omission, and would incorrectly have considered the study as not relevant. The Requestors also recall their claims that the available studies did not allow to negate the findings from literature studies and the DNT study on glyphosate-trimesium and that EFSA incorrectly classified the issue as merely a data gap.

298. The Commission refers to the detailed responses to all these points in the preceding subsections and, therefore, concludes that all grounds brought forward by the Requestors in relation to the alleged wrong assessment of developmental neurotoxicity are unfounded.

6. Alleged illegalities and manifest errors in the assessment of endocrine disrupting properties (paragraph 161 of the IRR)

299. In paragraph 161 of the IRR, the Requestors claim that the assessment of endocrine disrupting (ED) properties does not comply with Article 8(5) of the PPP Regulation and Article 7(1)(m) of Implementing Regulation (EU) No 844/2012 due to a failure to include relevant literature published over the last 10 years. In particular, the Requestors claim that studies published between 2010 and 2013 were neither comprehensively identified by the GRG nor reviewed by the competent authorities.

300. According to Article 8(5) of the PPP Regulation "*Scientific peer-reviewed open literature, as determined by the Authority, on the active substance and its relevant metabolites dealing with side-effects on health, the environment and non-target species and published within the last 10 years before the date of submission of the dossier shall be added by the applicant to the dossier".*

301. The Commission notes that, although the application for renewal was submitted in December 2019, the supplementary dossiers were submitted to the AGG in June 2020. The literature search for all topics, including ED, covered the period January 2010 - June 2020[226]. The GRG also provided an additional search specific for ED properties for the period 2016-2019 since that period was not covered by the mandate given by the Commission to EFSA for the assessment of ED properties of glyphosate in the context of the assessment previously undertaken by EFSA (2017), which covered the period 2014-2016 ([227]). This was thus done as a complimentary search, on a voluntary basis, beyond the legal requirements. A full description of the literature search can be found in the RAR ([228]). It has to be further noted that additional literature considered in the previous assessments as well as literature brought to EFSA's attention during the public consultation and published after the commenting period ([229]) were also considered in the assessment of ED properties of glyphosate. Finally, the Requestors do not provide any details of studies that would have been published between 2010 and 2013 that would not have been taken into account in the literature review.

([226]) See page 72 of the EFSA Conclusion and page 67 of 42 of "Technical and scientific assistance on the internal review" available at the following link https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2024.EN-8737

([227]) EFSA 2017 https://open.efsa.europa.eu/questions/EFSA-Q-2016-00663

([228]) See RAR, Volume 1, page 75.

([229]) For the latter see excel file 'Consolidated list of newly available publications on glyphosate brought to the attention of EFSA and AGG after the public consultation phase until the time point of drafting the EFSA conclusion. Available in the Peer review Report in Open EFSA, Supporting documents section under EFSA-Q-2020-00140, refer to 'List of newly available publications (after commenting period)': Consolidated list of newly available publications after commenting period EFSA+AGG_March 2023_public.xls'

Therefore, the literature search was in line with – and went even beyond – the legal requirements of Article 8(5) of the PPP Regulation.

7. Alleged illegalities and manifest errors in the animal toxicity assessment (paragraphs 162 to 176 of the IRR)

302. In this ground, the Requestors first recall their earlier claims that the assessment of ecotoxicity related to birds, mammals, and amphibians, particularly concerning the product for representative uses MON 52276, was incomplete. The Commission has already responded to these claims in Section III.1 - Subsection 1.c above.

303. In addition, the Requestors contend that there are serious deficiencies in the risk assessment regarding the risk for the health of domestic animals and unacceptable risk to wild fauna posed by glyphosate, which should have precluded EFSA and the Commission from concluding that the criteria set out in Article 4(3) of the PPP Regulation were met.

a. Harmful effects on (farm) animals (paragraphs 162 to 165 of the IRR)

304. In paragraph 163 of the IRR, the Requestors put forward their view that three studies on Japanese quails exposed to glyphosate-based PPPs (Ruuskanen *et al.)*, which revealed adverse effects, were disregarded in the risk assessment due to formulation differences. Nonetheless, in their view, in the absence of studies using the product for representative uses, these studies should have been considered relevant.

305. However, the mentioned studies were assessed by the AGG and discussed during the Pesticides Peer Review Experts' Meeting TC 82. The Peer Review meeting agreed that not all of the assessed endpoints were relevant for assessing effects on the population. Moreover, as the tested PPPs were not the product for representative uses under assessment, nor could their ecotoxicological comparability be confirmed, the studies were categorised 'less relevant but supplementary'. As such studies are not required by Commission Regulations (EU) No 283/2013 and 284/2013, EFSA did not identify a data gap.

306. Furthermore, endpoints other than embryonic development and reproductive output were not considered relevant for the risk assessment, which was performed in accordance with the agreed Guidance Document (EFSA, 2009) ([230]). The Peer Review concluded that the reliability of the endpoints should be reconsidered in line with the reliability criteria agreed during the meeting and, as a result, only some endpoints were assessed to be reliable by the AGG.

307. In paragraph 164 of the IRR, the Requestors claim that the recent independent studies Foldager *et al.* (2019), Estienne *et al.* (2022), Freville *et al.*, (2022), Estienne *et al.*, (2023) would confirm adverse effects of glyphosate-based PPPs on farm animals, including reduced hatching rates and other negative impacts on poultry health.

308. However, the time when the studies were published must be considered: Estienne *et al.*, 2022, Freville *et al.*, 2022, Estienne *et al.*, 2023 were published outside of the time period for which the assessment of the literature was performed. The study of Foldager *et al.* (2019), even though from 2019 was published in 2021 and therefore also outside the time period of the literature search. It is noted that these studies were not flagged by any party during the peer-review process.

309. In paragraph 165 of the IRR, the Requestors claim that a no observable adverse effect level (NOAEL) cannot be established (based on several studies in birds, as mentioned in the

([230]) EFSA (European Food Safety Authority), 2009. Guidance on Risk Assessment for Birds and Mammals on request from EFSA. EFSA Journal 2009;7(12):1438, 358 pp. doi:10.2903/j.efsa.2009.1438.

preceding paragraph 164 of the IRR) as even at very low doses, glyphosate-based PPPs would have an adverse effect on certain farm animals.

310. However, the Commission notes that the reliability of the endpoints from the wild bird reproduction studies provided in the dossier was discussed and agreed at the Pesticides Peer Review Experts meeting TC 82. The literature studies discussed at the same meeting were not considered to provide reliable endpoints for the risk assessment. Therefore, the endpoint agreed for use in the long-term avian risk assessment is well grounded and robust.

311. In addition, although the studies mentioned above were not part of the Peer Review of the risk assessment for glyphosate, it is noted that based on the scientific report from EFSA in 2018 ([231]) on the evaluation of the impact of glyphosate and its residues in feed on animal health, the reported margin of exposure for poultry was 44 ([232]), indicating a significant margin of safety when compared with the long-term endpoint agreed as part of the earlier renewal assessment, and even more significant compared to the endpoint agreed as part of the renewal in 2023 ([233]).

b. Unacceptable effects on insects (paragraphs 166 to 169 of the IRR)

312. In paragraph 166 of the IRR, the Requestors submit that the ESCORT 2 guidelines for the toxicity assessment of pesticides to insects would be influenced by industry and would not provide clear conclusions to risk managers. They also criticise the two-tier assessment system, demanding instead that the assessment should stop at the first tier (with the most sensitive species instead of allowing additional testing with a less sensitive species).

313. Indeed, the risk assessment for non-target arthropods other than bees was performed following the tiered risk assessment scheme from the applicable guidance document Guidance Document on Terrestrial Ecotoxicology ([234]), which refers to the report from the ESCORT 2 workshop. The guidance document was endorsed for use by risk managers from Member States without any participation from industry.

314. In paragraph 167 of the IRR, the Requestors claim that the two tier 1 studies submitted indicate high toxicity (i.e. 100% mortality) of MON 52276 to two insect species (*Aphidius rhopalosiphi* and *Typhlodromus pyri)*, which should have sufficed to conclude that there was an unacceptable risk to insects, particularly beneficial species necessary for natural pest control in integrated pest management systems. In paragraph 168 of the IRR, they claim that also the tier 2 studies showed unacceptable risks and that the Commission disregarded these when adopting the Reviewed Regulation. They criticise EFSA's Conclusion of a low risk to insects as not reflecting the results of the studies provided.

315. The regulatory studies ([235]) provided by the GRG included (i) tier 1 studies ([236]) conducted with the standard species considered the most sensitive (*Aphidius rhopalosiphi* and *Typhlodromus pyri*) and the formulation for representative uses 'MON 52276' and (ii) tier

([231]) https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5283.

([232]) It is noted that the most up-to-date dietary burden value for poultry from the latest Art 10 MRL Reasoned Opinion (EFSA Journal 2021;19(10):6880), and considering all authorised uses, is lower than the one estimated in EFSA 2018.

([233]) In the last renewal assessment the endpoint was established as 96.3 mg/kg whereas for the current renewal it was established as 117 mg/kg.

([234]) https://food.ec.europa.eu/document/download/424e71a2-5beb-4fa3-9198-89be916c1789_en

([235]) Relevant scientific peer-reviewed publications evaluating direct effects of glyphosate on non-target arthropods were not identified in the open literature in accordance with the criteria agreed at the Pesticides Peer Review Experts' TC 82.

([236]) i.e. Standard tier 1 testing comprises glass plate tests with Aphidius rhopalosiphi and Typhlodromus pyri and represents a worst case exposure

2 studies ([237]) with two standard species *A. rhopalosiphi* and *T. pyri*, as well as with the ground beetle *Poecilus cupreus*, the ground-dwelling spider *Pardosa* sp., the green lacewing *Chrysoperla carnea* and the rove beetle *Aleochara bilineata*.

316. All available studies and the risk assessment for non-target arthropods were discussed at the Pesticides Peer Review Experts' meeting TC 82. The experts at the meeting agreed that both tier 1 studies with the standard species presented several limitations and, therefore, they were only considered as supporting information i.e., the endpoints derived from the studies were considered unreliable.

317. The main reason for questioning the reliability of the endpoint from the tier 1 studies was that the test solution of formulated glyphosate used in the test produced a wet sticky layer on the treated glass plates that resulted in alterations of the moving behaviour of the arthropods to the point of sticking. Nevertheless, even if the endpoints from the tier 1 studies would have been considered valid for the risk assessment and indicating a high risk, following the tiered approach set out in the Guidance Document on Terrestrial Ecotoxicology ([238]) and in the data requirements on active substances and PPPs ([239]), the risk assessment would have been refined with the available tier 2 studies. Therefore, the conclusions of the risk assessment would not have changed.

318. Regarding the tier 2 studies, the experts also agreed that those with *C. carnea* and *A. bilineata* should be considered as supporting information.

319. Therefore, the risk assessment for non-target arthropods other than bees was based on tier 2 studies with the standard species (*Aphidius rhopalosiphi* and *Typhlodromus pyri)* and with *Pardosa* sp. and *P. cupreus*. In line with the guidance document, since the rates causing 50% lethal and sub-lethal effects on all tested species were higher than the predicted environmental concentration for the different representative uses with MON 52276, EFSA correctly concluded on a low in-field and off-field risk for such uses.

320. In paragraph 169 of the IRR, the Requestors' state that the communication of the risk assessment for non-target arthropods to risk managers would have failed to reflect findings on acute toxicity and on the impact of exposure to the representative product on the reproductive capacity of certain insects, as a result of which EFSA would have failed to fulfil its obligations under the precautionary principle.

321. The Requestors' claims are incorrect. In fact, in line with the applicable Guidance Document on Terrestrial Ecotoxicology, it was concluded that there were for all representative uses and EFSA correctly provided all information in Appendix B to the EFSA Conclusion ([240]).

c. Unacceptable effects on amphibians (paragraphs 170 to 172 of the IRR)

322. In paragraph 170 of the IRR, the Requestors submit that the only regulatory test on glyphosate's effects on amphibians, a metamorphosis test on glyphosate alone (namely, the Amphibian Metamorphosis Assay or "AMA" study) provided by the applicants reveals concerning impacts – such as an increase in the incidence of mild thyroid hypertrophy and an increase in follicular ce–l hypertrophy – on tadpoles at very low concentrations, was allegedly dismissed without justification by the AGG and EFSA.

323. The Commission has already addressed earlier claims of the Requestors concerning the assessment of impacts on amphibians in Section III.1 - Subsection 1.c above. It must also

([237]) The tests shall provide sufficient information to evaluate the risk of the plant protection product for arthropods using a more realistic test substrate or exposure regime

([238]) https://food.ec.europa.eu/document/download/424e71a2-5beb-4fa3-9198-89be916c1789_en

([239]) See section 8.3.2 of Regulation 283/2013 and section 10.3.2 Regulation 284/2013.

([240]) See pages 331-333 of Appendix B (List of endpoints).

be underlined that the assessment of the endocrine disrupting properties of glyphosate was conducted following a structured and systematic approach in line with the ECHA/EFSA Guidance (2018) on the hazard identification of endocrine disruptors and thoroughly discussed with the EFSA Working Group on endocrine disruptors. All related documents are included in Annex 2 of the related background documents ([241]). The assessment included the AMA study and was extensively discussed at the Peer Review Experts' meeting TC 84.

324. Contrary to the Requestors' views, the outcome of the AMA study was overall considered to be negative for ED properties since it did not show a pattern of endocrine activity and/or adversity. In the study, no change in the developmental stage and/or nHLL (normalised Hind Limb Length) was observed in tadpoles exposed to five concentrations of glyphosate active substance. Only a very slight increase in the prevalence of thyroid gland hypertrophy and follicular size increase was observed at the highest tested concentration. However, this was only mild and not observed with a dose response. The effects in snout–vent length (SVL) were observed at the three highest tested concentrations. However, there was no dose response relation.

325. It should be borne in mind that while developmental stage and nHLL are T-mediated parameters, SVL is a 'sensitive to, but not diagnostic' parameter, according to the classification in the ECHA/EFSA Guidance on the hazard identification of endocrine disruptors ([242]).

326. As outlined above, a conclusion that glyphosate does not meet the criteria of point 3.8.2 of Annex II to the PPP Regulation, as amended by Commission Regulation (EU) 2018/605, was reached following a WoE approach in line with the ECHA/EFSA Guidance (2018) on the hazard identification of endocrine disruptors.

327. In paragraph 171 of the IRR, the Requestors claim that, while the above-mentioned study only refers to tadpoles, other studies, such as Relyea (2005), would prove a high mortality rate also for juvenile and adult amphibians exposed to glyphosate in agricultural areas.

328. However, the Requestors fail to recognise that several literature studies investigating the effects of glyphosate PPPs on terrestrial phases of amphibians were available for the assessment. The criteria for assessing the relevance and reliability of the studies were discussed and agreed at the experts' meeting (Pesticides Peer Review Experts' Meeting TC 82). Few studies were considered to provide endpoints which are potentially relevant to populations. However, when considering the available information, adverse and biologically relevant endpoints were not obtained. The Relyea (2005) study was not explicitly considered in the latest analysis of the literature, as it was outside of the temporal range, and it did not report relevant data (as a formulation containing polyethoxylated tallow amine "POEA", which is prohibited in the EU, was tested).

329. In paragraph 172 of the IRR, the Requestors then reiterate that numerous studies from the public literature would demonstrate toxicity of glyphosate to amphibians, particularly frogs, claiming that those studies would have been routinely disregarded because not involving the product for representative uses, while they should have been considered relevant for assessing glyphosate's effects under realistic conditions of use.

330. In reality, all endpoints on amphibians currently listed in the List of Endpoints (Appendix B to the EFSA conclusion) contradict the Requestors' assertion. They are in fact all derived from literature studies. EFSA noted that few studies were considered capable to derive

([241]) Available in the Peer review Report in Open EFSA, Supporting documents section under EFSA-Q-2020-00140, refer to the Peer Review Report: Part 3_Peer Review Report_Glyphosate_Annexes; Peer Review Report_Glyphosate_Annexes_TC84_16 August 2023_EFSA: Annex 2. EFSA ED WG Advice Non-target organisms (NTOs).

([242]) https://doi.org/10.2903/j.efsa.2018.5311.

endpoints which are potentially relevant to populations. However, when considering the available information, adverse and biologically relevant endpoints were not obtained ([243]). Based on the available data, a comparison of the hazard endpoints with fish was carried out and discussed at the Pesticides Peer Review Experts' Meeting TC 82.

331. For acute (lethal) effects due to exposure to glyphosate, the experts agreed that the lowest fish endpoint is protective for amphibians. For chronic exposure to glyphosate, a proper comparison between fish and amphibians was not possible, since relevant and reliable chronic endpoints for amphibians were not available. In any case, a full comparability between fish and aquatic stages of amphibians would be hampered by the different response types being measured for the two groups. Nevertheless, based on the information available, EFSA did not identify concerns about impacts on amphibians.

d. Conclusion (paragraph 173 to 176 of the IRR)

332. In their conclusion, the Requestors reiterate their view that the assessment of the toxicity of glyphosate for animals would not comply with the standard of excellence because it would not permit the conclusion that there is no adverse effect on animal health or on the environment. As a result, the Requestors consider the toxicity assessment carried out by the assessors as affected by manifest errors of assessment and in breach of the requirements applicable to the assessment, because it would be based on incomplete regulatory data, would not take into account or underweight data from independent literature and would not adequately communicate on identified risks.

333. However, as explained above in reply to paragraphs 166 to 169 of the IRR, the risk assessment for non-target arthropods was carried out according to the stepwise approach included in the guidance document currently in place, the Guidance Document on Terrestrial Ecotoxicology.

334. For amphibians, the regulatory study (i.e. the AMA test), as explained in the response to paragraph 170 of the IRR, did not show a pattern of endocrine activity and/or adversity.

335. While there are no specific data requirements for regulatory studies on amphibians and reptiles and for a specific risk assessment, literature data were provided and considered according to the data requirement in point 8.1.4 of the Annex to Commission Regulation (EU) No 283/2013.

336. Criteria for evaluation of the literature data for their relevance and reliability were extensively discussed and agreed with the experts (see expert consultation point 5.10 of the meeting report of the Pesticides Peer Review Experts' meeting TC 82 ([244])) and subsequently the studies were reconsidered by the AGG according to those criteria. No risks were identified. Therefore, the points raised by the Requestors do not call into question the outcome of the assessment nor the Reviewed Regulation.

8. Alleged illegalities and manifest errors in the assessment of the effect of glyphosate on biodiversity (paragraphs 177 to 199 of the IRR)

a. Poorly listed independent scientific literature (paragraphs 181 to 185 of the IRR)

337. In paragraphs 181 and 182 of the IRR, the Requestors point at a number of independent scientific studies allegedly demonstrating effects on biodiversity from the use of glyphosate-based PPPs.

([243]) See page 22 of the EFSA Conclusion.

([244]) Available in the Peer Review Report in the Open EFSA under 'Supporting documents' under EFSA Question number EFSA-Q-2020-00140: https://open.efsa.europa.eu/study-inventory/EFSA-Q-2020-00140 ; refer to Part 3_Peer Review Report_Glyphosate_expert meeting reports_public.pdf (TC 82, Expert consultation point 5.10)

338. The Commission recalls that the potential impacts of glyphosate on biodiversity have been thoroughly assessed as described in Section II.2.e above. A summary of the biodiversity assessment is reported in the RAR, Volume 3 – B.9 (PPP), B.9.14.1 ([245]). The assessment, as well as the criteria for evaluating articles from scientific literature for their relevance and reliability ([246]) was discussed at the Pesticides Peer Review Experts Meeting TC 82[247].

339. As also noted by the Requestors themselves, the studies mentioned in paragraph 181 of the IRR, Boutin *et al.* (2014), Damgaard *et al.* (2014), *Strandberg et al.* (2012 and 2021), Baker *et al*. (2014), Baker *et al.* (2016), Mudge and Houlahan (2019), were considered during the Peer Review.

340. Furthermore, the additional studies cited in paragraph 182 of the IRR as not being evaluated were also considered as part of the assessment: Van Bruggen *et al*. (2021), Newman *et al*. (2016), Motta *et al*. (2018), Vera *et al*. (2012) is not available in the RAR since it was excluded based on title and abstract ([248]). The papers from Silva *et al.* (2023) ([249]), De Lima Silva & Pelosi (2023) were not Peer Reviewed since they were published after the publication of the EFSA Conclusion. Sanchez-Bayo (2021) and Ruuskanen *et al.* (2023) were not considered in the Peer Review, since they are outside the time period of the literature search and, it is further noted that they are not specific for glyphosate. In fact, with specific regards to the paper Sanchez-Bayo (2021), due to its horizonal nature, it does not present original experimental data and is not specific to glyphosate, it is rather a horizonal review of the ecological principles behind the potential effects of pesticides on insects and arthropods. Therefore, this review does not provide information that calls into question the assessment carried out. Moreover, on the contrary, one of the aspects mentioned by Sanchez-Bayo is secondary poisoning of invertebrates as one of the underlying principles of indirect effects – here it has to be noted that this aspect is assessed in the framework of existing guidance and was done also for glyphosate, finding a low risk ([250]).

341. In paragraphs 183 to 185 of the IRR, the Requestors claim that the reason for the non-evaluation of these articles is the poor quality of the literature search provided by the GRG as would have been explicitly deplored by the experts. The Requestors claim that the GRG did not fulfil its obligations in accordance with Article 8(5) of the PPP Regulation and Article 7(1)m of Regulation (EU) No 844/2012 so that the AGG should have declared the application inadmissible, and that the deficiency prevented the AGG and EFSA to conduct a complete evaluation fully informed by all results from scientific literature.

342. The Commission considers this claim misguided. The GRG did provide a literature search and also responded to the request by EFSA to provide additional information during the Peer

([245]) Available in the Peer Review Report in the Open EFSA under 'Supporting documents' under EFSA Question number EFSA-Q-2020-00140: https://open.efsa.europa.eu/study-inventory/EFSA-Q-2020-00140 (refer to Glyphosate_Final RAR_public.zip)

([246]) The reference made by the requestors to TC80 is assumed to be a clerical mistake.

([247]) Available in the Peer Review Report in the Open EFSA under 'Supporting documents' under EFSA Question number EFSA-Q-2020-00140: https://open.efsa.europa.eu/study-inventory/EFSA-Q-2020-00140 (refer to Part 3_Peer Review Report_Glyphosate_expert meeting reports_public.pdf (TC 82, Experts' consultation point 5.25).

([248]) Excluded because the findings of the study conducted in Argentina were difficult to relate to the EU level ecotoxicology risk assessment. The formulation used differs to the representative formulation for the Annex I in the EU.

([249]) It is noted that the Requestors indicate that this study was evaluated, however, it was published in November 2023, after the peer review ended.

([250]) See page 22 of the EFSA Conclusion: "A low risk to birds and mammals via secondary poisoning was concluded since glyphosate and metabolites AMPA and HMPA have a log Kow < 3, meaning that a quantitative risk assessment was not required."

Review ([251]). However, experts from Member States and EFSA found indeed that a literature search according to the principles of systematic literature review was not available and a data gap was identified by EFSA in section 10 of the EFSA Conclusion (2023) (i.e. *to perform a systematic literature search for data collection)*. Nevertheless, there is no legal requirement in the PPP Regulation or in Regulation (EU) No 844/2012 to carry out a systematic literature review ([252]), and all the scientific literature brought to the attention of the AGG and EFSA during the Peer Review was evaluated or screened as set out in Section III.1 - Subsection 7, point d, above.

343. Furthermore, this claim starts from the erroneous assumption of equivalence of two different concepts: admissibility and data gaps. In fact, while admissibility concerns the initial eligibility of an application by the RMS (if a dossier is incomplete the RMS can refuse admissibility), data gaps relate to uncertainties or further need for information identified during the Peer Review of the renewal application, which can only be known once the Peer Review is finalised and do not necessarily lead to the non-approval (or non-renewal of approval) of an active substance. Not all data gaps identified during the risk assessment necessarily relate to mandatory information specified in Regulations (EU) No 283/2013 and (EU) No 284/2013 setting out the data requirements for the supplementary dossiers; some, like in this case, may involve complementary data necessary for a thorough risk assessment but not explicitly requested by any regulation.

344. This distinction is confirmed by the General Court, which considered that "*the fact that the application is formally declared to be admissible for the purposes of Article 8 of Implementing Regulation No 844/2012 does not preclude the Member State from requiring additional information in accordance with Article 11(5) of that regulation, or EFSA from requiring additional information in accordance with Article 13(3) of that regulation*" ([253]).

345. Lastly, it should also be recalled, as already mentioned in Section III.1 - Subsection 1.b and Subsection 2.d above, that data gaps as such do not necessarily lead to the non-approval (or non-renewal of approval) of an active substance, as they do not automatically imply a failure to demonstrate that the active substance complies with the approval criteria in Article 4 of the PPP Regulation ([254]).The scope, the extent and the importance of data gaps are weighed by the Commission as risk manager in the light of the overall findings of the risk assessors, and it is the risk manager that ultimately decides whether the existence of such gaps put in question the findings on a possible safe representative use in accordance with Article 4 of the PPP Regulation, also taking into account the Member States' role in authorising products subsequently. Since the data gap was listed in Section 10 of the EFSA Conclusion it was therefore an outstanding issue that was not deemed of such importance to have been flagged in Section 9 of the Conclusion (concerns) and therefore was not precluding the renewal of approval.

([251]) See Data requirements 5.62, 5.77 and 5.78 in the Evaluation Table found in Part 4 of 6 of the Peer Review Report.

([252]) Article 8 (5) of the PPP Regulation and Article 7 (1)(m) of Implementing Regulation No 844/2012 do not refer to the need for a systematic literature review. A systematic literature review (SLR) is in overview of existing evidence pertinent to a clearly formulated question, which uses pre-specified and standardised methods to identify and critically appraise relevant research, and to extract, report and analyse data from the studies that are included in the review.
EFSA's guidance on the submission of scientific peer-reviewed open literature under Regulation (EC) No 1107/2009 is based on the fundamental principles of systematic review, which are: methodological rigour; transparency; and reproducibility, but a SLR is not required.

([253]) Judgment of the General Court of 8 May 2020, Agrochem-Maks d.o.o, T-574/18, EU:T:2020:226, paragraph 106

([254]) See also Judgment of the General Court of 21 February 2024, *PAN Europe v Commission*, T-536/22, EU:T:2024:98, paras. 272, 309 and 314.

b. *Deficient evaluation proposal (paragraphs 186 to 191 of the IRR)*

346. In paragraph 186 of the IRR, the Requestors further their criticism of the deficiency in the assessment of independent literature argument by denouncing the absence of a field study to assess the impacts of glyphosate on biodiversity.

347. However, the Requestors do not provide specific details of the type and nature of such study that they believe should have been submitted by the GRG. In this regard it must be noted that there are no specific data requirements, decision making criteria and/or harmonised approaches for assessing (indirect) impacts on biodiversity – while there are indeed numerous requirements to provide data on the impacts of a range of environmental species (which the GRG has duly complied with). Therefore, the lack of such a field study as claimed by the Requestors cannot be considered as non-fulfillment of the legal requirements. Furthermore, it is highly questionable whether a single study could have been sufficient to identify or exclude risks for biodiversity, considering that, as an example, in the report from the Swedish Chemicals Agency (Kemi), it is noted that multiple approaches would be needed to address the issue ([255]).In paragraphs 187 and 188 of the IRR, the Requestors claim that the applicant provided a study, namely, *Glyphosate: Indirect effects via Trophic interaction – A Practical Approach to Biodiversity Assessment*, which seems to suggest using the category of *"specific protection goals"* already existing in certain EFSA documents and which the assessors found inadequate and of questionable quality, because the study allegedly did not apply the methodology proposed to the use of glyphosate (hence, not proposing any conclusion as to the acceptability of the environmental risk posed by the substance when indirect effects are take into account).

348. The study mentioned by the Requestors was indeed submitted by the GRG and it is summarised in the RAR, Volume 3 – B.9 (PPP), B.9.14.1. The report was considered during the Peer Review and the outcome was that a data gap was set (based on shortcomings in the report), as reported in section 10 of the EFSA Conclusion, in consideration of the lack of a harmonised approach and specific protection goals (SPGs).

349. In paragraphs 189 and 190 of the IRR, the Requestors criticise the assessment approach put forward by the GRG to assess biodiversity. The Requestors in particular criticise the approach that possible indirect effects can be mitigated and allege that this represents a fundamental misunderstanding of the PPP Regulation. They also claim that in the view of experts from Member States it was possible to identify a method capable of assessing the impact on biodiversity ([256]).

350. First, it is noted that the use of risk mitigation measures may be considered as part of the risk assessment if such measures are considered realistic conditions of use. Article 6(i) of the PPP Regulation provides that the approval of active substances may be subject to risk mitigation measures. As part of the data gap set for consideration of indirect effects on biodiversity, EFSA reflected the need to consider the effectiveness of possible risk mitigation measures at landscape level, for all the uses being assessed.

351. In paragraph 191 of the IRR, the Requestors submit that methods for assessing the impacts of pesticide use on biodiversity have also been developed at national level, for example in Germany or Sweden, and therefore, in their opinion, it would have been easy to resort to one of these methods while waiting for the adoption of guidelines at EU level.

([255]) Methods for assessing the effects of plant protection products on biodiversity PM 2/21 - attached as Annex to the IRR. See for example in the summary: "According to several studies, future environmental risk assessment methods should to a larger extent than today combine laboratory, field and semi-field studies and mathematical models to capture indirect effects and direct effects on biodiversity."

(256) As indicated in Pesticide Peer Review TC 82, Experts' consultation 5.25.

352. However, the PPP Regulation, in Article 4(3)(e)(iii), conditions the assessment of impacts on biodiversity and ecosystems on the availability of guidance accepted by EFSA and Article 13(1) of Regulation (EU) No 844/2012 explicitly prescribes the use of guidance documents available at EU level at the time of the submission of the supplementary dossiers for the risk assessment. Therefore, the suggestion made by the Requestors that in the absence of such guidance *interim* methods existing at national level could have been used for the assessment of biodiversity on a transitional basis is not valid. These methods have never been endorsed by the other Member States or by EFSA and there are no indication that their experts would have found them acceptable and applicable. Moreover, the Requestors do not justify how the use of those methods would have demonstrated that indirect impacts on biodiversity exist, let alone that these would not be acceptable.

353. Furthermore, contrary to the Requestors' view, no specific method is actually proposed in the report of the Swedish Chemicals Agency (Kemi). It merely includes a systematic literature review of existing approaches, and the authors conclude that a combination of those different approaches would be needed to address the evaluation of biodiversity and indirect effects, e.g. semi-field, field studies, modelling along with monitoring would be useful. These recommendations are valuable and can be considered in the context of the discussion within the forthcoming development of a harmonised method to assess indirect impacts on biodiversity for which the Commission has given a mandate to EFSA ([257]).

354. Therefore, no agreement on the methods to be used is yet available. In the absence of any agreed harmonised guidance, the GRG chose a particular method and assessment which, however, was not considered to be fully acceptable by Member States or EFSA. Accordingly, a data gap was set and was then considered as part of the decision on renewal. Considering the complexity of the topic, a robust approach is necessary to ensure that methods to assess the indirect effects are properly introduced and implemented. To this purpose EFSA considers as priority ([258]) the definition and agreement of specific protection goals (SPGs)[259] for non-target arthropods and non-target terrestrial plants. Indeed, arthropods and wild plants are fundamental elements of food networks and preserving both their biomass and diversity is pivotal to safeguard ecosystem services delivery and ecological function such as habitat provision, food web support, pest control, pollination. It is therefore clear that the updating of the guidance documents on non-target arthropods and non-target terrestrial plants is of fundamental importance also for the scientific evaluation of indirect effects.

c. Absence of a risk assessment (paragraphs 192 to 196 of the IRR)

355. In paragraphs 192 and 193 of the IRR, the Requestors state that the conclusion of the Member States and EFSA, in the absence of guidance documents on assessing the impact of active substances on biodiversity, to set a data gap, was erroneous.

356. First of all, as set out in paragraph 194 of the IRR, this conclusion would not reflect the discussion among experts who actually concluded "*that a sound assessment could have been performed by the applicants on which it seems that a least one meeting took place with the applicants for re-approval".*

([257]) The mandate will be made available in OpenEFSA following acceptance of the mandate by EFSA.

([258]) See page 105 of Technical and scientific assistance on the internal review under Regulation (EC) No 1367/2006 of Commission Implementing Regulation (EU) 2023/2660 renewing the approval of the active substance glyphosate in accordance with Regulation (EC) No 1107/2009 (wiley.com). See also the list of priorities for guidance development: https://food.ec.europa.eu/document/download/f383f32c-1e42-468c-a70a-85cc51337fe4_en?filename=pesticides_ppp_app-list-guidance_priority-list.pdf

([259]) i.e. the specific goals of an environmental risk assessment in terms of what to protect, where to protect it, over what time period and with what degree of certainty.

357. However, the "sound assessment" that could allegedly have been performed is explained in the position paper of the EFSA Working Group (WG) ([260]), where some recommendations were given to address the issue in the absence of a harmonised approach. These recommendations are very specific and do not refer to any existing approach in particular. EFSA, indeed asked the GRG to submit a scientific assessment compliant with these recommendations as set out in the request for additional information ([261]). The GRG submitted a revised assessment. However, the experts involved in the Peer Review and EFSA concluded that the approach to assess the risk to biodiversity was inadequate ([262]).

358. In any case, the fact that the GRG did not provide an assessment found acceptable by the experts involved in the Peer Review and EFSA does not mean that a sound assessment was not carried out on glyphosate as part of the renewal process. On the contrary, the AGG and EFSA conducted an assessment of indirect effects based on the available knowledge as part of the risk assessment of glyphosate (see page 28 of EFSA Conclusion). However, as noted in the EFSA Conclusion, the absence of specific protection goals and the fact that such effects are multifactorial by nature, i.e. not caused by pesticide use alone but also by other significant factors, makes it difficult for the assessors to identify and quantify risks due to indirect effects on biodiversity and decide on the appropriate level of protection.

359. As a second reason, in paragraph 195 of the IRR, the Requestors submit that the condition of Article 4(3), point (e), of the PPP Regulation that scientific methods accepted by EFSA are available would not oppose the acceptance of "ad hoc" assessment methods. Furthermore, in accordance with Article 4(3), point b, of the PPP Regulation, the taking into account of indirect impacts on biodiversity on the health of animals would not be conditional to the adoption of such guidance.

360. The Commission considers the claim unfounded. Whether used "ad hoc" or not, the fact remains that Article 4(3), point (e), of the PPP Regulation requires, for the assessment of indirect impacts on biodiversity, that scientific methods accepted by the EFSA to assess such effects are available and that a guidance document with a harmonised approach to assess possible indirect effects on biodiversity, as was acknowledged during the peer review of glyphosate, is not available. Despite some scientific insights and developments in the area, a validated approach, which requires the definition of SPGs and specific data requirements, agreed by the Commission and the Member States is not yet available.

361. Moreover, Furthermore, the claim that the assessment of biodiversity could have been undertaken based on other available methods in accordance with Article 4(3), point (b), of the PPP Regulation, is incorrect. The assessment required to fulfil Article 4(3), point (b), of the PPP Regulation, i.e. to ensure that there are no harmful effects on animal health, relates to different aspects of the assessment of an active substance.

362. Lastly, in paragraph 196 of the IRR, the Requestors claim that it was not plausible to conclude on a data gap given the ample number of studies in scientific literature, which was simply not systematically referenced, and they refer to a specific example related to aquatic organisms.

363. However, the Requestors fail to recognise that, as reported in the EFSA Conclusion, most of the literature studies were considered to be of low relevance for the representative uses,

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([260]) Annex to TC82 "Annex - Discussion Paper Biodiversity Assessment_public" - can be found in the Peer Review Report documents published by EFSA

([261]) See Reporting Table point 5(435) available in the Peer Review Report in the Open EFSA under 'Supporting documents' under EFSA Question number EFSA-Q-2020-00140: https://open.efsa.europa.eu/study-inventory/EFSA-Q-2020-00140 (refer to Part 2_Peer Review Report_Glyphosate_reporting tables_public.pdf (electronic pages 1870-1872 of 2930)

([262]) See Data requirement 5.79 in the Evaluation Table (Part 4 of 6 of the Peer Review Report).

therefore the experts correctly agreed that a conclusion cannot be reached to exclude possible negative impacts on non-target species, habitats and ecosystems due to indirect effects via trophic interactions. Moreover, as stated earlier in section 8(IV)(a), there is no legal requirement to provide a systematic literature search, Finally, the claim that no conclusion could be reached on aquatic organisms due the lack of a systematic literature search reflects the outcome of the expert meeting but it is also important to consider the overall assessment for aquatic organisms reported in the EFSA Conclusion ([263]).

d. Conclusion (paragraphs 197 to 199 of the IRR)

364. In paragraphs 197 to 199 of the IRR, the Requestors claim that the evaluation of risks for biodiversity does not comply with requirements for completeness and excellence, repeating the earlier arguments about the incompleteness of the search provide by the GRG which, in their view should have led the AGG to declare the application for renewal inadmissible. They also criticise that the GRG did not even attempt to demonstrate the absence of harmful effects of the use of glyphosate-based products on the environment, including effects on biodiversity and on the other, the competent authorities only noted a lack of data, rather than acknowledging the absence of a comprehensive method for assessing risks to biodiversity. They then claim that methods existing at the Member State level should have been used in the absence of a formal guidance document.

365. The Commission has responded to all these arguments in the preceding subsections and recalls that in the EFSA Conclusion no risks were identified which would lead to the conclusion that the approval criterion in Article 4(3)(e)(iii) of the PPP Regulation is not fulfilled. As explained in Section III.1 - Subsection 1.b above, the identification of a data gap (in this case related to indirect impacts on biodiversity via trophic interaction) itself does not imply the existence of a risk, nor did it require to not renew the approval of glyphosate.

366. In fact, the data gap identified for possible indirect effects on biodiversity was fully considered by risk managers and taken into account in the conditions set for using plant protection products containing glyphosate in the Reviewed Regulation, following a precautionary approach. To address this gap, the Reviewed Regulation includes a legal requirement for the GRG to provide confirmatory information on the possible indirect effects on biodiversity via trophic interactions, within 3 years from the date when relevant guidance is agreed at Union level. If this information is not provided or its assessment leads to the conclusion that there are unacceptable indirect impacts on biodiversity via trophic interaction, the approval will be withdrawn in accordance with Article 21 of the PPP Regulation.

9. Alleged failure to take into account exposure to glyphosate by inhalation (paragraphs 200 and 201 of the IRR)

367. With this ground, the Requestors argue that the risk assessment of exposure by inhalation carried out by the AGG and EFSA does not permit the conclusion that there is no adverse effect in health. The Requestors state than an acceptable assessment of the impacts of exposure to glyphosate through the air was not undertaken, in particular since the assessment

([263]) See page 25 of the EFSA Conclusion "For aquatic organisms, the experts agreed that in principle the ETO-RAC is suitable to cover both direct and indirect effects including trophic interaction among the aquatic food chain, as indicated in the EFSA PPR Panel (2013). However, the experts noted that some specific issues (e.g. disruption of the biofilm, community shifts in microbes, effects via contact on emergent macrophytes via spray drift, indirect effects driven by direct effects occurring outside of the water system) are not currently covered in the EFSA PPR Panel (2013). Overall, for aquatic organisms, the dataset was also considered too limited to reach a conclusion for indirect effects not covered by the direct effects.".

conducted in accordance with the relevant guidance took into account exposure during a 24-hour period only. They consider that the AGG and EFSA should have requested a long-term study of exposure by inhalation in the light of the concentrations reported in literature and that in the absence of such a study they could not exclude a high risk for residents, in particular children. In order to justify their concerns about exposure through inhalation, the Requestors refer to four publications allegedly demonstrating the volatility and long-range transport of glyphosate through the air and its presence in air and dust.

368. The Commission considers that this claim is unfounded. First, the risk assessors from EFSA and Member States did not consider the performance of a long-term inhalation toxicity study necessary for glyphosate. In fact, no local effects in the respiratory tract are anticipated at the expected concentrations of glyphosate in the air compartment or in house dust ([264]). Those levels would likely contribute in a marginal way to the overall systemic exposure to glyphosate for the general population**.** From the review of available biomonitoring data performed in the Peer Review, estimated systemic exposure levels (resulting from different exposure pathways in the population, including by inhalation) were below the derived toxicological reference values for the EU population.

369. Regarding the monitoring data of glyphosate in the air compartment, despite the few data available and the intrinsic properties of glyphosate (i.e. non-volatile), the information provided from literature (including Kruse-Plass et al., 2021) showed a high frequency of quantified samples with values above the LOD (limit of detection) for glyphosate. However, the sampling apparatus (passive samplers) used in these studies measured particulate-bound glyphosate and not gas phase only. Transportation to air was therefore likely to be caused by wind-eroded particles transportation rather than volatilisation or transport of aerosols formed during spraying ([265]).

370. EFSA did conduct an assessment of impacts on health via inhalation for bystanders/residents with the EFSA model (belonging to the EFSA operator exposure guidance ([266]). EFSA used a default concentration in air of 1 µg/m^3 (hence 0.001 mg/m^3), resulting in systemic exposure estimations for residents and bystanders below the (A)AOEL for all the representative uses (all < 20% of the applicable reference values) ([267]). Importantly, this default value used in the risk assessment is above the monitored concentrations determined in air samples, therefore the risk assessment performed is fully protective for human health.

371. The studies Zaller *et al.*, 2022 and SPRINT, Navarro et al., 2023 were not considered as they were published after the timeframe of the literature search performed according to the regulatory requirement and they were also not brought to EFSA's attention during the public consultation on the draft RAR. The Requestors do not explain how those studies would impact the outcome of the risk assessment for glyphosate, as they merely state that the studies show the presence of glyphosate in house dust and exposure via inhalation. Neither of the articles indicate a specific risk from exposure to glyphosate via dust and does not provide estimations of air concentrations of glyphosate. Therefore, it is not possible to

([264]) See page 110 of Technical and scientific assistance on the internal review under Regulation (EC) No 1367/2006 of Commission Implementing Regulation (EU) 2023/2660 renewing the approval of the active substance glyphosate in accordance with Regulation (EC) No 1107/2009 (wiley.com)

([265]) See page 110 of Technical and scientific assistance on the internal review under Regulation (EC) No 1367/2006 of Commission Implementing Regulation (EU) 2023/2660 renewing the approval of the active substance glyphosate in accordance with Regulation (EC) No 1107/2009 (wiley.com)

([266]) EFSA (European Food Safety Authority), 2014. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874, 55pp.https://doi.org/10.2903/j.efsa.2014.3874.

([267]) See pages 34-35 of Appendix B to the EFSA Conclusion for the exposure calculations for residents and bystanders.

conduct a comparison with the default concentration used in the non-dietary exposure assessment of glyphosate.

372. It is noted that the Requestors do not provide a reference to the report from the NGO Générations Futures that is mentioned in paragraph 200 of the IRR, therefore it is not possible to provide any specific comment on it. In any case, the Requestors do not explain how the statement that glyphosate is "qualitatively and quantitatively, the most found pesticide in the air in northern France" would alter the outcome of the risk assessment carried out for glyphosate.

10. Alleged systematic failure to take independent scientific literature into account (unnumbered paragraph following paragraph 201 of the IRR)

373. In this ground, the Requestors note that a significant percentage of peer-reviewed scientific literature studies was considered not reliable or supplementary and did thus not impact the risk assessment. They consider that this questions the application of the ruling in the Blaise case concerning the taking into account of literature and the opinion of Advocate-General Medina in Joined Cases C-309/22 and C-310/22. Although this ground is not further substantiated, the Commission understands these references to concern the obligation to take into account the most recent and reliable relevant evidence and not to give in all cases preponderant weight to the studies provided by the applicant.

374. The Commission has already responded to the ground regarding the alleged unjustified dismissal of literature studies in Section III.1 - Subsections 2, 6, 8 above. As explained there, the consideration of literature studies and how they have been assessed in terms of reliability and relevance in line with the relevant guidance is fully explained in the RAR. All related documents are included in Annex 1 and 2 to the Expert Meeting Reports for TC 84 ([268]). Both regulatory studies and studies retrieved in the peer reviewed open literature throughout the process of the renewal of glyphosate were evaluated following the above-mentioned approach.

375. The assessment of guideline regulatory studies as well as available scientific literature ensures that scientific assessments are comprehensive and rigorous (as a standard set of safety studies is always required), taking into account all available information so that conclusions are scientifically sound. Risk assessors are therefore provided with information from various sources and not only from the specific applicant for renewal. However, the acceptance of both studies conducted by applicants and literature studies is not automatic but rather evaluated on a case-by-case basis to determine their relevance and reliability in contributing to the overall risk assessment.

376. During the initial assessment by the RMS and the subsequent Peer Review, experts from the Member States and EFSA carefully assess the relevance and reliability of studies conducted by applicants and from the scientific open literature. Specific guidance on how to identify and select scientific peer-reviewed open literature and how to report it in a dossier exists and is used by applicants and risk assessors in Member States and EFSA. Likewise, regulatory studies conducted by applicants are also not accepted by default and are fully evaluated before being accepted. Risk assessors may decide to exclude them from use in risk assessment if they are considered deficient.

377. In the case of glyphosate, it is clear from the RAR, the EFSA Conclusion and its background Peer Review Report that the extensive scientific review took into account a range of peer-

([268]) Available in the Peer review Report in Open EFSA, Supporting documents section under EFSA-Q-2020-00140, refer to the Peer Review Report: Part 3_Peer Review Report_Glyphosate_Annexes; Peer Review Report_Glyphosate_Annexes_TC84_16 August 2023_EFSA: Annex 2. EFSA ED WG Advice Non-target organisms (NTOs)

reviewed scientific literature. However, in line with the above-mentioned requirements, not every literature study on any glyphosate-containing plant protection product was considered relevant or pertinent. For example, studies carried out on formulations containing the co-formulant POE-tallowamine, which was banned in the EU for use in products containing glyphosate due to concerns about its toxicity in 2016, were not considered to be relevant for the risk assessment, as any effects observed could not be attributed unequivocally to glyphosate.

378. This thorough review process is also reflected in a document prepared by the AGG, which briefly outlines the methodology used for assessing public scientific literature in the assessment of glyphosate ([269]). The detailed literature search strategy, described in the draft RAR, demonstrates the transparency and rigor in the selection and evaluation process. Relevant literature is summarised and assessed, while non-relevant literature, such as studies on socio-economic effects, is appropriately excluded. In addition, the reliability of studies is carefully evaluated, with those not meeting standards of reporting or methodology deemed less reliable.

379. As follows from the above, the comprehensive and rigorous approach taken for the assessment of independent scientific studies is fully in line with the principles outlined in the Blaise judgment and in the opinion of Advocate-General Médina. Therefore, this claim is unfounded.

III.2 ALLEGED DEFICIENCES AT RISK MANAGEMENT STAGE (PARAGRAPHS 202 TO 222 OF THE IRR)

380. In this ground, the Requestors contend that the Commission committed a manifest error of assessment when considering that glyphosate fulfils the conditions in Article 4 of the PPP Regulation and renewing its approval.

381. First, in paragraphs 203 to 210 of the IRR, the Requestors submit that a risk management measure can only be adopted on the basis of a risk assessment that is 'complete' and that is 'excellent, transparent and independent', which in their view, is not the case for the risk assessment conducted for glyphosate.

382. In paragraph 205 of the IRR, the Requestors list the elements that they consider incomplete, notably the alleged absence of the long-term toxicity (including carcinogenicity) of the product for representative uses, absence of toxicological information for one co-formulant, absence of consideration of literature information and other data on the impacts of glyphosate on the microbiome, and the absence of an assessment of the impacts on biodiversity. They contend that, as a result, the Commission could not lawfully have concluded that the conditions in Article 4 of the PPP Regulation were fulfilled.

383. The Commission considers that the Requestors' claim is unfounded. As set out in detail in Section III, and in particular Subsections 1, 4 and 8 above, none of the arguments brought forward by the Requestors demonstrate that the risk assessment conducted by the AGG, ECHA and EFSA, including in relation to the elements referred to, would not have been complete.

384. Furthermore, even if the EFSA Conclusion had not been as complete as it was in fact submitted, this would not necessarily have prevented the Commission in making an adequate risk management decision. As explained in Section III.1 - Subsections 1.b and 2.d above, the presence of data gaps and issues that could not be finalised does not prevent a decision to renew the approval of an active substance. Furthermore, the Commission must "take into account" the conclusions of EFSA and these conclusions are the starting point for the risk

([269]) https://food.ec.europa.eu/document/download/ba487ec2-3e60-4db2-8bc8-e095cf6e792e_en?filename=pesticides_aas_agg_report_202106.pdf

management decision and have significant weight as a reflection/expression of the current scientific and technological information available to the Commission at the time of its decision. ([270]). In any case, the Commission did consider the EFSA Conclusion and its background documents as well as the RAR, throughout its decision-making process, and exercised its risk manager role when considering data gaps–and uncertainties.

385. In paragraph 206 of the IRR, the Requestors list the elements that they consider show that the risk assessment does not comply with the requirement of excellence, notably that the AGG would not have reacted to the insufficient literature search by the GRG, alleged factual errors in the assessment of carcinogenicity by ECHA, and the alleged incapacity to deploy a method for the assessment of impacts on biodiversity although such methods exist at Member States level.

386. The Commission considers that the Requestors' claim is unfounded. As set out in detail in Section III.1, in particular Subsections 1, 3, 4, 5 and 8 above, none of the arguments brought forward by the Requestors demonstrate that the risk assessment would not have complied with the requirements of excellence.

387. In paragraph 207 of the IRR, the Requestors list the elements that they consider to show that the risk assessment conducted does not comply with the requirement of independence, notably the biased evaluation of carcinogenicity, systematic under-valuation of scientific literature and over-valuation of studies provided by the GRG, and a consistent approach to consider doubts/uncertainties in favour of a renewal of approval (in particular for DNT and genotoxicity).

388. The Commission considers that the Requestors' claim is unfounded. As set out in detail in Section III.1, in particular Subsections 2, 3, 4 and 5 above, none of the arguments brought forward by the Requestors demonstrated that the risk assessment would not have been independent.

389. In paragraph 208 of the IRR, the Requestors list the elements that they consider to show that the risk assessment conducted does not comply with the requirement of transparency, notably, absent or incomplete reasoning for certain methodological choices (e.g. the statistical methods in the evaluation of carcinogenicity or the not taking into account of certain positive results in relation to ecotoxicity), the over-valuation of non-published studies not reviewed by independent scientists, and the inadequacy of certain conclusions by EFSA and the content of discussions between experts from the Member States.

390. The Commission considers that the Requestors' claim is unfounded. As set out in detail in Section III.1, in particular Subsection 3, 5 and 7 above, none of the arguments brought forward by the Requestors demonstrate that the risk assessment would not have been transparent.

391. As all of the above claims are unfounded, the Requestors' conclusion, in paragraphs 209 and 210 of the IRR, that these issues would "inevitably" have affected the conclusions of the risk assessment and would have deprived its conclusions of plausibility is also unfounded.

392. Second, in paragraphs 211 to 215 of the IRR, the Requestors refer to the "high number" of "issues not finalised" and "outstanding issues" identified by EFSA and argue that, faced with "such a number of uncertainties", the precautionary principle should have prevented the renewal of glyphosate. The Requestors submit that the possible clastogenicity of an impurity should have been identified by EFSA as a critical area of concern instead of an outstanding issue, as done for another active substance, cypermethrin, and that several other

([270]) Judgment of the General Court of 21 February 2024, PAN Europe v Commission, T-536/22, EU:T:2024:98, paras. 89 and 90.

outstanding issues should also be considered pertinent. The Requestors also argue that insofar as these outstanding issues relate to exclusion criteria and concern all representative uses, these should have been qualified as issues not finalised. Finally, they attempt to reinforce their position by referring to a decision by the Tribunal administratif de Montpellier, which ruled that in the absence of an assessment of the impacts on biodiversity, the precautionary principle would prevent the granting of a product authorisation.

393. The Commission has already responded to these points in Section III.1, Subsections 1a, 1b, 2b and 2c above, and recalls that the definition of an "issue not finalised" is set out in the EFSA Conclusion (Section 9.1). EFSA did not consider the issues listed "as other outstanding issues" (Section 10) as fitting into that category. For example, the issue of the 'Genotoxic potential of certain glyphosate metabolites', to which the Requestors refer in paragraph 213 of the IRR - related to the need for more data on genotoxicity of metabolites formed in genetically modified (GM)-crops. First, there was no indication of genotoxicity, while further data would have been needed for completing such an assessment for N-acetyl glyphosate, N-glyceryl AMPA and N-malonyl AMPA. However, use of glyphosate in GM-crops was not a representative use in the application and, therefore, the further assessment of these metabolites was, not relevant for the renewal.

394. As regards the comparison with the active substance cypermethrin, in the assessment of which EFSA did find a critical area of concern, the Commission notes that this substance is different from glyphosate and that, as these two substances are not inherently comparable, an attempt to demonstrate disparities in their assessment becomes illogical. Furthermore, despite those critical areas of concern, the approval of cypermethrin could be renewed. ([271]).

395. Furthermore, the Commission notes that all data gaps, issues not finalised and other important uncertainties (including outstanding issues) are taken into account by risk managers when determining if an approval can be renewed or not and setting possible conditions and measures to manage any risks or uncertainties. This was also done in the case of glyphosate as documented in the Renewal Report, which provides the risk managers' reasoning why they did not preclude renewal.

396. As confirmed by the General Court in Case T-536/22 ([272]) and explained in Section III.1 - Subsection 2.d above, the Commission, as a risk manager, must take into account the risk assessment and consider whether any identified risks and/or uncertainties can be adequately mitigated and managed to meet the approval/renewal criteria. This includes the application of conditions and restrictions, as necessary, to result in the identification of at least one safe use.

397. Accordingly, the Commission exercises discretion in selecting risk mitigation measures to address risks and/or uncertainties, taking into account various elements such as scientific evaluations and opinions, in particular those of ECHA and EFSA. The Commission also evaluates the significance of any identified data gaps in light of the overall findings of the risk assessors. Ultimately, it is the Commission's responsibility to determine whether the existence of data gaps raise concerns regarding the feasibility of a safe representative use in accordance with Article 4 of the PPP Regulation, while also considering the role of Member States in subsequent product authorisation.

([271]) PAN Europe also submitted a request for internal review of Commission Implementing Regulation XXX renewing the approval of cypermethrin, to which the Commission responded on YYY; PAN Europe subsequently challenge the Commissions response in Court, leading to the Judgment of the General Court of 21 February 2024, *PAN Europe v Commission*, T-536/22, which PAN Europe subsequently appealed (reference EU:T:2024:98).

([272]) Judgment of the General Court of 21 February 2024, *PAN Europe v Commission*, T-536/22, EU:T:2024:98, paras. 80 and further.

398. As regards the reference made by the Requestors to the exclusion criteria (which the Commission assumes refers to the so-called 'cut-off' criteria – i.e. those listed in Article 4(1), second subparagraph, of the PPP Regulation), the Commission notes that the Requestors do not explain how the issues that could not be finalised and the outstanding issues would be linked to those criteria and notes that no such cut-off criterion was found to be met in the risk assessment.

399. As regards the Requestors' reference to a ruling from the Tribunal administratif de Montpellier, the Commission notes that this case seemingly concerns the authorisation of a specific PPP at Member State level. The Requestors do not explain how the circumstances of the case relate to the renewal assessment for glyphosate. In addition, it is noted that the Tribunal administratif de Montpellier did not ask for a preliminary ruling from the European Court of Justice.

400. Third, in paragraphs 216 to 222 of the IRR, the Requestors criticise the restrictions and conditions imposed by the Reviewed Regulation as risk mitigation measures. First of all, in paragraph 216 of the IRR, the Requestors consider that the Commission cannot remedy the gaps and insufficiencies of the evaluation by accompanying the renewal with conditions or by "transferring its own responsibility" for adopting measures ensuring safety of health and the environment to the Member States. They also claim that many of the conditions are not mandatory, badly described and/or clearly go against the precautionary principle.

401. The Commission considers that these claims are unfounded. First of all, Article 6(i) of the PPP Regulation clearly foresees that the Commission may impose risk mitigation measures in approvals if needed to ensure safety of the use of products containing an active substance. Moreover, where only specific safe uses are identified, the Commission is still obliged to renew an approval when there is at least one safe use (Article 4 (1): shall), as long as it can be ensured, through appropriate conditions and restrictions pursuant to Article 6, that PPPs containing the substance concerned are only authorised for such safe uses ([273]).

402. Furthermore, the claim that the Commission would "transfer its own responsibility" for adopting measures to ensure the safety for health and the environment disregards the two-step procedure foreseen in the PPP Regulation with approval/renewal at EU level and authorisation of the product at Member State level.

403. Under the first step, the Commission approves or renews the approval of an active substance where one or more representative uses of at least one PPP containing that active substance meet the approval criteria laid down in the PPP Regulation. Under the second step, Member States assess individual PPPs containing that active substance and their uses at national level. Accordingly, the authorisation of each specific PPP containing approved active substances falls under the responsibility of individual Member States, but it is also done in accordance with harmonised criteria set in the PPP Regulation. This approach not only allows Member States to account in their assessments and decisions the local environmental and agricultural conditions and acknowledges that the uses and the safety profile of PPPs might vary significantly across different regions of the Union. Consequently, while some

([273]) The Requestors' reference to the ruling of 20 April 2023 in case C-144/21, paragraph 83 does not support their argument for several reasons: the cited case concerns the socio-economic benefits of uses of chromium trioxide versus the risks to human health, specifically under Regulation (EC) No 1907/2006. The ruling emphasises the need for a sound and conclusive judgment on risks before authorising substances of very high concern in the context of that Regulation. The Court's findings in case C-144/21 highlight deficiencies in risk assessment and data representativeness specific to the case of chromium trioxide. The court noted that uncertainties and lack of representative data undermined the Commission's decision. However, this does not directly translate to the present case under the PPP Regulation, where the regulatory framework explicitly permits approvals subject to conditions to ensure safety, and the imposed measures are designed to address and mitigate identified risks effectively.

Member States may find that same PPPs containing glyphosate meet their safety standards and can be authorised for certain uses, others may determine that no safe use can be established, leading to a refusal to authorise such products. When taking that decision, the Member States remain obliged to apply the provisions of the PPP Regulation and other relevant legislation and to implement the condition and restrictions set in the approval of an active substance at EU level.

404. It is clear at this point that, in a two-step process foreseen by the legislator, the approval/renewal stage is not the conclusive step directly leading to the placing on the market of a plant protection product nor can it replace the authorisation stage. In fact, the relevance of the authorisation stage in the assessment of a plant protection product has been emphasised in several judgments of the General Court and the Court of Justice ([274]), from which it is clear that the approval/renewal and authorisation processes play their individual (even though interconnected) role in determining which PPPs can be safely put on the market.

405. Next, in paragraph 217 of the IRR, the Requestors put forward four examples of measures that the Commission would have left to the Member States and that would allegedly not be mandatory, badly described and/or clearly go against the precautionary principle. In the first indent of paragraph 217 of the IRR, the Requestors claim that the Reviewed Regulation should have prohibited all uses which were not found to be safe at EU level. The Commission considers that this claim is incompatible with the principles of the PPP Regulation. Article 4(5) of the PPP Regulation, in conjunction with point 2.1 of Annex II, unequivocally states that the identification of a single safe use in at least one Member State is sufficient for the renewal of approval. In line with the two-stage process described in the preceding points, it is for Member States to assess - following the same approach of scientific risk assessment and normative risk management as at EU level for approvals, in accordance with Article 28 et seq. of the PPP Regulation - the risk of each and every use of every PPP, containing the active substance, that they may authorise at national level. Only where the risk assessment at EU level clearly demonstrates that a particular use cannot be safe under any circumstances in any Member State can the Commission prohibit such use in the approval. However, this is not the case for glyphosate.

406. In the second indent of paragraph 217 of the IRR, the Requestors claim that Member States may derogate from the maximum application rates determined by EFSA in order to address the risk to small herbivorous mammals. This is indeed possible but, as specified in the Reviewed Regulation, only when the outcome of the risk assessment undertaken for the specific uses for which authorisation is applied for demonstrates (e.g. on the basis of additional data submitted by applicants) that a higher rate does not lead to any unacceptable effects on the environment in respect of small herbivorous mammals.

407. In the third indent of paragraph 217 of the IRR, the Requestors claim that Member States can authorise uses by non-professionals where no use of this type has been considered in the context of renewal and health risks are well documented. However, firstly, no details about the alleged health risks are provided. Secondly, as indicated in recital 26 of the Reviewed Regulation, uses by non-professionals were not part of the representative uses submitted by the applicant and therefore were not assessed. However, no risk to human health was identified in the assessment that would have justified a prohibition of uses by non-professionals. Nevertheless, considering that non-professionals do not have the same knowledge in relation to the safe use of pesticides as professionals, it was considered a

(274) Judgment of the General Court of 21 February 2024, *PAN Europe v Commission*, T-536/22, EU:T:2024:98, paras. 109-115, judgment of the Court of 25 April 2024, *PAN Europe*, C-308/22, EU:C:2024:350 and judgment of the Court of 25 April 2024, C-309/22 and C-310/22, *PAN Europe*, EU:C:2024:356.

prudent approach to oblige Member States to pay particular attention to uses by non-professional users when considering applications for authorisation of products.

408. Finally in the fourth indent of paragraph 217 of the IRR, the Requestors claim that Member States would be able to derogate from drift reduction measures that aim to protect non-target organisms outside treated areas. Here it should be recalled that the Reviewed Regulation lays down default measures to reduce spray drift that must be implemented *'unless the outcome of the risk assessment undertaken for the specific plant protection product use indicates that such risk mitigation measures are not needed or can be lowered because there are no unacceptable risks caused by spray drift'* ([275]). Thus, Member State may indeed deviate from the requirement, but only when the outcome of the risk assessment undertaken for the specific uses for which authorisation is applied for demonstrates (e.g. on the basis of additional data submitted by applicants) that less stringent drift reduction measures to suffice non-target organisms outside treated areas.

409. Thereafter, in paragraphs 218 and 219 of the IRR, the Requestors argue that the Reviewed Regulation leaves to the Member States the task of assessing certain risks that should have been assessed at European level, notably the indirect impacts on biodiversity, which Member States are tasked to assess '*without the least harmonisation, guidance nor safeguard*' and of assessing the toxicity of co-formulants. In their view, this is wishful thinking as the European authorities were not in a position to do so and Member States are not in a position to assess co-formulants without a complete REACH dossier.

410. The Commission considers these claims unfounded. With regards to biodiversity, the Reviewed Regulation foresees harmonisation, guidance and safeguards as it requires Member States to pay particular attention to indirect effects on biodiversity via trophic interactions once relevant methods and guidance to identify such effects are agreed at EU level ([276]). It is because such methods and guidance at EU level are currently still absent, that the Reviewed Regulation provides that Member States may apply methods which they consider appropriate to determine the potential indirect effects of PPPs containing glyphosate and which take into account their specific agro-environmental conditions. When doing so, if they identify any such possible indirect effects on biodiversity, Member States must set specific conditions or restrictions of use for PPPs containing glyphosate, considering in particular if practical alternative control or prevention methods with lower impacts on biodiversity are available.

411. With respect to the toxicity of co-formulants ([277]), contrary to the Requestors' claim, the absence of a full REACH dossier does not prevent the assessment through other methods, also applicable without a 'full' dataset. Furthermore, Member States notably have the possibility, in accordance with point 1.11 in the introduction to the Annex to Regulation (EU) No 284/2013 setting out the data requirements for applications for authorisation of PPP, to require the same data as for active substances.

412. Next, in paragraph 220 of the IRR, the Requestors argue that, by leaving risk mitigation measures to the discretion of Member States, the Commission has not fully exercised its role as risk manager.

([275]) Annex I to the Reviewed Regulation, under the column 'Specific provisions'.

([276]) See Section 8(IV)(b) of the reply for further details on the mandate to develop such guidance.

([277]) For a more detailed overview of the Co-formulants Regulation please refer to the Commission reply to the request for internal review (IR/2023/498428) of Commission Implementing Reg. (EU) 2023/574 of 13 March 2023 setting out detailed rules for the identification of unacceptable co-formulants in plant protection products pursuant to Reg. 1107/2009 Ares(2023)6685241, available at the following link https://environment.ec.europa.eu/law-and-governance/aarhus/requests-internal-review_en.

413. Contrary to the Requestors' argument, the Commission did provide for specific risk mitigation measures where so required in the light of the results of the risk assessment, e.g. the setting of maximum levels for 5 toxicologically relevant impurities in glyphosate as manufactured, the setting of maximum rates of application that should normally apply to ensure protection of small herbivorous mammals, and the setting of drift reduction measures to protect non-target plants.

414. In addition, in line with the two-step procedure foreseen in the PPP Regulation, it is for the Commission to set general conditions and restrictions as required on the basis of the assessment of the active substances but for the Member States to set specific conditions of use for each PPP as deemed necessary on the basis of the assessment of that PPP, taking into account the conditions and restrictions set by the Commission in the approval of the active substance. Accordingly, in approving an active substance or renewing an approval, the Commission must define the conditions that – based on the assessment of the active substance – are relevant for all PPPs in all Member States, but it is not called on to and cannot define all exact conditions of every use of any PPP containing the active substance concerned in any Member State. In fact, the conditions are rather, according to Article 31 of the PPP Regulation, established as part of the individual authorisation of each PPP, issued on the basis of the risk assessment carried out by the responsible Member State, in light of up-to-date scientific information and the specific climatic and agro-environmental conditions of that same Member State ([278]).

415. Furthermore, the need for specific mitigation measures for a specific PPP depends on the particular parameters of use – including the rates and timings of application, as well as the crop and the specific climatic and geographic conditions in Member States. Therefore, Member States are best placed to determine such measures when assessing each use of each PPP to be placed on the market and it can well be that as an outcome of their risk assessment, certain risk mitigation measures found necessary as a result of the EU risk assessment need to be reinforced or, conversely, can be relaxed. The Reviewed Regulation accommodates this possibility in the risk mitigation measures set to protect non-target plants ([279]).

416. Still in the same paragraph 220, as also in the following paragraph 221 of the IRR, the Requestors then criticise the zonal authorisation system (as set out in Articles 35-37 of the PPP Regulation), inferring that a concerned Member State could not deviate from the conclusion of the zonal Rapporteur Member State and would thus be deprived of the control of the products used in their territory. The same would apply for mutual recognition of an authorisation granted by another Member State as set out in Article 40-42 of the PPP Regulation.

417. Despite this claim being outside the scope of the IRR (i.e. a request should only address concerns regarding the provision of the administrative act allegedly contravening environmental law, in this case the Reviewed Regulation), a reply will be provided for completeness.

([278]) See also judgment of the General Court of 21 February 2024, *PAN Europe v Commission*, T-536/22, EU:T:2024:98, para. 115.

([279]) Annex I to the Reviewed Regulation, under the column 'Specific provisions': "*Conditions of use shall include risk mitigation measures, including combinations thereof, as required. In particular, drift shall be reduced for spray applications made by professional users in agricultural fields. By default, to protect non-target terrestrial plants, an in-field non-sprayed buffer strip of at least 5 to 10 m from the field border depending on the particular use and drift reduction nozzles reducing spray drift by at least 75 %, or other risk mitigation measures with equivalent reduction of drift, shall be required, unless the outcome of the risk assessment undertaken for the specific plant protection product use indicates that such risk mitigation measures are not needed or can be lowered because there are no unacceptable risks caused by spray drift.*" .

418. The zonal system is a core element of the PPP Regulation. It allows for efficient use of resources while enabling each Member State to make decisions based on concrete technical considerations. In fact, the zonal system does not lead to a "lack of control": each Member State is responsible for the authorisation of PPPs in their own territory and on the basis of Article 36(3) of the PPP Regulation additional risk mitigation measures can be taken or the authorisation (and use of PPPs) can be refused if justified. The same applies to mutual recognitions (Article 41(1) refers back to Article 36(3)).

419. Therefore, as each use of each PPP must be assessed prior to the authorisation (in accordance with Article 29 and 31 of the PPP Regulation) and in no manner the zonal system precludes such evaluation, it is unclear how the zonal system and the Reviewed Regulation could force Member States to grant authorisations for PPPs intended for private individuals or authorisations for representative uses not considered safe by EFSA.

420. In paragraph 222 of the IRR, the Requestors define the setting of a requirement for the GRG to provide confirmatory information in relation to indirect impacts on biodiversity as "cosmetic and legally ill-founded". They criticise the lack of a mandate to EFSA on the topic and submit that, as the Reviewed Regulation does not set any specific deadline for submission of confirmatory information, it fails to comply with the conditions laid down in Article 11(5) of Regulation (EU) No 844/2012 and it would also disregard point 2.2 of Annex II to the PPP Regulation ([280]), according to which such requests for information are intended to "increase confidence in the decision".

421. Article 11(5) of Regulation (EU) No 844/2012 is irrelevant, as it refers to a different part of the assessment process (i.e. the Assessment by the rapporteur Member State and the co-rapporteur Member State). Second, as already explained above, the Commission has already sent a mandate to EFSA to develop a guidance document to assess potential indirect effects on biodiversity via trophic interactions under agro-environmental conditions within 36 months of receipt of the request.

422. With regard to the claim that the Reviewed Regulation would disregard point 2.2 of Annex II to the PPP Regulation, the Commission notes that this requirement to provide confirmatory information was not set on the basis of point 2.2. of Annex II to the PPP Regulation, but in accordance with Article 6(f) of the PPP Regulation, which allows such a requirement to be imposed where new requirements are established during the evaluation process or as a result of new scientific and technical knowledge. This is clear from recital 24 of the Reviewed Regulation, which explains that *"given that no agreed methods or guidance on the assessment of indirect effects on biodiversity are currently available at Union level, confirmatory information on any possible indirect effects on biodiversity via trophic interactions, should be submitted by the applicant once suitable methods and guidance are available".* Therefore, the Requestors' argument is unfounded.

423. Finally, contrary to the Requestors' conclusions in paragraph 223 of the IRR, the Requestors have not demonstrated any errors, let alone any manifest errors of assessment, in the Commission's conclusion that, based on the latest scientific and technical information, pesticides containing glyphosate can be expected to comply, with the conditions and restrictions added to address the identified issues, with the criteria set out in Article 4 of the PPP Regulation.

([280]) The Requestors mistakenly refer to Regulation (EU) No 844/2012.

IV. CONCLUSION

424. In the light of the above, the Commission considers that none of the grounds for review invoked by the Requestors have exposed any breach of EU environmental law by the Reviewed Regulation. The IRR must therefore be rejected as unfounded.