Ref. D(2023)0927

Claire Bury
Deputy Director-General for Food Sustainability
Directorate-General for Health and Food Safety
European Commission

Subject – Request for a statement on the carcinogenicity assessment of glyphosate following criticism by European civil society organisations

Dear Ms Bury,

On 12 September 2023 you requested EFSA and ECHA to respond to the points raised by 15 European civil society organisations in a letter addressed to you on 7 September 2023.

After careful analysis, our experts concluded that the points raised do not provide any new elements to the ECHA's RAC opinion published in July 2022 and the EFSA conclusions published in July 2023.

ECHA and EFSA are fully committed to transparency in our processes. In this regard, we would point out that many of the questions included in your letter have already been addressed publicly by both agencies.

Further details about our assessments and previous public responses can be found in the annex to this letter.

We trust that this information is useful to you and your services and we remain available to provide continued support on this file.

Yours sincerely,

Digitally signed by Bernhard Url
Date: 2023.10.04 17:27:12 +02'00'

Bernhard Url
Executive Director
European Food Safety Authority

Digitally signed by:
SHARON JANE MC GUINNESS (EUROPEAN CHEMICALS AGENCY (ECHA))
Date: 2023-10-05 05:32:04 UTC

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Encl: Annex

Cc: Ms M. Tiramani, Ms T. Molnar, Ms V. Villamar (EFSA)
Mr P. Ryan, Mr. A. Karjalainen (ECHA)
Mr J. Pinte (DG GROW)
Mr S. Bintein (DG ENV)
Mr K. Berend, Ms. A Tuijtelaars, Ms A. Bitterhof, Ms K. Nienstedt, Mr N. Tzvetkov, Mr M. Williams (DG SANTE)

Annex

ECHA Responses to technical questions in your letter

As mentioned above ECHA has previously commented publicly on many of the issues raised in the letter you have received. For example, ECHA's response[1] to a report by HEAL addressed many of the issues raised. Additionally, ECHA has made public its reply[2] to MEP Bas Eickhout, on the similar issue of "two missing genotoxicity OECD studies". ECHA's dedicated glyphosate page on its website[3] includes these detailed responses together with other relevant information.

Please note also that the RAC opinion[4] along with its supporting documentation was published on the ECHA website on 5 July 2022. Given the vast amount of information covered by the opinion and the public interest in the process, ECHA also published an "Explanatory note"[5] to accompany the RAC opinion on glyphosate.

The issues raised in the letter are addressed below in the order in which they appear in the letter.

1. ***"Missing industry genotoxicity studies"***

As regards the concern that key tests were not conducted due to a statement in the RAC opinion referring to the absence of specific assays in relevant target organs (OECD TG 489 "the comet assay" and OECD TG 488 "TGR"), firstly, it should be noted that the CLH process assesses available data – there is no mechanism to generate additional information. Secondly, please note that ECHA has addressed these particular issues in a letter to Bas Eickhout MEP, who raised this in the Exchange of views on 11 July 2022. ECHA addressed these concerns in our letter as follows:

"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"

And

"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

[1] ECHA response to HEAL report
[2] Letter to MEP Eickhout
[3] Glyphosate - ECHA (europa.eu)
[4] Registry of CLH intentions until outcome - ECHA (europa.eu)
[5] 9a6bdbf8-0d3c-c029-8256-2112189a6f85 (europa.eu)

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."

2. **"Tumour incidences were observed in glyphosate cancer studies"**

The reference for this issue as cited in the letter is the publication by HEAL on 8 June 2022. As mentioned above, there is a detailed response to the claims made in this publication on ECHA's website[6].

While we welcome the opportunity to further increase transparency about the reasoning in the RAC opinion on certain issues, we do not agree with the conclusions of the HEAL report and consider the criticisms unfounded for the reasons explained in our published response.

RAC experts, in accordance with their mandate, applied the CLP Regulation's criteria to toxicological and epidemiological findings and weighed all the evidence in arriving at their conclusions on classification. They considered the strength of the statistical evidence, dose-response relationships, concurrent and historical control data and the biological relevance of the findings.

3. **"ECHA's Deception by claiming a "limit dose" of 1,000 mg/kg"**

The deliberations of RAC on this particular issue are clearly and transparently set out in the published opinion, therefore, there is no deception. 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) were given lower weight, for the reasons explained in the Opinion as well as in the CLH report. In short, while there were low incidences of tumours at the highest doses in these studies, this was in combination with other effects (body weight gain data suggesting general toxicity) and therefore RAC, following recommendations in the relevant OECD guideline, gave these findings lower weight amongst all the other information available to inform on carcinogenicity.

4. **"Malignant lymphomas in animal studies complement the evidence in epidemiology studies"**

RAC concluded that the lymphoma incidences in male mice showed a slight, but clearly variable increase, but the biological and human relevance of the findings is uncertain because (among other reasons)

- The maximum incidences were mostly within the available historical control range
- The increases tended to be confined to the highest dose
- The increases were not seen in female mice (or in rats)

[6] 40ee075a-8b57-f524-9a82-b492a77a53f1 (europa.eu), 5 July 2022

Attempts have been made to draw a link between the findings in mice to non-Hodgkin's lymphoma in humans.

The role of non-Hodgkin's lymphoma was addressed in detail in the RAC opinion. No association between exposure to glyphosate-based herbicide and non-Hodgkin's Lymphoma was found in the AHS cohort study, which is the only prospective cohort study available (ref Andreotti et al, 2018[1]) and was considered by RAC as the most robust epidemiological study since it includes appropriate controls, a balanced assessment, and due consideration of bias or confounding factors. Weak positive associations have been observed in some case-control studies (but not consistently) and in meta-analyses (which depend on assumptions made about both exposure level and latency period).

RAC agreed with the dossier submitter that there is no epidemiological evidence of an association between exposure to glyphosate-based herbicide and the risk of Hodgkin's Lymphoma.

Considering the lack of evidence for biological and human relevance of the findings of malignant lymphoma following exposure to glyphosate in animal studies and the absence of epidemiological evidence of an association between exposure to glyphosate-based herbicide and the risk of Hodgkin's Lymphoma, the argument that there is a link between the findings in animals and humans is untenable.

5. "Oxidative stress"

The main claim in the letter on this point is that *"oxidative stress was not adequately taken into account during the assessment of ECHA's RAC, leading to underestimation of the potential of glyphosate to cause cancer"*.

Firstly, it is useful to explain that 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.

ECHA's independent assessment is based on a large number of scientific studies designed to examine the hazardous properties of glyphosate, including whether it causes cancer. All available evidence was carefully examined to arrive at a conclusion. No important findings were dismissed. Tumour incidences in the available studies were examined in detail and the conclusion was that there was no convincing evidence that glyphosate induces tumours.

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 a study are not on their own sufficient for classification. In particular, potential mode of action considerations arising from one study cannot provide support in the absence of convincing evidence for carcinogenicity in another study.

The mechanistic data from the Gao study were included in the CLH report and considered in the RAC opinion. The arguments put forward by the authors of the publication (Clausing et al, 2023) were heard and considered by RAC during opinion making.

ECHA conclusions

We trust that the above information helps to reassure you and the public that the latest assessment of glyphosate by RAC was complete and robust. The Committee, composed of independent experts from all EU Member States, has a long history of rigorous assessments against the criteria set out under the CLP Regulation. The integrity of RAC as the competent body to opine on hazard classification is well established with 550 opinions adopted to date. Substances routinely receive recommendation from RAC for the most severe of classifications (CMR category 1), 145 different substances have received such a recommendation to date. This demonstrates that the system works to deliver scientifically reliable and legally sound opinions, to better inform on the hazards of chemicals and allow actions on the most harmful chemicals to mitigate risks.

ECHA remains committed to open, transparent discussion and resolution of any lingering concerns.

EFSA responses to questions contained in your letter

Most of the issues contained in the NGOs' letter have been replied to by ECHA, as relevant to the work carried out by RAC in 2022.

In the letter the following points are addressed to EFSA:

1. **"Deception by claiming a 'limit dose' of 1,000 mg/kg"**

The claim in the letter says that EFSA, *in its conclusions, 'refers to a limit dose of 1,000 mg/kg, above which any tumour incidence should be considered irrelevant. Not only some cancer incidences were observed below these doses, but "the OECD limit dose of 1,000 mg/kg" does not even exist for carcinogenicity testing (see Annex).'*

What was reported in the letter seems factually incorrect. The limit dose of 1,000 mg/kg bw per day is not mentioned in relation to the carcinogenic studies in the 2023 EFSA conclusions, where instead this was mentioned in relation to the two-generation reproductive toxicity study. In the annex to the letter, reference is made to the ECHA opinion, therefore we believe this likely to be a mistake.

2. **"EFSA failed to correct ECHA's assessment flaws"**

The letter maintains that *'While affirming ECHA's flawed approach EFSA also creates confusion with the following sentence: "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." According to the CLH report and ECHA's Opinion, there is no group of male mice in any of the five mouse studies with the dose of 988 mg/kg body weight per day. More importantly, what does the phrase "up to" mean? Does EFSA acknowledge carcinogenic effects above 988 mg/kg (which in fact have been demonstrated), but at the same time continues to*

*consider glyphosate as "unlikely" to be a carcinogen?) This does **not** align with the hazard approach of Regulation 1272/2008. It also raises the following question: Does EFSA consider an increased tumour incidence seen in the mid-dose as irrelevant although this incidence increases even further at a dose above 1,000 mg/kg (see Tables in ECHA Opinion on p.66 for kidney tumours and p.69 for malignant lymphoma)?"*

In respect to the assessment of the genotoxicity and carcinogenicity studies, EFSA agrees with the conclusions reached in the ECHA RAC opinion. In particular, there is agreement that there was overall no convincing evidence that glyphosate exposure induced malignant lymphoma tumour in mice (see also ECHA's reply to point 4 above). Regarding the combined incidence of kidney adenomas and carcinomas, no convincing evidence of a treatment-related increase was concluded up to the dose of 988 mg/kg bw per day (mean achieved dose level; the nominal dose is 1000 mg/kg bw per day as reported in RAR Volume 3CA_B.6.5; B.6.5.14. Long-term toxicity – mouse, study 4, Table B.6.5.14-3[7]). Increased incidence of combined kidney adenomas and carcinomas above this dose was reported at the highest tested doses in two out of five carcinogenicity studies in mice. In those studies, top doses exceeded 4000 mg/kg bw per day. The NOAELs for these two studies were identified at the lowest tested doses (157 and 165 mg/kg bw per day) and, based on the effects observed, the highest doses > 4000 mg/kg bw per day were considered to possibly exceed the maximum tolerated dose (MTD).
Overall, the human relevance of renal tumours observed at those high doses was considered to be low. Differently from the ECHA hazard-based approach for the classification of substances, EFSA considers the substance in the context of risk assessment, and therefore a reference point for potential carcinogenic effects can be established. In this respect it was concluded that, based on all the available evidence, glyphosate is not considered to be carcinogenic in mice up to the dose of 988 mg/kg bw per day. Taking the established toxicological reference values (TRVs) for glyphosate into account, the effects observed at these high doses are of low relevance for the human risk assessment.

3. **"ECHA's deception by claiming a 'limit dose' of 1,000 mg/kg"**

'Does EFSA follow ECHA's deceptive use of an alleged "limit dose"? It needs to be emphasized that "the OECD limit dose of 1,000 mg/kg" (ECHA Opinion, p.52) does not exist for carcinogenicity testing. While it is clear from OECD Test Guideline 453 (Combined Chronic Toxicity and Carcinogenicity Testing) in its Article 24 that this limit dose exclusively applies to chronic toxicity testing[8], Test Guideline 451 (Carcinogenicity Testing) does not even mention this limit dose. Ironically, ECHA "assessed five OECD TG 451 compliant long-term studies in mice" (Opinion, p.51), followed by the claim that "these doses were above the OECD limit dose of 1,000 mg/kg bw/d".
*It should be noted that OECD recommends the concept of the Maximum Tolerated Dose (MTD), because "emphasis was on testing at high levels in order to maximise the potential of such studies to detect effects", i.e. "to assess the **qualitative** potential of a test substance" (OECD Guidance 116, p.53 emphasis added).'*

See previous paragraph (and ECHA's reply to point 3 above). The assessment included effects observed at all dose levels throughout the different carcinogenicity studies in a

[7] Available in 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 Renewal Assessment Report (final); Volume 3CA_B.6.5; B.6.5.14. Long-term toxicity – mouse, study 4, Table B.6.5.14-3.
[8] *For the chronic toxicity phase of the study, a full study using three dose levels may not be considered necessary, if it can be anticipated that a test at one dose level, equivalent to at least 1000 mg/kg body weight/day,is unlikely to produce adverse effects. ... A limit of 1000 mg/kg body weight/day may apply …"*

weight of evidence approach and there was no cut-off of effects observed above 1000 mg/kg bw per day. This notwithstanding, as discussed in the previous paragraph and as reported in the published Peer Review Report[9], EFSA agrees that tumour incidences observed at excessively high doses have a low human relevance and are not informative of possible effects in the framework of the human health risk assessment, taking into account the estimated human exposure levels and the TRVs established for glyphosate.

EFSA conclusions

The latest EFSA and EU Member States risk assessment and peer review on glyphosate is the most comprehensive and transparent assessment carried out for a pesticide active substance in the EU. The assessment took into account ca 2,400 studies related to human and animal health or the environment. It involved dozens of scientists from EFSA and approximately 90 experts from 27 national public authorities across the EU.

Since 2003, EFSA has been responsible for the EU peer review of the pesticide risk assessment for active substances used in plant protection products. This task is carried out by EFSA's Pesticides Peer Review Unit, in close cooperation with EU Member State competent authorities, following procedures that are set out in the applicable legislations and according to the latest scientific standards and methods.
The EFSA independent scientific advice is submitted to risk managers for their decisions on regulatory matters, including the approval of active substances. It is worth noting that, over the years, this process has led to the non-approval of hundreds of harmful substances, which are no longer approved in the EU (see EU Pesticide database for further details:https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/start/screen/active-substances).

[9] available in Open EFSA under 'Supporting documents' under EFSA Question number EFSA-Q-2020-00140: https://open.efsa.europa.eu/study-inventory/EFSA-Q-2020-00140); Peer Review Report, Part 3, REPORT OF PESTICIDE PEER REVIEW TC 80; Experts' consultation 2.5 identified following comments by public.