Ms. Stella Kyriakides
European Commissioner for Health and Consumer Policy
European Commission
B-1049 Brussels - Belgium

September 7th, 2023

Subject: Stop the reapproval of glyphosate due to major deficiencies in carcinogenicity assessment

Dear Commissioner Kyriakides,

We, the undersigned 15 European civil society organisations, are writing to you to express our concerns regarding the Commission's intention to present a renewal regulation proposal for glyphosate at the SCoPAFF meeting on the 15th of September and invite the Member States to vote at the meeting in October. In this letter we centre our concerns around the equivocal claims in the EU carcinogenicity assessment regarding the observed tumour incidences in glyphosate-exposed animals, two missing genotoxicity OECD studies and -as highlighted in a recent publication- important mechanistic evidence indicating that glyphosate induces oxidative stress, a recognised mechanism that can lead to cancer. These issues were neglected by ECHA leading to the flawed opinion that glyphosate is unlikely to be a presumed human carcinogen, an opinion unfortunately endorsed by EFSA[1] and serving as the basis for the Commission's forthcoming renewal proposal.

At the beginning of the re-assessment of glyphosate, NGOs and independent scientists alerted about important incoherences in the EU scientific evaluation of glyphosate's genotoxicity and carcinogenicity potential[2]. Three independent scientists who participated in the discussions of ECHA's Risk Assessment Committee (RAC), provided evidence supporting the classification of glyphosate as a presumed carcinogen and as genotoxic based on OECD cancer studies and

[1] https://doi.org/10.2903/j.efsa.2023.8164

[2] https://www.env-health.org/health-and-environmental-groups-raise-alarms-over-eu-chemicals-agencys-failure-to-classify-glyphosate-as-a-carcinogen-for-human-health/ https://www.env-health.org/wp-content/uploads/2022/06/HEAL-How-the-EU-risks-greenlighting-a-pesticide-linked-to-cancer-2022.pdf

peer-reviewed scientific literature. In a recent paper[3], these scientists[4] show that oxidative stress was dismissed during the EU assessment as a mechanism of action for carcinogenicity, leading to serious deficiencies in the hazard evaluation of glyphosate. If these incoherences were corrected, the classification of glyphosate as a presumed carcinogen would be clearly justified, and according to Regulation (EU) 1107/2009, glyphosate's license should not be renewed. Unfortunately, neither ECHA nor EFSA corrected these inconsistencies.

Here, we would like to highlight the following:

1. **Missing industry genotoxicity studies.** The absence of two genotoxicity OECD protocol studies in the applicant's dossier[5], is a clear data gap in the assessment of the capacity of glyphosate to cause DNA damage to specific organs. Such DNA lesions have been reported in independent scientific literature in laboratory animals and humans following glyphosate exposure. While the RAC acknowledged the data gap, the missing studies were never requested either by ECHA nor by EFSA, and the additional evidence from independent literature were never endorsed, leading to the adoption of an equivocal opinion.
2. **Tumour incidences were observed in glyphosate cancer studies.** In contrast to the claims of ECHA and EFSA, many of the tumour incidences observed in animal cancer studies provided by the applicants were statistically significant according to the tests recommended in the relevant OECD Guideline. In fact, in all five mice studies provided by the industry, the males developed either malignant lymphoma or kidney tumours or hemangiosarcomas, which were statistically significant. In four out of the five studies the number of tumours increased with increasing exposure (dose-response)[6].
3. **Deception by claiming a "limit dose" of 1,000 mg/kg.** In its conclusion, EFSA 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).
4. **Malignant lymphomas in animal studies complement the evidence in epidemiology studies**. An analysis of the human epidemiological studies, including the recent cohort Agricultural Health Study (AHS) and five case-control studies, found a compelling link between exposures to glyphosate herbicides and increased risk for non-Hodgkin lymphoma[7]. Although this evidence is still considered limited, the fact that male mice exposed to glyphosate developed malignant tumours in four out of the five mice studies, strengthens the evidence of non-Hodgkin lymphoma observed in humans.

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[3] Clausing et al, 2023. Glyphosate and Oxidative Stress: ECHA's superficial approach neglects existing hazards https://zenodo.org/record/8270189

[4] Prof. Siegfried Knasmüller (Medical University of Vienna Center for Cancer Research)
Dr. Christopher J. Portier (expert in the design, analysis and interpretation of environmental health data with a focus on carcinogenicity)
Dr. Peter Clausing (senior toxicologist)

[5] https://echa.europa.eu/documents/10162/17090/3_glyphosate_eeb_rac60_en.pdf/bff8a83d-5b86-d4ee-ecb3-de873121cfd9?t=1649331309977
https://www.env-health.org/wp-content/uploads/2022/06/HEAL-How-the-EU-risks-greenlighting-a-pesticide-linked-to-cancer-2022.pdf

[6] https://www.env-health.org/wp-content/uploads/2022/06/HEAL-How-the-EU-risks-greenlighting-a-pesticide-linked-to-cancer-2022.pdf

[7] Weisenburger DD. A Review and Update with Perspective of Evidence that the Herbicide Glyphosate (Roundup) is a Cause of NonHodgkin Lymphoma. Clin Lymphoma Myeloma Leuk. 2021 Sep;21(9):621-630. doi:10.1016/j.clml.2021.04.009

5. **Oxidative stress**. In the recent paper[8], the same scientists[9] reveal 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. As the scientists point out, oxidative stress is not covered by OECD test guidelines. Therefore, it is particularly crucial to properly integrate the results of studies on oxidative stress published in the peer-reviewed scientific literature into the hazard assessment. However, as argued by the scientists, ECHA failed to do so[10], and therefore contrary to its claim, it failed in using an appropriate "weight of evidence approach". While mentioning the research of Gao et al. (2019)[11], which highlighted the potential of glyphosate to cause oxidative stress in kidneys of animals, ECHA avoided considering in parallel that glyphosate also caused an increase in incidences of kidney tumours in male mice in three out of five cancer studies. Therefore, these tumours are in fact supported by evidence of oxidative stress in the same sex and the same organ (kidneys of male mice). By endorsing ECHA's RAC Opinion, EFSA supported this flawed approach.

In conclusion, there is crucial evidence[12] of glyphosate's carcinogenicity, such as studies showing promotion of malignant lymphomas and other tumours in animals, and its potential to cause oxidative stress and DNA lesions. This evidence has not been acknowledged by the Assessment Group on Glyphosate, ECHA, or EFSA.

Unfortunately, the carcinogenicity assessment is only the tip of the iceberg of the problems in relation to glyphosate. Exposure to glyphosate has been linked to neurotoxicity[13] and Parkinson's disease[14] in humans, as well as endocrine disruption[15] and alternations in the microbiome[16]. It can also lead to toxicity in a wide range of terrestrial[17] and aquatic[18] non-target species, potentially causing serious impacts on biodiversity.

As it was put forward in a letter to EFSA's director, Mr Url, the conclusions published by EFSA,

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[8] Clausing et al, 2023. Glyphosate and Oxidative Stress: ECHA's superficial approach neglects existing hazards https://zenodo.org/record/8270189

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Dr. Peter Clausing (toxicologist)

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

[11] 10.1002/jat.3795

[12] Robinson et al, 2020. Achieving a High Level of Protection from Pesticides in Europe: Problems with the Current Risk Assessment Procedure and Solutions. European Journal of Risk Regulation, 11(3), 450 -480. https://doi.org/10.1017/err.2020.18

[13] Costas-Ferreira et al 2022. Toxic Effects of Glyphosate on the Nervous System: A Systematic Review. *Int. J. Mol. Sci.* 2022, 23, 4605. https://doi.org/10.3390/ijms23094605

[14] Caballero, et al 2018. Estimated Residential Exposure to Agricultural Chemicals and Premature Mortality by Parkinson's Disease in Washington State. *Int. J. Environ. Res. Public Health*, 15, 2885. https://doi.org/10.3390/ijerph15122885

[15] Lesseur C et al, 2021. Maternal urinary levels of glyphosate during pregnancy and anogenital distance in newborns in a US multicenter pregnancy cohort *Environ Pollut.* 10.1016/j.envpol.2021.117002

[16] Mesnage R et al. 2021. Use of Shotgun Metagenomics and Metabolomics to Evaluate the Impact of Glyphosate or Roundup MON 52276 on the Gut Microbiota and Serum Metabolome of Sprague-Dawley Rats" *Environ Health Perspect.*

[17] Klátyik et al, 2023. Terrestrial ecotoxicity of glyphosate, its formulations, and co-formulants: evidence from 2010–2023. Environ Sci Eur 35, 51. https://doi.org/10.1186/s12302-023-00758-9

[18] Gonçalves et al 2020. 'Ecotoxicology of Glyphosate-Based Herbicides on Aquatic Environment'. Biochemical Toxicology - Heavy Metals and Nanomaterials. IntechOpen. 10.5772/intechopen.85157

where no ‘critical areas of concern’ have been identified, underline significant failures regarding their compliance with the EU law, which requires that pesticides placed in the EU market should cause no harm. However, despite the several data gaps found by EFSA and the impossibility to finalise the risk assessment of crucial endpoints, the Commission is moving forward with proposing a reapproval. This situation is a reckless disregard of your duty to protect public health, as well as a disregard of the protection of the environment.

Not only is the Commission moving forward, but the rushed timeline, which it has set to vote on the reapproval of glyphosate is shocking, if not a deviation from democratic procedures. With the background documents including the Renewal Assessment Report and all additional data only being made public by EFSA between August and October, the public and scientific community has little to no time to scrutinise thousands of pages of documents on the EU assessment of glyphosate. This is extremely worrying as serious deficiencies have already been identified in ECHA’s evaluation, as we have put forward.

Considering the widespread use of glyphosate-based products, neglecting these adverse effects poses an unacceptable health risk to both farm workers and the general population. Given the evidence presented, glyphosate **does not meet the approval criteria laid down in Regulation (EC) 1107/2009**, according to which pesticide active substances, pesticide products and their residues placed on the market should not have any harmful effect on humans, animals, and no unacceptable effects to the environment.

Therefore, we urge you, as Commissioner for Health, to stop the reapproval of glyphosate, based on the evidence presented and the implementation of the precautionary principle, which is at the heart of the Treaty on the Functioning of the European Union and EC Regulation (EC) 1107/2009, aiming at ensuring a higher level of human health and environmental protection.

Less than 1 year before the European elections, by moving forward with a reapproval, your services are discrediting the seriousness and independence of EU institutions and favouring agribusiness' interest over citizens' health and environmental protection, while turning your back on independent science.

We respectfully ask you to reconsider your position and not renew the approval of glyphosate.

Thank you in advance for your consideration.

Yours sincerely,

Angeliki Lysimachou,
Head of Science and Policy
PAN Europe

Gabriela Strobel
Board
PAN Germany

Co-signatories:

Coordination against BAYER-dangers, Germany

Corporate Europe Observatory, European

Ecologistas en Acción, Spain

European Federation of Trade Unions in the Food, Agriculture and Tourism (EFFAT), European

Ekō, International

Générations Futures, France

Health and environment alliance, European

International Society of Doctors for the Environment (ISDE), Italy

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Pesticide Action Network (PAN) Europe

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Velt, Belgium

ANNEX -

Glyphosate: EFSA failed to correct ECHA's assessment flaws

By Peter Clausing

EFSA's conclusion (p.11) on the "Peer review of the pesticide risk assessment of the active substance glyphosate" dated 06 July 2023 states that glyphosate is unlikely to be genotoxic and unlikely to be a carcinogen for humans, adopting ECHA's assessment for both hazards.

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)?

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[19], 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).

ECHA's misleading claim of "no plausible mechanism" for kidney tumours

While acknowledging that out of five studies "renal tumours were reported in three studies with CD-1 mice" (ECHA Opinion, p. 53), ECHA claimed that "there was no plausible mechanism". This claim is in strong contradiction to the mechanistic study by Gao et al. (2019) "considered as

[19] "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 …"

reliable" by ECHA (Opinion, p. 23)[20]. On p.46, ECHA dismisses the Gao study at large (together with 4 other studies) as "equivocal due to deficiencies in reporting" without going into detail.

The crucial point is that (a) oxidative stress is a known mechanism of carcinogenicity; (b) glyphosate is causing oxidative stress – even ECHA acknowledged this; (c) Gao et al. (2019) demonstrated **oxidative stress in kidneys of male mice** including the provision of an explanation of the molecular basis how this oxidative stress is generated by glyphosate[21]; and (d) in contrast to ECHA that claimed Gao et al. (2019) "**postulated** that glyphosate could affect" the NMDA receptor, these researchers provided proof, because in an additional experiment they demonstrated lack of oxidative stress, when glyphosate and a NMDA antagonist were co-administered.

These are just two examples of ECHA's flawed approach adopted by EFSA. Further flaws exist regarding their assessment of the statistical methods used and their reference to historical control data.

[20] ECHA states „reliable with restrictions", but it should be noted that these "restrictions" refer to the fact that this study was non-guideline and non-GLP. However, no Guidelines exist for mechanistic studies and normally GLP is not used at academic institutions

[21] via upregulation of the NMDA receptor which in turn causes the oxidative stress