

ECHA again fails to address scientific arguments contradicting its glyphosate assessment

On 8 August 2017 ECHA responded¹ to the Global 2000 report,² "Glyphosate and cancer: Authorities systematically breach regulations", published on 13 July.

ECHA repeated its concern that the report represented "an attempt to publicly malign the integrity of EU institutions", and announced that "at this critical decision-making stage (it will) not engage in any public discussion that could be perceived [...] as ECHA reopening its opinion."

We, the author and editors of the Global 2000 report, believe that it is not ECHA's responsibility, but the responsibility of the Standing Committee on Plants, Animals, Food and Feed (SCOPE) to reopen the debate in order to correct the flaws in BfR's, EFSA's and ECHA's assessments. We are of the opinion that a failure to do so would jeopardize the health of 500 million EU citizens.

We do not agree that our scientific critique publicly maligned the integrity of EU institutions. The damage has been inflicted by the European institutions themselves through their unscientific handling of the issue of the safety of glyphosate.

In its response, ECHA misrepresented our arguments and failed to address our scientific concerns.

First ECHA admitted that we correctly combined "the definitions for 'sufficient evidence' for carcinogenicity" with the criteria for classification as a category 1B carcinogen (known human carcinogen primarily based on animal evidence). However, then ECHA claimed that we ignored other central principles to be considered, such as expert judgement and a weight of evidence approach.

But in fact, large parts of our report deal with the authorities' failure to properly apply the weight of evidence and use expert judgment. We stated in our report that "it is crucial to acknowledge that this expert judgment needs to sail within the limits of [...] guidance documents in order to avoid shifting the assessment away from science-based decisions to

1 https://echa.europa.eu/documents/10162/0/global_2000_glyphosate_echa_response_final_en.pdf/92487f17-aa44-0bae-56d4-a7616862c65a

2 https://www.global2000.at/sites/global/files/Glyphosate_authorities_breach_regulations.pdf

the advantage of certain interest groups.”³

It appears to us that ECHA has acted in contravention of applicable guidance documents and EU law in inventing a policy to not classify a chemical as carcinogenic, if there is evidence only for one or two tumour types, even when that evidence is consistent, dose-dependent, and supported by historical control data.

Only with the assumption of such a policy it can be explained why ECHA contends that the animal studies are “giving variable and conflicting indications of carcinogenicity”, that the findings lack a dose-response relationship, and that they are not supported by historical control data. However, looking at malignant lymphoma, with 3 out of 3 studies show a significantly increased tumour incidence, two of them dose-dependent (see Table 2 in the Global2000 Report), with the high doses not exceeding the maximum tolerated dose and two of them supported by historical control data. The idea that these results could be due to chance or confounding factors rather than to treatment with glyphosate is scientifically absurd. ECHA should acknowledge this fact rather than elusively repeating its mantra that “the study results were given appropriate treatment in the weight of evidence”.

Moreover, a fourth study was useless with regard to malignant lymphoma. In claiming that “IARC did find the study acceptable”, ECHA is misleading the reader. To repeat: we did not say that the study is invalid, but that it is invalid for the assessment of malignant lymphoma. IARC used this study with regard to haemangiosarcoma, not malignant lymphoma. It is hard to imagine that the ECHA authors of the response to our report failed to understand this fact, so the most reasonable conclusion to draw seems to be that they are deliberately misleading the public.

ECHA’s statement that “according to the OECD GD 116 there would be no specific indication on whether either or both pair-wise and trend tests should be performed”, is contrary to the contents of Guidance 116. In its flow chart on page 123 this Guidance explicitly recommends trend tests.

For any organization obliged to protecting public health it is morally, ethically and scientifically unacceptable to a priori exclude statistical significant findings from the evaluation by simply refusing to applying the statistical evaluation that reveals the significant result. This is even more disturbing, given the fact that the specific trend test that ECHA refuses to apply or to give proper weight to its outcome is explicitly recommended in OECD Guidance 116 by mentioning it in its decision tree on page 123.

3 https://www.global2000.at/sites/global/files/Glyphosate_authorities_breach_regulations.pdf, p. 14

ECHA claims that “in rats, all findings were in male rats in 2 studies out of 7 evaluated”. How can ECHA continue to simply deny the statistically significant findings in 4 more rat studies that Christopher Portier has identified in the raw data of industry studies?

The basic prerequisite for a thorough weight of evidence approach is to gather all evidence in order to get a full picture, and then make a transparent decision about how this evidence was weighed. This transparency in the decision-making process is lacking just as much as the assessment of eight additional significantly increased tumour incidences⁴ which ECHA claims to have considered although they were neither mentioned in the CLH report nor in RAC’s opinion. This claim is therefore impossible to believe.

There are three lines of evidence for glyphosate’s carcinogenicity:

- Animal studies – as described in more detail above – with strong evidence for malignant lymphoma (but also for renal tumors) in mice.
- Epidemiological evidence for an increased risk for the same type of tumour/cancer (non-Hodgkin lymphoma) is limited, **but it does exist** (BfR and IARC agreed on that);
- The evidence for oxidative stress as a mode of action for glyphosate’s carcinogenicity is “strong”, according to IARC, but this evidence was not even discussed by ECHA in the context of carcinogenicity. In the context of genotoxicity, ECHA concluded, “the in vitro and in vivo data suggest that glyphosate may induce oxidative stress. However, increased levels of oxidative stress was not reliably demonstrated in the repeated dose studies where this was examined.” It should be emphasized that the *absence* of “increased levels of oxidative stress was not reliably demonstrated” either.

Taking all this together the following questions arise:

1. Given that 3 of 3 mouse studies conducted with three different mouse strains, two of them with comparable doses, showed a statistically significant increase in malignant lymphoma, what is ECHA’s justification to claim that the animal studies are “giving variable and conflicting indications of carcinogenicity”?
2. Given that 2 of the 3 mouse studies valid with regard to malignant lymphoma

4 see Portier and Clausen (2017)

- clearly showed a dose-dependent increase (the third study showed an increase too, but it was only visible at the top dose), what is ECHA's justification to claim "lack of dose response relationships"?
3. Given that the findings of 2 of the 3 mouse studies valid with regard to malignant lymphoma are supported by historical control data, what is ECHA's justification to claim "Not supported overall, based on historical control data"?
 4. Given that there is limited epidemiological evidence for non-Hodgkin lymphoma and that "increased levels of oxidative stress" were demonstrated, though not reliably, what is ECHA's justification for failing to use these findings as supporting evidence for the observation of a significant increase of malignant lymphoma in 3 of 3 mouse studies?
 5. Given that reaching the maximum tolerated dose (MTD) is a requirement for the validity of carcinogenicity studies, what is ECHA's rationale for mentioning this fact to claim a confounding effect of excessive toxicity? Besides: 2 of the 3 mouse studies that are valid with regard to malignant lymphoma showed a statistically significant increase at doses not exceeding the MTD and in the third study the presumed excessive toxicity was probably due to reduced food intake because of the lack of palatability of the dietary admixture in the high dose group.
 6. Given that the observed tumour types are similar in mice and humans (malignant lymphoma and non-Hodgkin lymphoma) what is ECHA's justification for failing to consider the significant increase in malignant lymphoma as biologically relevant?

We believe that if ECHA were to answer these questions – something it has thus far failed to do – this would not "reopen" the debate, but end it. As emphasized before, it is these contradictions, and not our demands for consistent answers to these questions, that are eroding the public trust in the European institutions.

Sincerely



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