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Helsinki, 21 September 2022

Mr Bas Eickhout, Member of the European Parliament
Vice-Chair of the Committee on the Environment, Public Health and Food Safety (ENVI)
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By email only

Subject: Unresolved question from the ENVI Exchange of Views on glyphosate (11 July 2022)

Dear Mr. Eickhout,

Thank you for your questions to ECHA during the ENVI Committee's *Exchange of Views* on the latest developments linked to the renewal of the approval of glyphosate, held on 11 July 2022. We realise that we did not adequately respond to the question on genotoxicity testing and the Comet assay.

Your question

Your question related to the following statements on page 48 of the RAC opinion (at the end of the Germ Cell Mutagenicity section): "*Glyphosate appears to induce transient DNA strand breaks as observed in the in vitro and in vivo Comet assays or by using the alkaline elution assay; however, no reliable in vivo Comet assays were included in the CLH dossier in relevant target organs*" and "*there is also some evidence that glyphosate may induce oxidative stress in certain cells and tissues with the potential to induce oxidative DNA-lesions that may lead to mutations if not repaired*".

We understand that you observe that RAC seems to agree that glyphosate appears to induce transient DNA strand breaks (which has potential carcinogenic consequences) but there were no reliable *in vivo* Comet assays included in the CLH dossier that were conducted in relevant target organs. If underlying effects were seen but the file did not contain the relevant information to explore this further and if suitable tests were not provided or adequately conducted, then it is not possible for RAC to conclude on the relevance/irrelevance of such effects. Similarly, regarding oxidative stress – elements are seen but tests have either not been done or have not been available. This made you raise questions regarding the completeness of the file, sufficiency of the tests and subsequently on how conclusions could have been reached.

ECHA's response

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

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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.

In relation to oxidative stress, the opinion also noted that "*in general, it is considered that the investigated endpoints like oxidative stress, oxidative DNA damage and/or induction of proteins involved in DNA recombination do not directly measure effects on heritable mutations or events closely associated with chromosome mutations. Especially the stimulation of oxidative stress is not conclusively indicative for mutagenicity but may point to a possible mechanism of toxicity and induced cellular biological effects*".

For the above reasons, taking all data into account and the numerous and consistent test results with negative outcomes, the opinion concluded that no classification was warranted.

We hope that the above answers your enquiry. Please note that to ensure transparency, we plan to make this letter also available on ECHA's website dedicated to glyphosate. Kindly let us know should you wish to obtain any further information.

Best regards,

Mike Rasenberg
Director of Hazard Assessment
[e-signed][1]

Encls.

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Cc:

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[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.