Helsinki

D(2017)2493
GD/JdB/ak

Global 2000
Helmut Burtscher, Peter Clausing, Claire Robinson

Subject: ECHA's response to Global 2000's response to ECHA of 21 August on glyphosate

Dear Dr Burtscher, Dr Clausing, Dr Robinson,

Further to our response (published on ECHA's website on 8 August 2017), ECHA has considered Global 2000's reply.

In general, ECHA considers that the issues raised and the documents referred to in Global 2000's reply were adequately responded to in our previous reply to the Global2000 report of 13 July 2017, in particular in the parts of our response which addressed the statistical analyses and application of weight of evidence. The main part of our current response therefore simply reiterates the relevant parts of the RAC's Opinion to help direct the reader to the relevant parts of RAC's analysis and conclusion.

ECHA agrees with the authors of Global 2000's reply that RAC had to consider three main lines of evidence when considering classification for the carcinogenicity hazard of glyphosate: animal data, epidemiological data and genotoxicity data. ECHA is of the opinion that RAC has done so and hence has acted fully in line with the CLP Regulation and related guidance documents. The authors raised 6 questions at the end of the document, all addressing only the malignant lymphoma findings. These are briefly addressed below (in the order presented in the document). ECHA would like to stress that the RAC opinion and associated documents[1] are essential reading to get the full understanding of the view of RAC - the relevant EU scientific body assessing proposals for classification.

Concerning questions 1-3, in which you raise consistency of the findings, dose relationships and historical control data: RAC considered five studies in mice – all were considered valid, having been conducted according to GLP and were consistent with the relevant OECD guidelines. Although the Global2000 report actually did also refer to the Atkinson study (1993) as invalid, we appreciate the clarification by the authors that this study was only considered to have been invalid with respect to the malignant lymphoma findings. The answers to the questions are covered in the Opinion: "*RAC considered that the findings in the individual mouse studies were not by themselves strong enough to warrant classification. This is based mainly on an evaluation of statistical significance, biological relevance and consistency of the findings, including comparison with historical control data and differences in findings between the sexes".* Please also see the quotes from the conclusions of the opinion reproduced below.

Specifically concerning the conclusion on malignant lymphomas, the Opinion states that: "*Looking at the overall pattern of tumour incidences, RAC notes a tendency for increased incidences of malignant lymphomas in male mice in the high dose groups in four of the*

[1] https://echa.europa.eu/opinions-of-the-committee-for-risk-assessment-on-proposals-for-harmonised-classification-and-labelling/-/substance-rev/16901/term

five studies available. However, the tumour incidences were highly variable, mostly within the available control incidences, and elevated tumour incidences were not supported by parallel increases in non-neoplastic lymph node lesions. Furthermore, the findings were not consistent between sexes and were not supported by findings in the rat studies."

RAC also described and considered the malignant lymphomas observed in male mice in each of the five studies in detail. Some of this detail was quoted in our previous response along with the conclusion in the Opinion on the mouse studies and is therefore not repeated here. Increased incidences of malignant lymphomas were not seen in female mice or in rats.

We fully agree that dose-response relationships are fundamental to the assessment of toxicological data. However, all data need to be considered in context and not in isolation. As noted in our previous response, "*In the individual studies, particularly when the overall incidences are low, or when the background incidences are high, it can be a matter of interpretation whether there actually is a dose response relationship or not, and the wider picture must then be considered*".

Concerning question 4, in which you raise the use of the data on oxidative stress: The possible role of oxidative stress was considered with the genotoxicity data. RAC noted in the carcinogenicity section of the Opinion that "*RAC does not consider that a genotoxic MoA has been demonstrated for glyphosate*". The basis for the decision to not classify for germ cell mutagenicity is explained in detail in the relevant section of the Opinion. More specifically on classification for germ cell mutagenicity, RAC concluded that "*Glyphosate is only metabolised to a very limited degree and is not a DNA reactive substance. Bacterial and mammalian gene mutation assays were all negative. Thus, the genotoxicity observed for glyphosate in some studies is likely to be caused by indirect mechanisms. Glyphosate appears to induce transient DNA strand breaks as observed in the in vitro and in vivo Comet assays. However, as glyphosate does not induce gene mutations and bone marrow mutagenicity is considered negative, their biological importance in relation to mutagenicity is equivocal. Further, it is unclear whether oxidative stress is of biological importance as a MoA for glyphosate as the data are equivocal*". Taking all data into account, and based on the overall negative responses in the existing gene mutation and oral mutagenicity tests, RAC concluded that no classification of glyphosate for germ cell mutagenicity is warranted. The role of oxidative stress was considered by RAC in detail in the Opinion, taking into account the arguments put forward in the IARC report. In addition, other studies were considered, including a recent reproductive study mentioned in a comment from the public consultation (Dai *et al.,* 2016), because it included measurement of oxidative stress in the testis. In the end, however, RAC concluded on oxidative stress as cited in the concluding statement above.

Concerning the role of the maximum tolerated dose (MTD) in question 5: It is noted in the Opinion that "*Increased tumour incidences observed at doses above 4000 mg/kg bw/day were given less weight by RAC because the doses used were excessive and exceeded the MTD".* ECHA agrees that reaching the MTD is a requirement for the validity of carcinogenicity studies. Additional consideration is required when there is evidence that the MTD has been exceeded and the doses are unusually high, as was the case in two of the studies. The issue has been extensively considered in our previous response.

Concerning the relationship between malignant lymphoma in mice and non-Hodgkin lymphoma in humans (question 6): The relationship between the findings in mice and humans was indeed given serious consideration by RAC. Concerning the epidemiological data, RAC concluded in the Opinion, that "*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." Specifically concerning the non-Hodgkin's lymphoma findings, RAC concluded that "*No association between exposure to glyphosate and cancer was found in the AHS, which is the only prospective cohort study available. A weak positive association has been observed in some case-control studies, and in meta-analyses between exposure to glyphosate and cancer, especially NHL, as concluded in the meta-analyses by Chang and Delzell (2016) and Schinasi and Leon (2014), and also in IARC monograph 112. 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. The increased risk observed in some case-control studies was not consistently observed in all case-control studies nor in the only cohort study available. When the whole database of epidemiology is taken into consideration, RAC concludes that the criteria for assigning glyphosate to category 2 (or any of the other categories) are not fulfilled.*" RAC considered the malignant lymphoma findings in mice (among other tumour findings) as well as the epidemiological data relating to non-Hodgkins lymphoma, and concluded 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*".

In conclusion, ECHA is of the opinion, that in the RAC opinion and associated documents, all the findings were assessed in context, using a weight of evidence approach, taking into account the concerns relating to the findings in mice, lack of relevant findings in rats, lack of evidence for genotoxicity as well as the limited evidence for an association in humans. It seems inevitable that in view of the interest in the conclusions relating to the classification of this substance for carcinogenicity, areas of contention will remain, as it will always be possible to see a part of the large number of findings in a different light. We would like to re-iterate however, that for all the hazard classes RAC reached its conclusions as a result of extensive scientific discussion of the findings, using a weight of evidence approach which took into account all the available relevant data.

ECHA hopes that by drawing the attention to the relevant sections of the RAC opinion Global 2000 will be assured that the points they are making were indeed considered by the 40 experts present in the Committee during the several days of deliberation that took place on the glyphosate dossier.

As always, any new evidence would be welcome, but after careful assessment ECHA is of the view that there is currently none in Global 2000's correspondence. This response will also be published on ECHA's website, with our previous correspondence on this matter.

Yours sincerely,

SIGNED

Geert Dancet
Executive Director