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Global2000  
Helmut Burtscher, Peter Clausing, and Claire Robinson

**Subject: Global 2000's report on glyphosate**

Further to our initial response (published on ECHA's website on 13 July 2017), ECHA has fully examined the Global2000 report and provides the attached more detailed response. As indicated in our previous response, this further response will also be published on ECHA's website.

As noted previously, ECHA encourages and welcomes scientific debate and challenge – it is fundamental to our work. We therefore welcome the scientific content of the report and the challenges it poses on some of the issues raised.

However, we again most strongly refute the allegation made in the title of the Global2000 report and repeated in your response of 17 July. We have not breached the relevant regulations nor colluded with industry in arriving at the scientific opinion which is now considered by the policy makers in deciding whether to renew the approval of glyphosate as a herbicide.

ECHA notes your appreciation for the transparency and openness in welcoming observers from NGOs at the meetings of the scientific committees of ECHA and agrees that it is an important step to promote public trust.

During the plenary meeting in March 2017, ECHA's risk assessment committee (RAC) delivered its scientific opinion which was different to what your organisation would have liked. RAC's independent scientific experts assessed glyphosate's hazardous properties, including carcinogenicity, against the criteria in the CLP Regulation. They considered all the scientific data in coming to their opinion, including both published scientific studies and industry sponsored scientific studies that RAC considered relevant. The Committee used a weight of evidence approach in its assessment, as required by the CLP Regulation.

RAC approached the assessment, as it has done in every other case, without any anticipation of the outcome for any of the hazard endpoints. RAC also does not set out to please any stakeholder organisation with its conclusions. There was no collective preconception of whether or not the substance was hazardous for any of the endpoints, let alone any collusion with industry, as alleged in the Global2000 report. The decision of RAC was reached by consensus, with individual RAC members contributing their individual views on the subject as the discussion progressed.

Upon examination of all your arguments ECHA concludes that the dossier submitter (BAuA) and RAC have correctly followed all of the legal steps responsibly and with its usual scientific rigour during the process to harmonise the classification and labelling of glyphosate, respecting the CLP Regulation as well as all the OECD and ECHA's own guidance.

Therefore, ECHA rejects all of the allegations made in the report. Furthermore, ECHA is concerned of an attempt to publicly malign the integrity of EU institutions mandated to ensure safe use of chemical substances in the EU. This is of particular concern, when the process actually provides the opportunity to submit any further data and to make any science-based observations during the process.

Finally, ECHA will at this critical decision-making stage not engage in any public discussion that could be perceived by your or other organisations as ECHA reopening its opinion. Therefore, we will consider your invitation for a public debate after the decision of the policy makers has taken place.

Yours sincerely,

[signed]

Geert Dancet  
Executive Director

Annex      ECHA's response to the Global2000 report

## ANNEX: ECHA's response to the Global2000 report

### 1. Background

In 2015 and after considering the evidence submitted by the BfR for Germany in the Risk Assessment Report EFSA concluded that glyphosate is unlikely to represent a carcinogenic hazard for humans. The approval to use glyphosate as an active substance in plant protection products (PPP Regulation) expired at the end of June 2016. Based on the EFSA opinion the European Commission and the Member States decided to extend the approval for 18 months, by which time RAC will have adopted its opinion on glyphosate's harmonised classification.

ECHA's Committee for Risk Assessment (RAC) concluded, after considering the evidence reported by the Dossier Submitter (BAUA, Germany) as well as that provided during public consultation, that no classification for carcinogenicity is warranted under the CLP Regulation and that the harmonised classification for serious eye damage and toxic to aquatic life should be maintained. The RAC opinion and related documents were published on the ECHA website in June 2017.

Recently, the Global2000 report has made a number of allegations specifically targeting ECHA, EFSA and the German authority BfR. Central to these (as indicated in the sub-heading of the report) is that "industry has strategized (and regulators have colluded) in an attempt to save the world's most widely used herbicide from a ban". The picture presented is that EU agencies have colluded with industry to try to find ways to avoid classifying the substance.

ECHA notes the persistent attempts, repeated in the Global2000 report, to remove statistically significant findings from their context and to present them as isolated facts, while ignoring the weight of the evidence on carcinogenicity as a whole. The advice of the ECHA and EFSA nominated scientific experts from across the European Union is consistent and their evaluation responsible and thorough. All of the allegations in the Global 2000 report are unfounded and are categorically rejected by ECHA.

Many of the issues have been considered earlier, in correspondence published on the ECHA and EFSA websites as well as in correspondence published in Archives of Toxicology (Tarazona *et al*, 2017a,b; Portier and Clausing, 2017). The reader is referred to these documents for further details.

ECHA's role in the CLH process as well as the history of ECHA's involvement in the assessment of the classification of glyphosate is explained in detail at the end of this document (under "Supplementary information") and in the links provided there.

### 2. The role of RAC

ECHA's role in the CLH process is governed by Art 37 of the CLP Regulation, which states as follows; "*The Committee for Risk Assessment [RAC] of the Agency set up pursuant to Article 76(1)(c) of Regulation (EC) No 1907/2006 shall adopt an opinion on any proposal submitted pursuant to paragraphs 1 or 2 within 18 months of receipt of the proposal, giving the parties concerned the opportunity to comment.*"

The primary task of RAC in the CLH process is to assess the proposals submitted. In the process it takes into account any relevant information submitted during public consultation of the

proposal, whether it supports the classification(s) proposed by the dossier submitter or not. Beyond this, it is not the primary task of RAC to seek additional information.

In the CLH process the dossier submitter is given an opportunity to respond to the comments received, and may also revise their proposal for classification based on information provided during the public consultation.

### 3. The findings

The methodology used by the dossier submitter in relation to the findings is explained in the harmonised classification and labelling (CLH) report as follows: *"All toxicological studies included in this CLH dossier were evaluated and assessed by in-house staff toxicologists of the BfR. It is emphasised that the toxicological database for glyphosate is extremely large and that the studies have come from a great number of sources. Thus, completeness of the database and identification and compilation of relevant and reliable data are crucial. In the following, the approach taken by the dossier submitter (DS) is described with particular regard to the studies and publications that are referred to in this CLH dossier."*

*The information that is relevant for classification and labelling of glyphosate is based on original studies of the manufacturers that were performed on a routine basis under GLP conditions and in compliance with OECD Test Guidelines for the individual toxicological endpoints".*

In the CLH process, the Dossier Submitter and subsequently RAC have openly and transparently considered in detail the relevant findings, which are summarised below (which were also summarised in Table 1 of the report):

- (1) In rats, all findings were in male rats in 2 studies out of 7 evaluated
  - Pancreatic tumours in 2 studies (Lankas, 1981; Stout and Ruecker, 1990),
  - Liver tumours in 1 study (Stout and Ruecker, 1990)
  - Thyroid C-cell tumours in 1 study (Stout and Ruecker, 1990)
- (2) In mice (all findings were in male mice in 5 studies)
  - Renal tumours in 3 studies (Knezevitch and Hogan, 1983; Sugimoto, 1997; Kumar, 2001)
  - Haemangiosarcomas in 2 studies (Atkinson, 1993; Sugimoto, 1997)
  - Malignant lymphoma in 2 studies (Wood, 2009; Sugimoto, 1997)

Two studies in mice (Vereczkey and Csanyi, 1982 and Bhide, 1988) were negative for carcinogenicity but the top dose level was 300 ppm and thus much too low for meaningful assessment. These studies were therefore not included in the evaluation.

### 4. CLP requirements and application of Weight of Evidence

The authors of the Global2000 report have argued that the findings in the studies mentioned above should have been used to classify glyphosate for carcinogenicity in Category 1B. ECHA understands that this conclusion is reached based on the following logic, which combines the definitions for "sufficient evidence" for carcinogenicity with the criteria for meeting classification as Carc. 1B. The CLP Regulation describes what constitutes "sufficient evidence" of carcinogenicity based on animal studies as "a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols". One of the factors in the CLP Regulation justifying classification as Carc. 1B arises from "animal experiments for which there is sufficient evidence to demonstrate

animal carcinogenicity (presumed human carcinogen)". Furthermore the CLP Regulation states that "sufficient evidence" in animal studies is sufficient for classification as Carc. 1B.

This however ignores other central principles upon which the CLP Regulation is based and which the evaluators must take into account. In particular there is an obligation to weigh all of the available evidence in each case. In Recital 33, of the CLP Regulation, this is reflected as follows: *"Recognising that the application of the criteria for the different hazard classes to information is not always straightforward and simple, manufacturers, importers and downstream users should apply weight of evidence determinations involving expert judgement to arrive at adequate results."*

In CLP Art 9(3) and Annex I (Section 1.1.1 titled *"The role and application of expert judgement and weight of evidence determination"*) the following provisions are set:

- CLP Article 9(3): *"Where the criteria cannot be applied directly to available identified information manufacturers, importers and downstream users shall carry out an evaluation by applying a weight of evidence determination using expert judgement in accordance with section 1.1.1 of Annex I to this Regulation, weighing all available information having a bearing on the determination of the hazards of the substance or the mixture, and in accordance with section 1.2 of Annex XI to Regulation (EC) No 1907/2006."*
- In Section 1.2 of Annex XI to REACH (referred to above) it states that *"There may be sufficient weight of evidence from several independent sources of information leading to the assumption/ conclusion that a substance has or has not a particular dangerous property, while the information from each single source alone is regarded insufficient to support this notion"*
- In Annex I (1.1.1) (also referred to in Art 9(3), quoted above) it states that *"A weight of evidence determination means that all available information bearing on the determination of hazard is considered together, such as the results of suitable in vitro tests, relevant animal data, information from the application of the category approach (grouping, read-across), (Q)SAR results, human experience such as occupational data and data from accident databases, epidemiological and clinical studies and well-documented case reports and observations. The quality and consistency of the data shall be given appropriate weight. Information on substances or mixtures related to the substance or mixture being classified shall be considered as appropriate, as well as site of action and mechanism or mode of action study results. Both positive and negative results shall be assembled together in a single weight of evidence determination"*.

Some of the important principles relating to a weight of evidence assessment are raised in the text above. A weight of evidence assessment means that data is given different weight depending on factors such as the quality and consistency of the results. Also, both positive and negative results shall be assembled together in a single weight of evidence determination. This is not a matter of a majority of studies supporting one or the other outcome. The mere presence of either negative or positive data is not on its own sufficient to conclude on classification.

Thus, RAC is obliged to make an overall weight of evidence analysis of the complete data set and takes this responsibility very seriously. In the case of glyphosate, some studies were found to be of no weight, and were not included in the analysis, for example two studies which were negative for carcinogenicity were considered to be conducted with too low doses (Vereczky, 1982 and Bhide, 1988). The result of these studies were simply not considered to be of any value for the assessment, as there is no way to determine if the negative result was due to the low dose or due to the substance not being carcinogenic. One further study (Lankas *et al*, 1981) was included in the analysis, despite also having been conducted with low doses, because positive

findings in this study had been raised by IARC. A weight of evidence analysis also therefore involves much more than simply establishing whether there are any statistically significant effects.

In addition to multiple animal studies giving variable and conflicting indications of carcinogenicity, data from the epidemiology studies and genotoxicity studies also had to be considered in a wider weight of evidence assessment. This is what RAC has done and has concluded that despite some indications of carcinogenicity seen in some studies mainly in mice, the criteria for classification are not met when all the studies and findings are considered together. Thus the conclusion that no classification for carcinogenicity is warranted was reached.

The authors of the Global2000 report have made a comparison with the factors listed in the CLP regulation to help assess the concern arising from the outcome of particular studies. A total of 11 statistically significant increases in tumour incidences were observed in two rat and five mouse studies.

Important factors to consider in the weight of evidence assessment are presented in Regulation (EC) 1272/2008 (see Box 3 of the Global2000 report) and discussed in ECHA Guidance (ECHA 2015).

Applying the factors listed in Box 3 of the Global2000 report to the data available for the assessment of glyphosate, the conformance with these factors is as follows:

Factor	Global2000	ECHA
tumour type and background incidence	Supported by historical control data	Not supported overall, based on historical control data, lack of dose response relationships
multi-site responses	Supported, as demonstrated by experimental data	Not supported, mostly one tumour type per study
progression of lesions to malignancy	Supported for kidney tumours; not applicable for malignant lymphoma and hemangiosarcoma	Not supported. The reference to kidney tumours is covered in the opinion – RAC concludes that progression to malignancy is not supported for kidney tumours (equivocal in one study).
reduced tumour latency	Not supported because not demonstrated	Not supported, not demonstrated. However, survival was generally not affected by the treatment.
whether responses are in single or both sexes	Not supported because effects in males dominate, but some effects were also seen in females	Not supported, effects only in males, no case where both sexes were affected

whether responses are in a single species or several species	Supported: effects were seen in rats and mice	Not supported: Different tumours were seen in different species; findings in rats not considered relevant for hazard assessment
structural similarity to a substance(s) for which there is good evidence of carcinogenicity	Not supported: no known carcinogens with structural similarities are known	Not supported: no known carcinogens with structural similarities
routes of exposure	Supported: the oral exposure route is highly relevant for humans	Insufficient evidence for classification based on studies conducted via the oral route, which is a highly relevant route of exposure for humans
comparison of absorption, distribution, metabolism and excretion between test animals and humans	Not possible, as there is no human data available for absorption, distribution, metabolism and excretion	No known qualitative differences that could influence the results
the possibility of a confounding effect of excessive toxicity at test doses	Supported: effects were seen without excessive toxicity	Evidence for maximal tolerated dose having been reached in some studies; very high doses used in some studies
mode of action and its relevance for humans, such as cytotoxicity with growth stimulation, mitogenesis, immunosuppression, mutagenicity	Supported: genotoxicity and oxidative stress have been identified as possible mechanisms.	Not supported, a genotoxic MoA not supported by the evidence

Overall, RAC has concluded that the evidence from animal studies does not support classification for carcinogenicity.

## 5. Statistical analysis

The issue of statistical analyses used by the dossier submitter, which have also been taken into account in the RAC Opinion, has been considered in detail in previous correspondence (see e.g. the ECHA/ EFSA response to Dr. Portier at [https://echa.europa.eu/documents/10162/23294236/portier\\_echa\\_efsa\\_response.pdf/9e199ec a-af2f-96bb-9e61-d6bae2588f4b](https://echa.europa.eu/documents/10162/23294236/portier_echa_efsa_response.pdf/9e199ec a-af2f-96bb-9e61-d6bae2588f4b) and Tarazona *et al.* (2017a,b). They are therefore not repeated here.

In summary, as acknowledged by the authors of the Global2000 report, OECD guidance document 116 does not provide a clear preference for a one-tailed or two-tailed test. The pros and cons of one-tailed and two-tailed tests are discussed in OECD documentation. Similar comments can be made in relation to the use of trend-tests vs pair-wise comparisons. Both

analyses were used in the CLH report and the results from both types of analyses were considered by RAC, when considering the biological relevance of the findings.

In simple terms, statistical methods in toxicology usually assess whether the probability of obtaining a certain result by chance is smaller than a certain predefined value (p-value). It is not proof that the result did not occur by chance and it can never be used to prove the lack of an effect but when correctly used is a powerful tool to assess data. Usually if the probability of achieving a certain result is 5% or lower the results are considered to be statistically significant. Consistent with what is stated above, a p-value above 5% does not prove that there is no effect and a p-value less than 5% will be expected by chance within every 20 analyses. The probability of getting statistically significant results by chance increases with the number of tests done.

Statistical analyses conducted in the original study reports were summarised in the Renewal Assessment Report (RAR), which was included as an annex to the CLH Report, which was subjected to public consultation. Comments on these statistical analyses were not received during public consultation.

As noted in previous correspondence, the choice between a pairwise test and a test for trend is a matter of judgment which includes both the context as well as the relative advantages and limitations of the different approaches. According to the OECD GD 116 there is no specific indication on whether either or both pair-wise and trend tests should be performed.

## 6. Biological relevance of findings

The Global2000 report included a reference to *"a recent re-analysis of the original data which revealed eight further tumours in regulatory rat and mouse carcinogenicity studies that were not described in the original study reports by industry or noticed by the German Federal Institute for Risk Assessment (BfR), the European Food Safety Authority (EFSA), or the European Chemicals Agency (ECHA) (Portier 2017)"*. The issue was raised in a letter from Dr. Christopher J. Portier to Jean-Claude Juncker, the President of the European Commission, in which it was argued that *"the authorities should be instructed to review the evidence submitted in this letter and not make any decision on glyphosate until these positive findings are included in the assessment of the substance's carcinogenicity"*.

This issue was addressed in the EFSA/ECHA response to Dr. Portier, which is available at [https://echa.europa.eu/documents/10162/23294236/portier\\_echa\\_efs\\_a\\_response.pdf/9e199eca-af2f-96bb-9e61-d6bae2588f4b](https://echa.europa.eu/documents/10162/23294236/portier_echa_efs_a_response.pdf/9e199eca-af2f-96bb-9e61-d6bae2588f4b). Some pertinent issues relating to these findings are highlighted here. One of the findings was in fact included in the documents submitted by the Dossier Submitter and which were submitted to public consultation by ECHA.

The reasons why most of these were not considered in the CLH report or the Opinion, was that the Dossier Submitter considered that these tumours were not treatment-related and they were considered not relevant for hazard and risk assessment. A detailed explanation of each of these findings individually can be found in Tarazona *et al.* (2017a,b). Contrary to what has been stated in the Global2000 report, some of these were also specifically noted in the study reports and have been available online to our knowledge since 2015. The findings have also been presented in other documents to which RAC has had access during the process. Some of these findings were actually also mentioned in the report by IARC, but were not considered further.

It is of course required that the important findings relevant to the proposal are given serious consideration. ECHA is of the view that all important findings were comprehensively addressed in the CLH report and in the RAC opinion.

ECHA notes, however, that had any of these findings been considered to be a significant issue,



there was the opportunity during public consultation as well as later in the process (for example at the December RAC meeting) to suggest a more detailed consideration of the tumours referred to. Although almost 300 comments were received during public consultation, most of which addressed carcinogenicity, no concern over any of these tumour incidences not having been specifically referred to in the CLH report or related documentation was raised.

As noted in the EFSA/ ECHA response to Dr. Portier, 4 out of 8 tests for trend which were reported for these findings (i.e. Sugimoto et al. (1997); Atkinson et al. (1993); Enomoto (1997); and Brammer (2001)) were run on very sparse data, where most, if not all, tumour incidences by dose group are zero, except for the highest dose. It is doubtful whether these results point to a carcinogenic response in cases where data are so extremely sparse. In addition, for establishing biological relevance, care should be taken in applying the trend test in situations where the only dose triggering the linear association is so high as to imply that the maximum tolerated dose (MTD) was likely to have been exceeded (as in Sugimoto et al. – 4348 mg/kg bw per day).

Although the Cochran-Armitage test is generally considered one of the valid statistical methods to assess the possible association between exposure to a hazard and increase in tumour incidence, it can provide false positive results beyond the level expected by design when high doses are considered that exhibit excess of toxicity and a large number of outcomes and sites are tested concurrently. Moreover results of the test should never be interpreted in isolation but always put in the context of their biological relevance.

As also noted in the ECHA/EFSA response to Dr Portier, OECD Guidance 116 (OECD, 2012) highlights the *“need to remain aware of the distinction between statistical significance and biological importance. The increasing emphasis in the statistical community on estimation over hypothesis testing is a crucial development in the distinction between these two concepts with statistical analysis being a part of the interpretation of the biological importance, not an alternative”*. The same guidance guards against *“the reporting of significance levels arguing instead that the emphasis should be on emphasizing the size of effects and the confidence in them”*..

As noted earlier, the task of RAC has been to evaluate the weight of evidence for the whole dataset. This is different from just evaluating the presence of statistically significant findings. Statistical significance is one part of the evaluation, but the presence of statistically significant results does not automatically lead to classification.

As noted by Tarazona *et al.* (2017a,b) and the EFSA/ ECHA response to Dr. Portier, the OECD guidelines state that the statistical assay to be used should be selected before the study is conducted. To apply another statistical assay if the result of the first was not consistent with a preferred outcome is not scientifically valid practice and is contrary to the OECD guidelines. The OECD guidelines state that statistical re-evaluation can be performed if no analysis was done in the original study or if the wrong test was used. Although the OECD guidelines don't specify that both types of tests should be performed, the data have now been analysed using both types of tests, and consequently RAC have considered the results in the light of both types of statistical tests in the weight of evidence. However, the presence of statistically significant results by themselves are still not enough to conclude on classification.

The authors of the report claim that *“While statistical analysis is a cornerstone in the assessment of carcinogenicity, biological relevance also has to be considered”*. ECHA disagrees with this statement. It is clear from OECD Guidance Notes No. 35 (*“Guidance Notes for Analysis and Evaluation of Chronic Toxicity and Carcinogenicity Studies”*), as quoted below, that biological relevance needs to be established.

According to OECD No. 35: *"The use of statistics in toxicology has limitations (Gad & Weil, 1986): (1) statistics cannot make poor data better; (2) statistical significance may not imply biological significance; (3) an effect that may have biological significance may not be statistically significant; (4) the lack of statistical significance does not prove safety. The importance and relevance of any effect observed in a study must be assessed within the limitations imposed by the study design and the species being studied."*

And:

*"Findings should be considered on the basis of both statistical significance and likely biological significance. It is important to bear in mind the variability of biological data when assessing a statistically significant result: statistical significance does not necessarily equate to biological significance. Conversely, a finding that is not statistically significant may have biological significance when considered in the light of the likely toxicological or pharmacological action of the test compound, or when considered alongside results from other studies."*

Biological significance is therefore not any less of a "cornerstone". In fact, it is biological/toxicological significance of findings and their relevance to humans which determines their applicability to classification for carcinogenicity. Statistical significance of findings on its own is not enough, but is a tool to assist in arriving at a conclusion.

## **7. High-dose effects, lack of dose-response relationships and use of historical control data**

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. ECHA considers that an effect seen only at the high dose can be cause for concern, but also that the presence of a dose response relationship increases the concern. There is no basis for the claim that the Dossier Submitter or RAC have not acknowledged the presence of statistically significant trend tests, since positive trends have been clearly reported in the CLH report as well as the RAC opinion. However, in contrast to the authors of the report, RAC do claim a lack of any dose response relationship for pancreatic tumours and haemangiosarcomas in females. Thus, these allegations of the authors of the Global2000 report are not substantiated.

Concerning the use of historical control data, ECHA agrees, of course, that the concurrent control is more important than the historical controls. However, ECHA does not agree that historical controls are of value only in certain cases. The number of tumours in a study are often low and it is binary – either there is a tumour or there is not a tumour.

The authors of the report claim to have spotted an inconsistency in the reporting of historical controls for the Sugimoto (1997) study; *"authorities claimed that the historical control data for the Sugimoto (1997) study supported the conclusion of non-carcinogenicity, because the observed incidence in the high-dose group (12%) was below the upper limit of the historical control data range (19%). But this is not true. According to the authorities' own report, eight out of the nine studies forming the historical control data had an incidence of malignant lymphoma of 6% or lower (RMS Germany 2015a, Volume 3.B.6, p. 528). In contrast, the high-dose group of the Sugimoto (1997) study had an incidence of 12%. In other words, this high-dose group had an incidence at least twice as high as eight out of nine historical control data groups."*

The RAC opinion in fact addresses this specific point and these data were placed into perspective by RAC as follows: *"The tumour incidence of 12% at the high dose of 4348 mg/kg bw/d in the*

*study by Sugimoto (1997) was within the relevant historical control range for Crj:CD-1 male mice obtained from the laboratory in which the study was performed (mean 6.3%; range of 3.9% - 19.2%, the majority of the studies had a control incidence  $\leq$  6%, 9 studies initiated between 1993 to 1998". The fact that the range of historical control data covered the range of the findings in the study was taken into account along with the distribution of the data and other factors in the assessment.*

Concerning the use of historical control data, as well as concerning the issue of high dose levels, CLP Guidance (ECHA) states that *"Use of historical control data should be on a case by case basis with due consideration of the appropriateness and relevance of the historical control data for the study under evaluation. In a general sense, the historical control data set should be matched as closely as possible to the study being evaluated. The historical data must be from the same animal strain/species, and ideally, be from the same laboratory to minimise any potential confounding due to variations in laboratory conditions, study conditions, animal suppliers, husbandry etc. It is also known that tumour incidences in control animals can change over time, due to factors such as genetic drift, changes in diagnostic criteria for pathological changes/tumour types, and husbandry factors (including the standard diet used), so the historical data should be contemporary to the study being evaluated (e.g. within a period of up to around 5 years of the study). Historical data older than this should be used with caution and acknowledgement of its lower relevance and reliability. (RIVM, 2005; Fung et al, 1996; Greim et al, 2003).*

*Even when a particular tumour type may be discounted, expert judgment must be used in assessing the total tumour profile in any animal. However, appearance of only spontaneous tumours, especially if they appear only at high dose levels, may be sufficient to downgrade a classification from Category 1B to Category 2, or even no classification. Where the only available tumour data are liver tumours in certain sensitive strains of mice, without any other supplementary evidence, the substance may not be classified in any of the categories, (Battershill and Fielder, 1998). Expert judgment is required to evaluate the relevance of the results".*

The CLP Guidance thereby refers to the use of expert judgement in the use of historical control data and suggests caution in the interpretation of data at high doses. This was in fact taken into account by RAC: It is stated in the Opinion (in relation to the Giknis and Clifford historical control data referred to in the Global2000 report) that *"It should be noted that these control data are from different laboratories and should thus be used with caution".*

In the Kumar (2001) study, as reported in the RAC Opinion, the increases in incidences of renal tumours were at a low level, with a maximum incidence of 2 (4%) at the high dose (pair-wise, not statistically significant; statistically significant in the trend test). Increases in malignant lymphoma male rats were only seen at the highest dose (albeit above the HCD range) and were not statistically significant either by the trend test or the pair-wise test. However, it was disclosed in the Opinion as well as the CLH report that the findings were reported as statistically significant in the original study report using a (less commonly used) Z-test. The findings were seen against a high background rate (high incidences in concurrent controls) in a strain known to have high incidences of this tumour and the findings were higher still in females. As noted in the Opinion *"the high background incidence in this strain must be taken into consideration. The historical control data, according to information in the study report (no additional information given on the basis of these historical control data), was in males a mean of 18.4% with a range of 6 - 30% and in females a mean of 41.6 with a range of 14 - 58%. Thus, the incidences of malignant lymphomas were above the upper range of the historical control data for the male mice."* On the malignant lymphomas, the opinion concluded, based on the overall picture of the incidences of malignant lymphoma in all the five mouse studies, including the Kumar (2001) study, as follows:

*"No significant increases in malignant lymphomas were found in the mouse studies when assessed by the pairwise Fisher's exact test. However, in two of the five studies, a significant positive trend for malignant lymphoma incidences in males was reported. In two studies, increases were observed that were not statistically significant. In the fifth and oldest of the studies, the term malignant lymphoma was not used, but there was no statistically significant increase in lymphoreticular neoplasms reported in this study in response to glyphosate exposure. Thus, the lymphoma incidences in male mice show a slight, but clearly variable increase. Further, no increase in treatment related non-neoplastic lymph nodes were reported, thus supporting the conclusion that the tumours were of a spontaneous nature. The biological and human relevance of the findings is uncertain for the following reasons:*

- i) the maximum incidences were regarded to be within the historical control range for the CD-1 mice, although adequate historical control data were not available for all studies;*
- ii) the increases in malignant lymphoma incidences appeared to be confined to the high dose groups in the CD-1 mice;*
- iii) the incidence of malignant lymphomas is known to be related to the age of the animals. However, significant associations between exposure to glyphosate and induction of malignant lymphomas were not observed in the 24-month studies. Furthermore, there was no reduction in overall survival in the exposed groups;*

*no parallel increases were observed in female CD-1 mice. It is known that female CD-1 mice are usually more prone to develop spontaneous malignant lymphoma than male mice (Son and Gopinath, 2004, ASB2015-2533). The lymphoma incidences were generally higher in females than in males, but no glyphosate related increases were seen in female CD-1 mice".*

Concerning the use of HCD in relation to the study of Wood (2009), the (minuted) discussion from the RAC meeting provides the following insight: *"It was noted that historical control data (HCD) were not available for all the studies and in some studies the HCD that was available was not from the same test facility and/or from a relevant time period from the study, as advised in ECHA's guidance. Some reservations were expressed about the use of such data, but the absence of a complete set of HCD was not seen as a crucial factor for deciding on the classification. IND provided details of a "blank" study which had been conducted under the same conditions as the Wood (2009) study in which a control incidence of 12% for malignant lymphomas was seen. The data indicated that background incidences of tumours may indeed be high in the conditions of the Wood (2009) study, but as this was only one study the value of the study as a HCD is limited. Concerning the use of the HCD from the papers by Giknis and Clifford, HEAL noted that the housing conditions changed (from single housing to group housing, in both cases in wire bottom cages) and the tumour incidences decreased by half between 2005 and 2010 while in the studies the mice were group housed in solid bottom cages. A RAC Member responded that the data from 2010 were from fewer studies and therefore the data from 2005 were given greater weight. The incidences were also described as being uniformly spread across the range." As noted earlier, the CLP Guidance gives direction but also some discretion as to how the historical control data are used. The data have been used by RAC in accordance with current CLP Guidance and relevant OECD guidelines.*

Concerning the toxicity at the highest dose in the Sugimoto (1997) study (4348 mg/kg bw/d), it is noted in the Opinion that *"increased tumour incidences were only observed at very high doses (>4000 mg/kg bw/d) at which the body weight gain in males were decreased compared to controls by up to 11% and 15% in the Knezevich and Hogan (1983) and the Sugimoto (1997) study, respectively. The OECD TG 451 for carcinogenicity studies does not give a precise top dose recommendation, but states that the highest dose level should elicit signs of minimal toxicity, with depression of body weight gain of less than 10%. RAC therefore gives less weight to the findings at these very high dose levels".*

In OECD Guideline on interpretation of carcinogenicity studies No. 116, it is stated that "As

*indicated in the Test Guidelines, a top dose not exceeding 1000 mg/kg body weight/day may apply except when human exposure indicates the need for a higher dose level to be used".* This does not of course mean that doses above 1000 mg/kg bw/day should not be used or should automatically be discarded, particularly with substances which appear to be well tolerated at high doses. However, at some of the high doses used (particularly those in excess of 4000 mg/kg bw/d) the relevance of findings seen in long-term studies to humans may be questioned. Doses above 1000 mg/kg bw/day are high doses when used over 18 months or 2 years and the possibility that there are then other factors (not attributable to the direct effect of the substance) coming into play increases. All this needs to be (and has been) taken into account in the weight of evidence assessment.

## 8. Selection of studies

The authors of the report raised questions concerning the selection of studies in the evaluation of RAC. It is always part of the evaluation of the hazardous properties of a substance to assess the quality of the studies and to give lower weight to studies of low quality.

In particular the authors criticise the exclusion of Kumar (2001) and the inclusion of Atkinson (1993).

Concerning the study by Kumar (2001): Contrary to what the authors claim, and despite concerns about its quality, RAC did take the Kumar (2001) study into account as is clearly evident from the RAC opinion.

The question of a potential virus infection affecting this study has also been raised. The authors of the Global2000 report wrote: "In its opinion, referring to the CLH report, EFSA's RAC (*sic*) insisted upon a possible role of oncogenic [cancer-causing] viruses" (ECHA 2017 p. 30)". The actual quote is from the "Summary of the Dossier Submitter's proposal" and in full reads as follows: "*The Dossier Submitter also noted that a possible role of oncogenic viruses should not be ignored.*" This is the only context in which a virus infection is mentioned in the opinion. Thus, the claim that RAC dismissed the study and did so based on possible virus infection is not true.

The Global2000 report also states that they have asked ECHA whether the 18.4% incidence of malignant lymphomas in the historical control database should be considered as an indication that oncogenic viruses did not play a role in the Kumar (2001) study and that this question remains unanswered. Because ECHA has not dismissed the study, ECHA has no view on this matter and the question has not been considered relevant. It should be clarified, however, that RAC has not concluded that there was no viral infection, merely that they did not find the evidence for such an infection sufficient to dismiss the study.

The issue of the reliability of the study of Atkinson et al (1993) has been raised and the Global2000 report states that the study should have been dismissed. RAC, like EFSA and IARC did find the study acceptable. In the report it is stated "*And another study – Atkinson (1993) – that was severely deficient in the histopathological assessment of malignant lymphoma was kept as part of the assessment and served to strengthen the claims of lack of statistical significance (in pairwise comparison) and lack of dose-dependence.*" . Consistent with its approach in relation to other studies (such as Kumar et al, 2001), RAC does not lightly dismiss studies from consideration and hence the study results were given appropriate treatment in the weight of evidence assessment.

Concerning the findings being limited to a single sex only, the CLP Guidance states that "*Effects seen only in one sex in a test species may be less convincing than effects seen in both sexes, unless there is a clear patho-physiological difference consistent with the mode of action to explain the single sex response*". The fact that the findings were confined to a single sex in two

species (rats and mice) and that there was not a mechanism of action to explain this made the findings less convincing for RAC.

Finally, ECHA considers that all studies should be included in the CLH process (including the studies of Atkinson, 1993 or Kumar, 2001), but the data should be considered in an overall weight of evidence approach. This is what RAC has done. Accordingly, the weaknesses and strengths of each study need to be considered. This was appropriately done by RAC in arriving at its conclusion.

## 9. Conclusions

RAC approached the assessment without any anticipation of the outcome and adopted its Opinion on the classification of glyphosate following an independent assessment of all the scientific data. RAC does not set out to please any stakeholder organisation with its conclusions. Any classification outcome was possible in this case. There was no collective preconception of whether or not the substance was hazardous for any of the endpoints, let alone any collusion with industry, as alleged in the Global2000 report. During the process individual RAC members formed their own views on the subject and at the end the decision of RAC was reached by consensus. RAC came to its conclusion on all the considered endpoints only after considering the overall toxicological profile based on the data in the original study reports.

RAC did not evade or hide any data and no studies were dismissed from the assessment – all important findings were discussed openly and objectively. The methodology has been appropriately applied in the CLH process as prescribed in the relevant ECHA Guidance documents and relevant OECD guidance.

RAC has considered the evidence for classification from the animal studies, but has noted that the effects were observed inconsistently and generally only at the highest doses which in some cases were very high. Additional factors considered were the lack of evidence for mutagenicity and from epidemiology.

The Dossier Submitter as well as the experts of RAC considered all the relevant data in a weight of evidence determination conducted in accordance with the requirements in the CLP Regulation and applicable guidance, as it has done in every preceding case where the criteria cannot be applied directly to available identified information.

ECHA rejects all of the allegations made in the Global2000 report. Furthermore, ECHA is concerned of this attempt to publicly denigrate the integrity of EU institutions mandated to ensure safe use of chemical substances in the EU. It is of particular concern, when the process actually provides the opportunity to make all the points relevant to the case by legitimate means.

## 10. References

Tarazona JV, Court-Marques D, Tiramani M, Reich H, Pfeil R, Istace F, Crivellente F (2017a). Response to the reply by C. J. Portier and P. Clausen, concerning our review "Glyphosate toxicity and carcinogenicity: a review of the scientific basis of the European Union assessment and its differences with IARC" Arch Toxicol. 2017 Jul 25. doi: 10.1007/s00204-017-2032-8

Tarazona JV, Court-Marques D, Tiramani M, Reich H, Pfeil R, Istace F, Crivellente F (2017b). Glyphosate toxicity and carcinogenicity: a review of the scientific basis of the European Union

assessment and its differences with IARC. Arch Toxicol. 2017 Mar. doi: 10.1007/s00204-017-1962-5

Portier and Clausing (2017). Re: Tarazona et al. (2017): Glyphosate toxicity and carcinogenicity: a review of the scientific basis of the European Union assessment and its differences with IARC. doi: 10.1007/s00204-017-1962-5. Archives of Toxicology, DOI: 10.1007/s00204-017-2009-7

## Supplementary information

### *ECHAs role in the CLH process*

The approval to use glyphosate as an active substance in plant protection products (PPP Regulation) expired at the end of June 2016. The European Commission decided to extend the approval for 18 months, by which time RAC will have adopted its opinion on glyphosate's harmonised classification.

- ECHA is responsible for managing the harmonised classification and labelling (CLH) process for hazardous chemical substances.
- Active substances in plant protection products (PPP) are normally subject to harmonised classification and labelling.
- As part of the procedure for the renewal of glyphosate approval under the PPP legislation, a harmonised classification and labelling proposal was prepared by the German Federal Institute for Occupational Safety and Health (BAuA) and submitted to ECHA in March 2016. The CLH process for an active substance is triggered when a proposal for harmonised classification of that chemical substance is submitted by a Member State competent authority (MSCA) to ECHA.
- Glyphosate already had harmonised classifications for irreversible effects on the eye (Eye Dam. 1, H318) and toxicity to aquatic life with long-lasting effects (Aquatic Chronic 2, H411). In the CLH report submitted by Germany (BAuA) these existing harmonised classifications were reviewed and the dossier submitter proposed to add a classification for specific organ toxicity after repeated exposure (known as STOT RE 2, H373).
- RAC assessed the properties of glyphosate for several other hazard classes, including carcinogenicity, using the criteria in the CLP regulation. They considered extensive scientific data in coming to their opinion.
- ECHA organised a 45-day public consultation on the German proposal in from 2 June to 18 July 2016. Its results are publicly available here: <https://echa.europa.eu/harmonised-classification-and-labelling-previous-consultations/-/substance-rev/13838/term> . The dossier submitter (BAuA) has responded to comments submitted during the public consultation.
- RAC has independently assessed all the scientific data on glyphosate available to it (including any scientifically relevant data received during the public consultation). RAC's opinion is on the hazard classification of the substance, following the normal process described in the Framework for RAC opinion development on substances for harmonised classification & labelling.
- The classification is based solely on the hazardous properties of the substance. It does not take into account the likelihood of exposure to the substance and, therefore, does not address the risks of exposure. The risks posed by exposure are considered under the relevant downstream pieces of legislation, such as the PPP regulation in the case of glyphosate.



- RAC held its first discussion on glyphosate on 7 December by hearing six presentations from interested parties on the topic, including HEAL, IARC, Glyphosate Task Force, EFSA, the FAO/WHO JMPR and the dossier submitter Germany. These presentations are available here: <https://echa.europa.eu/-/the-committee-for-risk-assessment-starts-discussing-the-harmonised-classification-for-glyphosate>
- The legal deadline for the adoption of the RAC opinion was 30 November 2017, which is 18 months from the date that the dossier was declared to be in accordance with requirements. The RAC adopted its opinion already in its meeting on 15 March 2017.
- Before the March RAC meeting, the rapporteurs' draft opinion was circulated to committee members for their review. In the CLH process, draft opinion documents are not made publicly available (stakeholders who are involved with RAC's work do have access to them), because they are subject to detailed discussion and often change considerably before the opinion is final.
- ECHA has subsequently (in June, 2017) published the committee's final opinion on its website and forwarded it to the European Commission for final decision making. The opinion and related documentation is available at: <https://echa.europa.eu/opinions-of-the-committee-for-risk-assessment-on-proposals-for-harmonised-classification-and-labelling/-/substance-rev/16901/term>

More information on the harmonised classification and labelling process is available at:

[http://ec.europa.eu/growth/sectors/chemicals/classification-labelling/index\\_en.htm](http://ec.europa.eu/growth/sectors/chemicals/classification-labelling/index_en.htm)

<http://echa.europa.eu/addressing-chemicals-of-concern/harmonised-classification-and-labelling>

Also some information about glyphosate and links to further information:  
<https://echa.europa.eu/chemicals-in-our-life/hot-topics/glyphosate>

ECHA Newsletter: How ECHA is assessing glyphosate  
<https://newsletter.echa.europa.eu/home/-/newsletter/entry/how-echa-is-assessing-glyphosate>

EFSA's fact sheets on glyphosate:  
<http://www.efsa.europa.eu/en/topics/factsheets/glyphosate151112>