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Christopher J. Portier, Ph.D
Thun
Switzerland

Re.: Your letter Review of the Carcinogenicity of Glyphosate by ECHA, EFSA and BfR

Dear Dr Portier,

We write with reference to the letter you sent to President Juncker on 28 May 2017 in which you highlight concerns about the evaluation of the studies used in the EU assessment of glyphosate. As both ECHA and EFSA processes were referred to in your letter, and in response to a request from the European Commission (Ares(2017)2891256-09/06/2017), this reply has been jointly prepared by the two agencies and will be published on our websites. The German authority, Bundesinstitut für Risikobewertung (BfR), also played an important role in the glyphosate evaluation and it too has contributed to this response.

As you are aware, in 2015 EFSA concluded that glyphosate is unlikely to represent a carcinogenic hazard for humans. After the EFSA process had been completed, ECHA's Committee for Risk Assessment (RAC) concluded, after considering the evidence reported by the Dossier Submitter (DS, Germany) as well as that provided during public consultation, that no classification for carcinogenicity is warranted.

In your letter, you expressed the view that both EFSA and ECHA failed to identify all statistically significant cancer findings in the chronic rodent carcinogenicity studies with glyphosate. To support this argument, you refer to a re-analysis of eight specific tumour incidences reported in the original study reports from seven animal carcinogenicity studies.

Having carefully assessed the reasoning behind the arguments you make, EFSA and ECHA confirm that the original assessments considered all relevant findings. Our detailed technical assessment you will find in the Annex to this letter. We consider that none of the specific findings you bring forward are relevant for the hazard and risk assessment of glyphosate. In our view, the results of any statistical analysis and its related uncertainties have to be weighted for their biological relevance to arrive at a comprehensive toxicological evaluation of the substance at hand.

The underlying scientific principles used in the EFSA and ECHA processes in the evaluation of animal carcinogenicity studies consist of an integrated weight of evidence approach that reflects the criteria in the Classification, Labelling and Packaging (CLP) Regulation and the relevant ECHA guidance. We understand that views may differ on the level of detail that should be included in the pesticide Renewal Assessment Report (RAR), the harmonised classification and labelling (CLH) report or the Committee for Risk Assessment (RAC) opinion and reasons for not specifically documenting all these findings are explained in the Annex to this letter. However, in both processes, the full study reports were available to those responsible for the assessment.

Overall EFSA and ECHA are of the opinion that all the findings on the chronic rodent carcinogenicity studies referred to in your letter have been adequately considered and therefore we see no need for our evaluations to be revisited.

Yours sincerely,

Jack de Bruijn
ECHA Director of Risk Management

Guilhem de Seze
EFSA Head of Department of Scientific Evaluation of Regulated Products

Annex: Detailed technical assessment

ANNEX: DETAILED TECHNICAL ASSESSMENT

The EFSA and CLH processes

Both the EFSA and ECHA processes involve opportunities for interested parties to provide additional argument and information. The assessment by the Rapporteur Member State (RMS), Germany in the case of glyphosate, is subject to a public consultation, and all comments are published in the EFSA Peer Review Report mentioned in your open letter. In the harmonised classification and labelling (CLH) process which is managed by ECHA[1], the CLH report prepared by the dossier submitter (DS, Germany in the case of glyphosate) is subjected to public consultation (including, in this case, the addenda which included the Risk Assessment Reports (RAR)(Germany 2015) from the EFSA process). Subsequently, the Committee for Risk Assessment (RAC) assessed the data included in the CLH report (Germany 2016) (and in this case, the addenda) as well as the information received during public consultation and adopted an independent scientific opinion on the proposal.

The assessment of the quality of the studies and the identification of potential flaws that might influence the original results is an important part of the evaluation in both processes. The evaluation of the statistical significance of the results and their biological relevance is also crucial. Furthermore, the use of agreed procedures, guidance documents and guidelines is essential for ensuring consistency in regulatory scientific assessments.

Please note that this annex does not cover again those issues for which EFSA has already provided a response. EFSA considers to have adequately addressed the issues raised previously in your open letter to Commissioner Andriukaitis (Portier, 2015) on the overall assessment of the carcinogenic potential of glyphosate performed under the peer review (EFSA, 2016).

Review of the re-analysis

EFSA has carried out a review of the overall approach taken by Dr Portier in his re-analysis of some of the findings from the carcinogenicity animal studies as reported in his open letter.

In order to interpret the findings of the re-analysis, EFSA had to make a number of assumptions since the overall plan of the analysis is not reported with sufficient detail to allow replication and interpretation of its results (Table 1 of the open letter). Validity of the present EFSA assessment is conditional on the validity of the following assumptions:

- The whole set of studies included in the EFSA assessment and disclosed to the Parliament has been re-analysed.
- One-sided Fisher's Exact tests have been used to perform pairwise comparisons between control and treatment groups to identify possible differences in the incidence of tumours corresponding to a hypothesis of an increased incidence by specific individual doses.

[1] For further details on the CLH process, please refer to https://echa.europa.eu/view-article/-/journal_content/title/echa-s-role-in-assessing-glyphosate.

- One-sided Cochran-Armitage exact tests for linear trend with no adjustment for differential survival have been used to test for positive linear trends.
- Only outcomes/endpoints with results showing statistical significance ($p<0.05$) either for pairwise comparisons and/or for linear trend have been reported in Table 1 of the open letter.

I. Approaches to the evaluation: study quality assessment vs. raw data re-analysis

The open letter states that "IARC Working Groups routinely re-analyse some of the scientific data in the publications available to the working group to ensure that what is presented in a publication or technical document is correct".

As described in the background documents supporting the EFSA conclusion (Germany 2015; EFSA 2015a; EFSA 2015b), the scientific principles used by EFSA in the evaluation of animal carcinogenicity studies consist of an integrated weight of evidence approach which is consistent with the criteria in the Classification, Labelling and Packaging (CLP) Regulation[2] and the relevant ECHA guidance (ECHA, 2015). One of the pillars of the approach is the assessment of the quality of the studies and the identification of flaws that might influence the original results. This process aims at identifying the risk of bias, due to an inappropriate design and conduct of the studies, e.g. unacceptable deviations from the protocols in case of guideline studies as those mentioned in the open letter, or failure to control for confounding factors, and the possible role of chance. These sources of uncertainty are taken into consideration when weighing the evidence to draw conclusions about the carcinogenicity of the substance along with a series of qualitative elements. The latter include biological plausibility of the effect under evaluation and also consider the possible mode of action, the background variability of the tumour incidence, the evidence of a dose-response relationship and the possibility to exclude concomitant toxicity.

The choice made by EFSA to focus on the assessment of risk of bias and random error and avoid deviations from the original analyses performed by the authors stems from common practices validated by the scientific community (Cochrane 2011; GRADE 2008) and supported, among others, by OECD recommendations stating that: "experimental design represents the strategy for answering the question of interest and the specific statistical analyses are tactical methods used to help answer the questions. Therefore, the statistical methods most appropriate for the analysis of the data collected should be established at the time of designing the experiment and before the study starts" (OECD, 2012).

Approaches based on re-analysis of the original raw data represent a possible alternative to the systematic evaluation of the study that gives priority to the assessment of quality, reliability and results as originally produced. EFSA acknowledges that these alternatives can be considered equally valid provided that an integrated set of methods for re-analysis is established prior to looking at the original results thus preventing possible effect of cognitive bias (Kahneman 2011; Hilbert 2012). For regulated products EFSA considers that such an approach, if required, should be established in the guideline or guidance document, and not applied on a case-by-case basis.

[2] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, 1-1355.

EFSA acknowledges that appraising the quality of the studies versus re-analysing the raw data of the original studies are two approaches both considered valid by the scientific community. Re-analysis, though, needs to be performed according to a plan established prior to looking at the results and, in the context of regulated products, taking a consistent approach depending on the various applications.

II. One-sided vs. two-sided test

In two footnotes of the open letter the following statements are made as a rationale for the one-tailed hypothesis testing: "A two-sided test addresses the question of whether glyphosate increased or decreased the tumour incidence. In an evaluation of this type, you are only interested in increases". "A one-sided test addresses the question of whether glyphosate increased the tumour incidence".

In the OECD GD 116 (2012), it is mentioned that "a two-sided statistical hypothesis test tests for a difference from the negative control (in a pair-wise comparison) in either direction" and that "a one-sided comparison tests for a difference in only one pre-specified direction, but as a consequence has more power". Therefore, whenever an effect in only one of the two directions can be assumed the one-sided tests appear to be more efficient. If such an assumption is not met, though, the one-sided test will miss effects in the opposite direction.

Also, according to the OECD GD 116 (2012) in a carcinogenicity study "the expectation is often that the change will be an increase in tumours in the treated group so a one-sided test may be considered more appropriate, although this can be controversial".

It is important to note, though, that choosing a one-tailed test for the sole purpose of attaining significance is not appropriate. This could be the case in a post-hoc analysis where one-tailed testing is carried out where a two-tailed test was previously run in the original analysis that failed to reject the null hypothesis. In fact, the OECD GD 116 states that "the choice of whether to use a one- or two-side test should be made at the design rather than the analysis stage". This is to make the choice of the test fitting the objectives and the settings of the experiment. Planning the statistical analysis in the design stage also prevents being influenced by the results of analysis and avoids the impact of cognitive bias.

III. Results from the Cochran-Armitage test for linear trend

EFSA notes that 4 out of 8 tests for trend as reported in Table 1 (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. Although algorithms are available to compute the Cochran-Armitage test for linear trend in case of contingency tables with very low or zero counts, as expected in the instance of rare neoplastic lesions, and even considering that such a test has been run as an exact test, doubt can be cast on the interpretation of the results in cases where data are so extremely sparse. In addition, for establishing biological importance, care should be taken in applying the 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).

EFSA assumed that the Cochran-Armitage test for trend was applied without any correction for differential survival, as this information is not provided. According to the OECD GD 116 "A simple statistical analysis which does not account for inter-current mortality (described in paragraph 341) can underestimate the carcinogenic effects if the treatment decreases survival. Conversely, if the treatment increases survival then the tests may overestimate the carcinogenic effects. Failure to take intercurrent mortality into effect can, therefore, produce serious biases in the interpretation of results". Peto et al. (1980) argued that "to avoid this problem from occurring, adjustments are needed for differences in survival between the groups and this correction should be routinely used".

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.

IV. Pairwise comparisons vs. trend analysis

EFSA considers that the choice between a pairwise test and a test for trend is equally 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 tests should be performed, "A trend test is more powerful than the pair-wise test. A complication is that a trend test may fail to detect curvi-linear responses such as might arise from non-linear effects such as complications from saturation. In such situations, the pairwise tests may give more appropriate results". At the same time, a pairwise test is comparatively more prone to multiplicity issues, as, in case of n groups, it envisages n-1 tests vs. the one by the test for trend.

V. Multiplicity issues in the statistical analysis

EFSA notes that whenever multiple tests are run on the same data there is the case of a departure of the actual type I error from the nominal level, as set at the time the study and its original analysis were planned, and departure is increasingly important as the number of multiple comparisons increases. This translates into a higher risk of the null hypothesis being rejected when it is in fact true (more false positive results). Many procedures are available to adjust the Cochran-Armitage and Fisher's exact tests for the risk of inflation of the nominal type I error. The limited details provided in the open letter on the methodology used do not allow assessing whether adjustments have been considered to tackle the multiplicity issue.

VI. Biological relevance of the claimed additional tumour sites with significant increases due to glyphosate exposure (Table 1 of the open Letter)

Dr Portier has raised concerns about a number of findings reported in the original study reports. These are listed in Table 1 of the open letter.

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. This avoids the problem of a small biologically unimportant effect being declared statistically significant and the artificiality of trying to dichotomize a result into a positive or negative finding on the basis of a P value of, for instance, either 0.051 or 0.049".

A comparable approach is adopted by IARC that in its Preamble (2006) clarifies that in its assessment of carcinogenicity of experimental animals, consideration is given not only to quantitative results but also to qualitative aspects such as: (i) experimental conditions; (ii) consistency of the results; (iii) spectrum of neoplastic response; (iv) possible role of modifying factors.

Therefore, any isolated interpretation of the statistical analysis results, including statistical significance arising from the tests, is considered by EFSA (2011) and by the scientific community inadequate for the assessment of any potential associations.

The EFSA, ECHA and the peer reviews of MS relied on both the original study reports as well as on the summary reports of RMS or DS. Under these procedures, all results are carefully considered by the RMS/DS, Member States, EFSA and ECHA RAC. It is acknowledged that 7 out of 8 tumour findings reported by Dr Portier were not specifically documented either in the RAR or CLH report. As indicated below, the reason for that was not that they would have been overlooked or dismissed but they were considered not relevant for hazard and risk assessment. For clarification, the specific findings listed in Table 1 of the open letter are considered point-by-point below, in the order in which they are listed in the Table.

A) Lung adenocarcinomas, males only, in Wood et al. (2009) CD-1 Mouse

The incidences of concern were as follows:

Males; adenocarcinomas:	5 / 51, 5 / 51, 7 / 51, 11 / 51
Males; adenomas:	9 / 51, 7 / 51, 9 / 51, 4 / 51
Males; Total lung tumours:	14 / 51, 12 / 51, 16 / 51, 15 / 51

These results were discussed in the original study report and considered not linked to glyphosate administration.

Lung tumours of alveolar/bronchiolar cell origin, both adenomas and adenocarcinomas are commonly encountered in the aging CD-1 mouse and this was the case in this study. For male mice, slightly more adenocarcinomas were diagnosed among high dose animals compared to controls but the potential for progression from benign bronchiolar/alveolar neoplasms of the lung to malignant forms for this type of neoplasm makes an assessment of the combined incidence of adenomas and adenocarcinomas more reliable. If this approach is taken, there was no evidence of an increase.

The conclusion was that no treatment-related histopathological finding was observed in any dose group of either sex and that they were considered not relevant for hazard and risk assessment.

B) Haemangioma (any tissue), females only, in Sugimoto et al. (1997). CD-1 Mouse

The study author did not report the sum of haemangiomas (total for all tissues), but the incidences in individual tissues. This benign vascular neoplasm was found in females at different sites, i.e., in the spleen (1 x mid dose), in the uterus (1 x mid dose, 2 x high dose females), in the abdominal cavity (1 x high dose), in the liver (1x high dose), and in the ovary (1x high dose). No statistical significance was obtained for any of these sites. Even if these findings are summed up, an increased incidence in relation to controls was observed only at the high dose level of 4116 mg/kg bw per day.

As explained in the weight of evidence assessment, an increased incidence of benign tumours observed only at an extremely high dose (exceeding 4000 mg/kg bw per day) well above the MTD is less relevant for classification; even if they are not automatically excluded from any consideration.

It is important to note that no progression to malignant haemangiosarcoma was observed.

Furthermore, differential diagnosis is needed to make sure that it is actually the same tumour type in all affected organs. In contrast to the capillary type, the cavernous type of haemangioma is considered by some authors to be a congenital malformation rather than a neoplasm (IARC, 1992). The available data do not allow to distinguish between different types of haemangioma.

C) Thyroid follicular cell adenomas and carcinomas, males only, in Atkinson et al. (1993). Sprague-Dawley Rat

The incidence of the reported findings (0 /50, 0 /50, 0 /50, 2 /50, 2 / 49 in the control and the dose groups) was very low. Unilateral thyroid tumours in males were in fact observed only at the two upper dose levels. The difference to the control was not statistically significant in the pairwise comparison which is considered an appropriate test method for this parameter, taking into account the large group size. It must be emphasized that there is no evidence of progression since the only carcinoma was found in the group receiving 300 mg/kg bw per day whereas only adenoma were seen at the top dose level of 1000 mg/kg bw per day. In addition, there was no observed pathological continuum of non-neoplastic findings to support a carcinogenic effect of the test substance; this is regarded as a chance finding rather than an effect linked to glyphosate administration. Due to the overwhelming evidence that these tumours were not treatment-related, they were considered not relevant for hazard and risk assessment.

D) Thyroid C-cell Carcinomas, females only, in Lankas (1981). Sprague-Dawley Rat

As noted in the RAR and the CLH report (and its addenda) the study has been considered supplementary (and unreliable to assess carcinogenicity) since dose levels were too low to assess appropriately long-term toxicity and carcinogenic potential of glyphosate even though it was often used in the past for evaluations of glyphosate. In this study, the highest dose levels tested were 31.5 mg/kg bw per day in males and 34 mg/kg bw per day in females. In all the other long-term studies in rats, the dose levels were much higher (*ca.* 60 – > 1500 mg/kg bw per day). Minor effects were occasionally noted from

100 mg/kg bw per day onwards but, in most studies, the low-observed adverse level (LOAEL) was in the range from 350 - > 1200 mg/kg bw per day. Thus, one would not expect effects at such a low dose as the maximum one in the study by Lankas.

There is no effect on the incidence of C-cell hyperplasia, or C-cell adenoma or on overall C-cell adenoma and carcinoma. The results reported in the table below, particularly when placed in context with the other thyroid C-cell findings shown, are indicative of a chance finding. Therefore, they were considered not relevant for hazard and risk assessment.

Table 1- Incidence of thyroid C-cell histopathological findings reported in Lankas, 1981 study

Sex & Dose groups	Females			
	Control (0ppm)	30 ppm	100 ppm	300 ppm
Dose intake (mg/kg bw per day)	0	3.4	11.2	34.0
Interim deaths (killed in extremis or found dead)				
Number of animals	29	26	20	33
C-cell hyperplasia	8	8	4	13
C-cell adenoma	3	1	2	2
C-cell carcinoma	0	0	1	4
Terminal kill				
Number of animals	18	23	30	14
C-cell hyperplasia	11	18	21	5
C-cell adenoma	2	2	4	1
C-cell carcinoma	1	0	1	2
Total				
C-cell hyperplasia	19	26	25	18
C-cell adenoma	5	3	6	3
C-cell carcinoma	1	0	2	6
C-cell adenoma & carcinoma	6	3	8	9

E) Kidney adenoma, males only, in Enomoto (1997). Sprague-Dawley Rat

The incidence of kidney adenomas at the high dose (4/50) compared to the control was discussed in the study report. It was stated to be above the background incidence of this tumour in the strain of rat (0.7% - range 0.0 - 2.9%), but was not statistically significant in the pairwise comparison. The absence of pre-neoplastic renal changes, the fact that the four tumours were observed at a dose of 30000 ppm (ca. 1127 mg/kg bw per day in males) that was considered to exceed the Maximum Tolerated Dose (MTD)) - as evidenced by reduced body weight, body weight gain and food efficiency, and gastro-intestinal effects - and the lack of progression towards malignancy support the conclusion that they were not relevant for hazard and risk assessment.

F) Hepatocellular adenoma, males only, in Brammer (2001). Wistar Rat

Hepatocellular adenomas were discussed in the study report. The incidence of liver cell adenoma was in fact as given by Portier (with the exception that the total number of animals under investigation was 64 but not 53). Both affected low dose and three out of five high dose males died intercurrently. The remaining two cases in the high dose group were found at terminal necropsy. Whilst not statistically significant using the Fisher's

Exact test, the difference was statistically significant using the Peto test for trend. It must be also taken into consideration that survival in males was poor in this study save the highest dose group and, therefore, the study had to be terminated one month earlier than planned.

As there were no recorded preneoplastic foci or adenocarcinomas within the liver and there was no dose response relationship, the small increased incidence of hepatocellular adenomas observed in males treated with the high dose level of glyphosate (1214 mg/kg bw per day) was not considered treatment-related and therefore were considered not relevant for hazard and risk assessment.

G) Skin Keratoacanthoma, males only, in Wood et al. (2009). Wistar Rat

As indicated in the RAR and the Addendum to the CLH report, the incidence of skin keratoacanthoma was slightly but not statistically significantly elevated among high dose male animals compared with controls.

These findings actually were reported in the RAR which was included in the Addendum to the CLH report which was subjected to public consultation by EFSA and ECHA.

If all cutaneous tumours are summed up, the total incidence in the control, low, mid, and high dose groups were 6, 6, 1, 8 which becomes much less indicative of any effect of treatment than suggested by Dr Portier. In any case, no statistical significance was observed by the methods used in the original study and therefore the findings were considered not relevant for hazard and risk assessment.

H) Mammary gland adenomas and adenocarcinomas in Wood et al. (2009). Wistar Rat

Secretory glandular hyperplasia was seen in the majority of female animals examined and was graded from minimal to moderate in severity. The incidence of hyperplasia among terminal kill animals was statistically significantly lower for high dose female rats compared with controls but the numerical difference was small and this was not regarded as an effect of treatment. There was no indication of an effect of treatment on non-neoplastic mammary gland pathology.

Mammary neoplasia are relatively common finding among ageing female rats. In this study, 44 tumours were diagnosed, 28 of which were fibroadenomas, two adenomas and 12 adenocarcinomas.

Table 2 – Incidence of mammary gland tumours reported in Wood et al 2009 study

Sex & Dose groups	Females			
	Control (0ppm)	1500 ppm	5000 ppm	15000-24000 ppm
Dose intake (mg/kg bw per day)	0	105	349	1382
Number of animals	51	51	51	51
Fibroadenoma	7	9	7	5
Adenoma	0	0	0	2
Adenocarcinoma	2	3	1	6
Total	9	12	8	13

Multiple mammary tumours were seen in five rats. The findings were not considered to constitute evidence of treatment related effects upon the incidence of mammary neoplasia, upon multiplicity or malignancy in this investigation for premature death animals, terminal kill animals or for both these groups combined.

VII. Were the findings missed in the CLH process?

As noted above, in the CLH process the Committee for Risk Assessment (RAC) assessed the data included in the CLH report (and in this case, the addenda to the report) for all the hazard classes, including mutagenicity, carcinogenicity, reproductive toxicity and STOT RE (Specific Target Organ Toxicity – Repeated Exposure) as well as the information received during public consultation.

In the CLH report, the DS noted that in the original study reports, "mostly pairwise comparisons had been made", while in the IARC (2015) evaluation, "trend tests were the preferred statistical tool" and therefore the DS recalculated the statistical significance of the observed tumour incidences by taking both approaches. The statistical analyses conducted in the original study reports were also summarised in the RAR which was included as an annex to the CLH Report, which was subjected to public consultation.

The DS considered 7 studies in rats in the CLH report and noted that "no evidence of carcinogenicity was observed in the long-term rat studies after an evaluation of all data". However, the DS also referred to the public debate on glyphosate and the IARC evaluation (IARC, 2015) in which some neoplastic findings in two (older) studies (Stout and Ruecker, 1990; Lankas, 1981) had been subject to discussion. These findings comprised an increase in islet cell tumours of the pancreas in both of these studies, increases in liver tumours and C-cell adenoma of the thyroid in the study by Stout and Ruecker (1990) and an increase in interstitial cell tumours of the testis in the study by Lankas (1981).

Concerning the studies in mice, the DS noted that in the 5 studies there was evidence of increases in three types of tumours, all in males: malignant lymphoma, renal tumours, and haemangiosarcoma. In the CLH report as well as in the CLH opinion, all these tumour types were considered in detail. In any carcinogenicity study of this magnitude, there are likely to be a number of signals for carcinogenicity which need to be considered. Although the data referred to by Dr Portier in Table 1 of his document were not included in the CLH report, as explained in detail under the heading "Biological relevance of the claimed additional tumour sites with significant increases due to glyphosate exposure" (above), this does not mean that they were not considered by the DS in their assessment. Only those tumour types which the dossier submitter considered to have required further assessment were included in the CLH report. These comprised the 4 tumour types in rats and 3 tumour types in mice which are listed above.

RAC does not routinely examine the original study reports in depth for additional findings, unless there is reason to do so, but focuses on those findings reported in the CLH report. However, in the case of glyphosate, the data in the original study reports were consulted for example for independent verification of the data provided in the CLH report and when additional details on the findings are sought. In addition, in this case, a comparison with the evaluation by IARC was also included in the CLH Opinion both with respect to mutagenicity and carcinogenicity.

ECHA notes that all of the findings in Table 1 of the open letter have been available in the public domain in the supplemental data tables published by Greim et al (2015; available online since February 2015). In addition, some of these findings were also raised in the report by IARC, but were not considered further. Normally the most effective way to ensure that these particular findings are considered by RAC would be to point these out at public consultation of the CLH report (held in June-July 2016). Although a large number of comments were received, no concern that any of the tumour incidences in Table 1 of the letter were not specifically referred to in the CLH report was raised by any party at public consultation. This would suggest that at the time of the public consultation, the fact that most of these findings were not specifically referred to in the CLH report and its addendum was not considered by the parties concerned to have been a relevant omission from the documentation. Some of the findings presented in the table (e.g. the lung adenomas and hepatocellular adenomas) were also noted in the report on glyphosate of the Cancer Assessment Review Committee report of the US EPA, which was provided to ECHA as a confidential attachment during public consultation and were therefore available to RAC.

ECHA also notes that the presentation of Dr Portier to the RAC plenary in December 2016 (which was before a draft opinion of the committee was available[3] referred qualitatively (in slide 19) to liver adenomas in male rats in the Brammer (2001) study as well as mammary gland tumours in the Wood (2004 (*sic*)) rat study. The same presentation (slide 18) actually referred to no findings having been seen in the studies of Enomoto (1997) and Atkinson et al (1993), but Table 1 of the open letter now (correctly) lists the kidney adenoma and thyroid follicular cell adenomas and carcinomas from these studies. ECHA also notes that the incidences of skin keratoacanthoma in male rats (Wood et al, 2009) actually were reported in the RAR in the Addendum to the CLH report. IARC also stated that there were no increases in tumour incidences in the glyphosate treated groups in the studies by Atkinson (1993) and Brammer (2001).

The RAC rapporteurs (as is clear from their final presentation to RAC) also did consider findings in the original study reports other than those listed in CLH report. However, the findings listed in Table 1 of the open letter were not considered relevant for the assessment and were not separately reported in the opinion. Some issues not reported in the CLH report have in fact been specifically addressed in the Opinion. For example, in the Archives of Toxicology article (Portier and Clausing, 2017) it is stated that "they claim there is a lack of preneoplastic lesions, yet, for example, there was a significant increase in bilateral chronic interstitial nephritis (p=0.008, exact trend test) in study A which also showed kidney tumours" (study A being the Knezewitch and Hogan (1983) study). The issue was addressed in the CLH Opinion, where it states that "non-neoplastic kidney pathology in the form of chronic interstitial nephritis was reported to be increased, but is not considered to be a precursor for renal tubular cell adenoma". ECHA therefore rejects what effectively amounts to an accusation of lack of due diligence towards RAC and in particular the RAC rapporteurs.

Overall, it is concluded that the evidence from the findings in Table 1 is weaker than from the studies examined in detail in the CLH report. The findings are at low incidences, there is no dose-response relationship and the increased incidence is normally seen only

[3] The presentation can be accessed at https://echa.europa.eu/documents/10162/22863068/glyphosate_ngo_heal_en.pdf/b743ed14-d27d-b17f-7fec-dcb2866f8fe3

at the highest dose. Furthermore, the findings are not consistent between studies or even between sexes in a particular study. Proper analysis would also need to consider historical control data (HCD) for these findings. The principles for use of HCD as they have been expressed in the CLP Guidance have been followed in the considerations of the findings discussed in the CLH report and the opinion.

Conclusions

The EFSA and ECHA processes and the work on glyphosate of the relevant committees have been completed. EFSA and ECHA do not consider that the findings reported in Table 1 of the open letter were overlooked during both processes and therefore there is no need for the conclusions on glyphosate to be revisited.

The open letter states that: "Table 1 may be interpreted as a failure by the agencies involved in these assessments to carefully review and analyse all of the available data before rendering a decision that there is no evidence that glyphosate is carcinogenic to humans". In fact, in both the EFSA and RAC processes the key evidence reported by the Rapporteur Member State (RMS)/Dossier Submitter (DS) was considered in detail. Furthermore, the RMS/DS (Germany) has provided a detailed explanation as to why all these findings were not detailed in the RAR or CLH report. In any case, all the results presented in Table 1 of the open letter have been publicly available since they were published by Greim et al (2015).

The EFSA (EFSA conclusion, 2015a) and ECHA (RAC opinion) (ECHA, 2017) assessments of the carcinogenicity potential of glyphosate are based on an integrated evaluation of the statistical significance and the biological relevance of the study findings, in a weight of evidence approach conducted in accordance with the criteria in the Classification, Labelling and Packaging (CLP) Regulation and the relevant ECHA guidance document (ECHA, 2015).

A number of factors led to the conclusion that the available evidence from animal studies does not support the classification of glyphosate as a carcinogen. These include the following: the lack of a dose-response relationship in the findings, and/or consistency across multiple animal studies; the differences between the sexes not being explained by the toxicokinetic and toxicodynamic properties of glyphosate; the lack of pre-neoplastic lesions in organs where tumours occurred; the incidences of tumours being within the historical control range and, in some cases, apparent trends only being triggered by the results at a single and very high dose potentially at or above the MTD. These same factors apply to the findings presented in Table 1 of the open letter.

EFSA and ECHA seek to work transparently and openly and welcome the opportunity of sharing practices and methods with the scientific community. Therefore, the two institutions are always open to have - in the proper fora - a scientific discussion around the different approaches that are currently taken across relevant bodies in the field of pesticides and chemical risk assessment.

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