European Food Safety Authority

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Subject: Open letter: Review of the Carcinogenicity of Glyphosate by EFSA and BfR

Dear Professor Portier,

First of all, I would like to thank you for sight of the open letter dated 27 November 2015 which you sent to the EU Commissioner for Health and Food Safety Vytenis Andriukaitis regarding EFSA's recent re-assessment of glyphosate. I am writing directly to you and to the co-signatories of your letter, with whom I trust you will share my response.

I would first like to address some of the general points you raise, particularly regarding the regulatory process for the peer review of pesticides in the European Union and the transparency of that process.

Enclosed is also an Annex that gives detailed answers to the scientific questions you raised in your letter. These include, for example, explanations on the evidence from animal carcinogenicity studies, EFSA's interpretation of the tumours reported in the IARC monograph, and mechanistic information.

I would like to make one over-riding point. Glyphosate is currently a keenly debated issue, which makes it especially incumbent on those of us involved in its evaluation to describe clearly the legal frameworks in which we work. In that way, we avoid confusing the policy makers who rely on our advice and the general public who depend on us to maintain the highest standards in protecting public health.

IARC assessment as a possible first step in a full assessment

As the WHO states on its website in the Preamble to the IARC Monographs, IARC evaluations can represent a first step in carcinogen risk assessment to be considered – if available – by national and international authorities such as EFSA when carrying out their own assessments.

I agree that IARC carries out an important role in the screening assessment of the carcinogenic potential of agents. However, we should not compare this first screening assessment with the more comprehensive hazard assessment done by authorities such as EFSA, which are designed to support the regulatory process for pesticides in close cooperation with the Member States in the EU.

Glyphosate is not the first chemical where there has been a difference between the IARC screening and the final comprehensive assessment by regulatory bodies. If you compare IARC categorisations with the EU harmonised classifications, you will find substances with equivalent classifications and others with different classifications. This shows that although the IARC screening has been considered, it has not always been confirmed.

EFSA's assessment of glyphosate is an essential part of the EU regulatory system in relation to pesticides - widely regarded as one of the strictest in the world. This system was most recently updated in 2009 through co-legislation agreed by the European Parliament and the Member State governments acting within the Council of the European Union (EU Regulation 1107/2009).

This is the system EFSA has followed in the assessment of hundreds of active substances since 2003. These assessments have identified potential concerns for human health and the environment and allowed the European Commission and Member States to establish requirements for the safe use of pesticides in Europe. They have also led to the removal from the EU market of more than 40 active substances and their corresponding formulations. It is the same system that was used to assess the risk to bees from neonicotinoids, which were latterly subject to an EU moratorium.

EFSA's assessment was the first published after the release of the IARC monograph in July and other organisations worldwide are conducting similar assessments, including the Joint FAO/WHO Meeting on Pesticide Residue, which is scheduled to publish its own assessment of glyphosate in May 2016 and has asked EFSA for all available scientific information from its own recent assessment to allow it to do this.

Different classification systems

EFSA uses a classification system developed specifically for chemicals by the United Nations (UN-GHS for classification and labelling of chemicals). The EU was one of the first jurisdictions in the world to implement this system, which allows for the identification of the hazards of each chemical and mixtures (e.g. pesticides formulations)

The screening aim of the IARC classification scheme explains why chemicals in pesticides such as glyphosate, or red meat, or frying food at high temperatures, can be included in the same IARC category as being *probably carcinogenic.* But it is important to remember that these classifications are only one part of the body of information in a risk assessment and on which public health decisions may be based.

IARC's broad screening covered both the active substance glyphosate and glyphosate-based pesticide formulations, whereas EFSA focused only on the active substance as it is required to do by EU legislation. In the EU, individual Member States are responsible for evaluating the safety of pesticide formulations used on their territory, including the assessment of the other ingredients (the co-formulants).

EFSA invites IARC to discuss scientific divergences

In an effort to clarify scientific divergences, and in line with EFSA's principles of openness and transparency, EFSA and IARC have agreed to meet early in 2016 to discuss the different evidence and the different methodologies that the two organisations have used. Both of these elements play a role in explaining the divergences between the IARC and EFSA assessments of the carcinogenic potential of glyphosate and we look forward to exchanging views with IARC along these lines.

EFSA carried out open and transparent assessment

Finally, I would like to address the issue of transparency. I strongly disagree with your contention that EFSA has not applied open and objective criteria to its assessment. EFSA implemented the legal requirement to carry out a scientific peer review with Member States, alongside expert and public consultations, in a transparent manner, as it does with all pesticide active substances.

The EFSA Conclusion and all related background documents which run to around 6,000 pages have been published on EFSA's website[1]. These documents include the public consultation report showing how all comments were addressed, both from Member States and from the 29 submissions which came from individuals and organisations, including a number of environmental NGOs.

An essential element of any regulatory scientific assessment is to ensure consistency across evaluations. The views of Member State experts, who may collect input from several public organisations within their Member State before submitting consolidated comments, are discussed in expert groups covering different scientific areas, such as ecotoxicology or mammalian toxicology. Experts from IARC, the JMPR, ECHA and US EPA were invited as observers to the expert consultations to discuss the carcinogenicity of glyphosate. Reports of these meetings or teleconferences are also published in the background documents on EFSA's website.

Additionally, for the sake of transparency, EFSA invites the Member State scientists who take part in the peer review to submit a Declaration of Interest (DoI), although they are not obliged in the legislation to do so. These DoIs are published on EFSA's website. The Member State scientists are affiliated to a broad range of public institutions across the EU.

I wish to make a final but important point regarding transparency. The background documents display detailed information on how EFSA and Member States appraised each study, including industry sponsored studies, and how all those which participated, except Sweden, concluded that glyphosate is unlikely to pose a carcinogenic hazard to humans.

The type and amount of information published by EFSA about these studies is comparable to that found in the US EPA and JMPR reports used by IARC for the assessment of carcinogenicity in animals. It is also comparable to the type and amount of information provided in papers in the open scientific literature. IARC, and any interested parties, are welcome to review the information EFSA has published on its website.

In conclusion, I hope very much that this letter goes some way to clarifying any doubts you may have had about the process which EFSA has followed in its assessment of glyphosate or about our commitment to ensuring that this process is as open and transparent as possible.

Additionally, I also trust the scientific detail you find in the attached Annex will help to further your understanding of the approaches and methods we used in reaching our conclusions.

Yours sincerely,

Bernhard Url

[1] http://www.efsa.europa.eu/en/press/news/151119a

Annex: Specific responses to the open letter sent by Prof. Christopher Portier and others to Vytenis Andriukaitis, EU Commissioner for Health and Food Safety

cc (email only):

Dr. Vytenis Andriukaitis, European Commissioner for Health and Food Safety

Mr. Phil Hogan, European Commissioner for Agriculture and Human Development

Mr. Xavier Prats Monné, Director-General, European Commission DG Health and Food Safety

Dr. Ladislav Miko, Deputy Director-General, European Commission DG Health and Food Safety

Dr. Giovanni La Via, Chair, ENVI Committee of the European Parliament

Mr. Christian Schmidt, German Federal Minister of Food and Agriculture

Dr. Helmut Tschiersky, President, BvL

Professor Dr. Dr. Andreas Hensel, President, BfR

Dr. Christopher Wild, Director, IARC

Mr. Jim Jones, Assistant Administrator, USEPA

ANNEX

Specific responses to the open letter sent by Prof. Christopher Portier and others to Vytenis Andriukaitis, EU Commissioner for Health and Food Safety

This annex addresses specific scientific comments made in the open letter of 27 November 2015 to Commissioner Andriukaitis on a review of the carcinogenicity of glyphosate by EFSA and the BfR, signed by Prof. Christopher Portier and 95 scientists (hereafter referred to as the 'open letter'). The annex responds also to direct quotes from the open letter.

I. General comment

The open letter states: "Addendum 1 (the BfR Addendum) of the RAR[2] discusses the scientific rationale for differing from the IARC WG conclusion."

It is noted that the open letter does not always refer correctly to a) the German Rapporteur Member State (RMS) assessment and proposal; b) the outcome of the experts' discussions; and c) the final conclusion by EFSA (EFSA, 2015a).

The revised Renewal Assessment Report (Germany, 2015) presents the final views of the Rapporteur Member State (Germany), taking into account the comments received from the public consultation and the discussions held with the other EU Member States and EFSA. It includes the Addendum assessing the findings of the IARC monograph.

The Peer Review Report (EFSA, 2015b) captures transparently all comments received on the draft Renewal Assessment Report (Germany, 2013) and follow-up submissions thereof, including Addendum 1, the report from the discussions at the various expert meetings, the comments on the additional information requested by EFSA and the comments submitted on the draft EFSA Conclusion and how these have been addressed.

The two documents mentioned above support EFSA's final view, presented in the EFSA Conclusion (EFSA, 2015a). EFSA has also published a complementary paper summarising its assessment of the genotoxicity and carcinogenicity assessments, which is also available on the EFSA website (EFSA, 2015c).

EFSA notes that the EU assessment on the potential carcinogenicity hazard of glyphosate is based on the UN Global Harmonised System of classification and labelling of chemicals (United Nations, 2003 and posterior revisions every two

years), implemented in the EU through the Classification, Labelling and Packaging (CLP) Regulation[1]. The hazard categories are:

- Category 1: Known or presumed human carcinogens
  - Cat 1A: Known to have carcinogenic potential for humans (human data)
  - Cat 1B: Presumed to have carcinogenic potential for humans (animal data)
- Category 2: Suspected human carcinogens
- No classification: classification criteria not met

IARC uses a different classification scheme, with different groups[2]; however, "there is a strong link between IARC and CLP classification criteria" (ECHA Guidance on the Application of the CLP Criteria 2013, 2015), as the definitions for sufficient and limited evidence as defined by IARC are part of the CLP criteria.

II. Evidence from human epidemiological studies

a) Overall considerations on scientific evidence from epidemiological studies

The open letter states: "The EFSA conclusion that 'glyphosate is unlikely to pose a carcinogenic hazard to humans' is inappropriate when available data support the determination of limited evidence of carcinogenicity in humans."

According to the Guidance on the Application of CLP criteria (ECHA 2013, 2015): "*The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:*

> *— sufficient evidence of carcinogenicity: a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence;*
> *— limited evidence of carcinogenicity: a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence"*

[1] 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.

[2] IARC classification for carcinogenic agents (not just chemicals)

- Group 1. The agent is carcinogenic to humans
- Group 2.
  - Group 2A. The agent is probably carcinogenic to humans
  - Group 2B. The agent is possibly carcinogenic to humans
- Group 3. The agent is not classifiable as to its carcinogenicity to humans
- Group 4. The agent is probably not carcinogenic to humans

With regard to the criteria for the definition of "sufficient" and "limited" evidence, IARC acknowledges the possibility of deviating from the indications based on experts' judgement, as all relevant scientific data may be assigned with a higher or lower category than a strict interpretation of the criteria (as referred to in the IARC preamble 2006).

Regarding epidemiological studies, the IARC and EFSA assessments are based on the same evidence.

In line with the CLP criteria and ECHA guidance (ECHA, 2013; 2015), the two key points considered in the EU assessment are:

- The assessment of chance, bias or confounding effects in the statistical associations.
- The credibility of the causal interpretation. In this sense, it should be noted that the different conclusions regarding genotoxicity and carcinogenicity in animals from IARC and EFSA lead to different views regarding the credibility of the causal interpretation.

In the IARC Non-Hodgkin Lymphoma (NHL) meta-analysis, Schinasi and Leon (2014) reported on the relationship between 14 groups of herbicides and insecticides. In nine (64%) of the groups they found either the group as a whole, or one or more of the individual pesticides within those groups, to be statistically significantly associated with risk for NHL.

Considering the above CLP criteria and, in particular, "the assessment of chance, bias or confounding effects in the statistical associations", the question needs to be addressed as to whether these statistical relationships are supportive of a causal relationship between exposure and the specific active ingredients in these pesticides. As discussed in the epidemiological literature, specific concerns in this regard include:

- characterisation and assessment of the risk factor of interest, i.e. in this case the active ingredient glyphosate itself;
- variation in disease definition;
- characterisation and measurement of exposure to the risk factor;
- confounding by other risk factors – including other pesticides; and
- exploratory statistical analyses, without correction for multiple testing.

In contrast to the IARC evaluation of the epidemiological studies as being of limited evidence, the EU experts have concluded that the human evidence is very limited and, therefore, insufficient for classification under the CLP criteria. There is a minority view (one EU Member State) considering that the information is sufficient for limited evidence in humans according to the CLP Regulation (Category 2); this minority view can be considered in line with the IARC assessment of epidemiological studies as limited evidence. This conclusion and the minority opinion are both reported in the Conclusion (EFSA, 2015a) and the details are presented in the Peer Review Report (EFSA, 2015b).

b) Specific considerations on scientific evidence from epidemiological studies

The open letter states: "To provide a reasonable interpretation of the findings, an evaluation needs to properly weigh studies according to their quality rather than simply count the number of positives and negatives. The meta-analyses cited in the IARC monograph and done by WG are excellent examples of an objective evaluation of the existence positive association; both meta-analyses showed a statistically significant association."

EFSA notes that, in reality, the meta-analyses that are mentioned weigh the studies based on the confidence limits of the Odds Ratio, which is based on its standard error, which in turn depends on the study size. Thus the weighing does consider the number of cases/subjects at least indirectly. Furthermore, among the studies included in this meta-analysis, there was no other stated weight-adjustment for study design or elements of study quality.

The open letter states: "There were only 92 NHL cases included in the AHS [Agricultural Health Study] unadjusted analysis and fewer in the adjusted analyses, compared to 650 in a pooled case-control analysis from the Unites States."

EFSA notes that a comparison is made between the relative strength of the De Roos *et al*. (2003) case-control study versus the De Roos *et al*. (2005) cohort study, by using just one figure from each of these two studies. This is misleading. EFSA suggests that the following numbers from the two studies should be considered instead.

De Roos *et al*. (2003) case control study (analyses of pooled data from three studies)

	Cases	**Controls**	**Total**
Exposed	36	61	97
Non-exposed	614	1,872	2,486
	650	1,933	2,583

De Roos *et al*. (2005) cohort study

	NHL	**No NHL**	**Total**
Exposed	71	40,964	41,035
Non-exposed	21	13,259	13,280
	92	54,223	54,315

Taking this full set into account, it is not clear why the power of the De Roos *et al*. (2005) study would be in doubt, when comparing it to its predecessor case-control study (De Roos *et al*., 2003). In fact, please note that even the IARC meta-analysis (Schinasi and Leon, 2014) gives a (somewhat) higher weight to the De Roos *et al*. (2005) study (21%) than to the De Roos *et al*. (2003) study (15%).

c) Conclusions

As highlighted by Nordström *et al*. (1998), and in contrast to other occupational exposures, farming can involve exposure to many chemicals. This is one reason why the question as to whether human exposure to glyphosate formulations, let alone glyphosate by itself, lead to NHL is difficult to answer through epidemiological studies. One approach to dealing with such an issue is to assess an entire class of compounds, without determining which specific chemical(s) might be responsible. For pesticides the approach is to examine each pesticide active substance independently, as is being done for these and other regulated substances in various jurisdictions worldwide.

III. Evidence from animal carcinogenicity studies

a) General comments

In the open letter it is assumed that the use of historical control data was the only reason in the EFSA assessment for considering that the studies indicating non-statistically significant differences in the pair-wise analysis but significant trends were insufficient for supporting classification under the CLP Regulation.

This is not correct, as the EFSA assessment (EFSA, 2015a) is based on weight of evidence, fully in line with the CLP criteria and the ECHA guidance (ECHA, 2013; 2015), regarding the biological relevance of observed incidences for the assessment of the carcinogenicity potential of glyphosate:

*"No evidence of carcinogenicity was confirmed by the large majority of the experts (with the exception of one minority view) in either rats or mice due to a lack of statistical significance in pair-wise comparison tests, lack of consistency in multiple animal studies and slightly increased incidences only at dose levels at or above the limit dose/MTD, lack of preneoplastic lesions and/or being within historical control range. The statistical significance found in trend analysis (but not in pair-wise comparison) per se was balanced against the former considerations." (*EFSA, 2015a*)*

In addition, the open letter claims that the historical control data were not considered properly, but as explained below this is not correct either.

The scientific principles used by EFSA in the evaluation of animal carcinogenicity studies, in line with the regulatory context of our evaluation, are summarised below; the details are included in the background documents supporting the EFSA conclusion (Germany 2015; EFSA 2015b).

EFSA and the experts of the member countries, including the RMS, had access to and evaluated the original studies. Comprehensive description and evaluation of the new long-term studies by the RMS in its Renewal Assessment Report was not taken into consideration by IARC even though this information was publicly available from April 2014. IARC used a new interpretation and statistical evaluation (by trend

tests) of tumour incidences that are from older studies and have been discussed by the JMPR and the US-EPA.

b) Statistical assessment

EFSA is of the opinion that the planning of a study before the initiation of the experimentation as established in the respective protocol – which includes the planned statistical analysis – is a key element in assessing the quality of a study; therefore deviations from the statistical analysis used by the study authors should be limited and properly justified. This is in line with OECD recommendations: "*The central concept of this document is that the experimental design represents the strategy for answering the question of interest and that 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).

The studies under consideration were designed for pair-wise comparisons, and this was the statistical method considered in the EU assessment. IARC based its assessment on previous evaluations of studies as carried out by the US-EPA and the FAO/WHO JMPR, which included a Cochran analysis. In 2014 the US-EPA decided to disregard the result of the analysis because the biological relevance of the findings could not be proven.

As indicated in the open letter, in some studies the same data are statistically significant or not, depending on the selected statistical method. It should also be noted that there are no valid studies with statistically significant effects confirmed by both statistical approaches. Based on these results, the biological relevance of the results (see below) was balanced against the inconsistency observed in the statistical results.

c) Assessment of biological relevance

As indicated before, the EFSA conclusion regarding carcinogenicity in animals considered the different statistical assessments (significant trends but non-significant effects in the pair-wise comparison with the concurrent control group) and conducted a scientific assessment of the biological relevance of the observed tumour incidences.

As mentioned in the EFSA Conclusion (EFSA, 2015a), the EU assessment is based on weight of evidence, in line with the CLP criteria and ECHA guidance (ECHA, 2013; 2015), focusing on four main arguments:

- Lack of consistency in multiple animal studies. The CLP criteria (Section 1.1.1.) require that: "*The quality and consistency of the data shall be given appropriate weight*" and that: "*Both positive and negative results shall be assembled together in a single weight of evidence determination*." Based on the evidence available for the EU assessment, which included five additional valid long-term toxicity-carcinogenicity studies known of but not assessed by

IARC, inconsistent effects were observed in the tumour incidences both within (lack of dose response) and between studies (inconsistency between results observed at the same dose in different equivalent studies). Some trends were observed only in one sex. On this point the ECHA guidance (ECHA, 2013; 2015) considers that: "*If tumours are seen only in one sex of an animal species, the mode of action should be carefully evaluated to see if the response is consistent with the postulated mode of action.*" However, no assessment of a sex related mechanism is provided in the IARC assessment.

- Incidences only at dose levels at or above the limit dose/maximum tolerated dose (MTD). The IARC monograph reports for several studies significant body weight reductions at the highest doses, which are in fact the doses triggering the statistical significance of the trend analysis. No further assessment of the possibility of a confounding effect of excessive toxicity at these test doses is reported in the monograph. Excessive toxicity – for instance, toxicity at doses exceeding the MTD – can affect the carcinogenic responses in bioassays. Such toxicity can cause effects such as cell death (necrosis) with associated regenerative hyperplasia, which in turn can lead to tumour development as a secondary consequence, unrelated to the intrinsic potential of the substance itself to cause tumours at lower and less toxic doses (ECHA, 2013; 2015).

  In line with the CLP and UN-GHS criteria, ECHA has provided clear guidance on this aspect of the assessment: "*If a test compound is only found to be carcinogenic at the highest dose(s) used in a lifetime bioassay, and the characteristics associated with doses exceeding the MTD as outlined above are present, this could be an indication of a confounding effect of excessive toxicity. This may support a classification of the test compound in Category 2 or no classification.*" In addition, it is clear that the trend analysis should not be used for studies where high tumour incidences are observed only at doses exceeding the MTD; and the statistical assessment should focus on the pair-wise comparison with the concurrent controls, which did not show statistically significant differences for any of the valid studies on glyphosate. In addition to the significant body weight loss reported in the IARC monograph, other signs of excessive toxicity reported at high doses included hepatic centrilobular hypertrophy, bladder epithelial hyperplasia, ulcerations, etc.

- Lack of preneoplastic lesions in organs where tumours occurred, as indicated in the histological evaluations of several studies, which failed to show a histopathological continuum possibly indicating an evolution to frank neoplasms.

- Incidences being within historical control range. EFSA notes that, of the four key elements used by EFSA, this is the only one mentioned in the open letter. It is also noted that the open letter incorrectly reports how historical control data are used in the EFSA assessment. First, the open letter includes the following reference to the IARC preamble: "*It is generally not appropriate to discount a tumour response that is significantly increased*

compared with concurrent controls by arguing that it falls within the range of historical controls." However, it should be noted that all incidences reported from reliable studies were not statistically significant when compared to the concurrent controls in the pair-wise comparisons. Second, it seems that the letter signatories have misinterpreted the efforts made by the German RMS to get supportive information for those studies with no valid historical controls. The Peer Review Report (EFSA, 2015b) confirms that EFSA conducted a specific check regarding the use of historical control data, requested additional information during the clock-stop procedure and only considered valid the historical control data from the performing laboratory in line with the international recommendations (e.g. ECHA, 2013; 2015).

d) Additional considerations of the tumours reported in the IARC monograph

For the assessment of tumours in mice, IARC and EFSA considered two and five studies, respectively.

Renal tumours reported in mice
The open letter mentions *inter alia a* significant positive trend for renal tumours in CD-1 mice.

In a 1983 study, a marginally increased incidence of renal tumours was reported in male Charles River CD-1 mice, not statistically significant in a pair-wise comparison after adjusting for higher survival in the high dose group; no renal tumour was observed in females. The renal tumours could not be linked to glyphosate administration due to several considerations: the trend analysis reported by IARC does not take into account the higher survival rate at the high dose and the fact that no preneoplastic lesions were observed and therefore a morphological continuum could not be established. Additionally, concomitant general toxicity was observed at the high dose level (4,841 mg/kg bw per day) – such as reduced body weight, histopathological changes in the bladder and liver – that could be responsible for the occurrence of tumours and not a direct effect of the test substance. It is therefore concluded that the reported incidence of renal tumours is most likely a chance finding, not related to glyphosate administration.

Three more recent studies (1993, 1997 and 2009) performed on CD-1 mice did not show dose-related increased incidences of renal tumours. In the 1993 study, renal tubular adenoma and carcinoma cases were observed in the control and low-dose groups only. In the 1997 study, no renal carcinomas were observed, and two adenomas occurred only at a very high dose (exceeding 4,000 mg/kg bw per day). No renal tumour or other renal lesions were observed in the 2009 study in any group.

A fifth study performed on Swiss albino mice (2001) was concluded to be unreliable since the health of the animals in the study was clearly compromised due to viral infections in all groups including concurrent control.

In conclusion, the evidence from four valid studies using CD-1 mice does not indicate that the observed incidences of renal tumours are test substance-related. This was also the conclusion in the EPA publication (US-EPA, 1986), which was analysed by IARC.

Haemangiosarcomas reported in mice
With regards to haemangiosarcomas, for which statistically significant trends by Cochran-Armitage test but not by pair-wise comparisons could be observed in two out of four valid studies at the highest dose tested, both incidences observed were within the performing laboratory's historical control data and therefore concluded not to be linked to glyphosate administration.

Malignant lymphomas reported in mice
Increased trends of malignant lymphomas, one of the most common spontaneously occurring neoplasms in mice, were observed in male mice in three (1997, 2001 and 2009) of the five studies. Females presented in general higher incidences than males but statistical significance was not achieved and dose-response was not evident. In one study (1997), there was a positive trend test but the incidences remained clearly within the performing laboratory historical control data. A second study using lower dose levels, and for which no reliable laboratory historical control data were available, also showed a positive trend (2009). However, for both studies pairwise comparisons did not reveal a statistically significant increase. The third study (2001) was concluded to be unreliable for the reasons expressed above (occurrence of viral infection). Two additional studies (1983 and 1993) neither showed a positive trend nor revealed a significant increase in tumour incidences in pair-wise comparison. Using a weight of evidence approach by also considering the known high background incidence of this tumour type in mice, it was concluded that these tumours are spontaneous in origin and not test substance-related.

For the assessment of tumours in rats, IARC and EFSA considered six and nine studies, respectively.

Pancreatic islet cells in rats
Regarding rat studies, from nine studies submitted, seven did not present any increased incidence of neoplastic lesions that could be related to glyphosate administration. Nevertheless, IARC reported significant positive trends in two studies. In one study from 1981, a statistically significant (according to a pair-wise comparison) increased incidence of islet cells adenomas was limited to the low dose level; in the absence of a dose-response relationship, the finding cannot be linked to glyphosate administration. Similarly, in a 1990 study using much higher dose levels, a significant increase over the control incidence was observed only for the low dose group. There was no progression to carcinoma. Thus, no dose-response relationship could be established with regards to the incidence of pancreatic islet cells adenomas and no confirmation was obtained in any of the other long-term studies in rats.

Hepatocellular and thyroid C-cell adenomas in rats
Regarding positive trends reported by IARC for hepatocellular adenomas in males and for C-cell adenomas in females, the lack of statistical significance in a pair-wise

comparison, the comparable incidence observed in the opposite sex and the lack of consistency of the finding in the many other studies (eight studies) led to the conclusion that the neoplastic findings are unlikely to be test substance-related.

e) Conclusion

The arguments expressed in the open letter reflect a misunderstanding of the evidence used for the EFSA evaluation. The biological relevance of each study and the overall evidence on animal carcinogenicity was properly assessed during the EFSA evaluation. In contrast, the IARC assessment focused on finding statistically significant "trends" in specific studies, but presented no information on how it considered the biological relevance and in particular the inconsistencies and effects only observed at doses at or exceeding the MTD, even when it is clear that the trend was significant only due to the incidences observed at the highest dose at which significant weight reduction and other indications of excessive toxicity had been observed. In fact the statistical trend, without assessing the biological relevance of the results, seems to be the only justification in the IARC monograph for deviating from the previous evaluation of the same animal studies by the WHO/FAO JMPR expert group, which concluded that glyphosate does not have carcinogenic potential (JMPR, 2004).

IV. Mechanistic information

a) Genotoxicity

No scientific elements are presented in the open letter and the allegations focus on procedural issues. The first allegation related to genotoxicity is that BfR's use of unpublished evidence makes it impossible for any scientist not associated with the BfR to review its conclusions. This is not the case: EFSA and the BfR's appraisal of the studies you refer to is available in the EFSA Conclusion and supporting documents (published on our website) with a level of detail at least comparable to the US-EPA and WHO/JMPR reports relied on in the IARC monograph. The studies are made publicly available for scientific scrutiny and were available at the time you wrote your letter.

Regarding the weight given to the different studies, as the EFSA assessment focuses on the active substance glyphosate and the assessment of genotoxicity in humans, *in vivo* mammalian studies conducted with the active substance were considered more relevant, particularly when the technical specifications and impurity profile of the tested substance were reported. According to the IARC monograph, the studies with exposed humans were conducted with formulated products, not with the active substance, and there is no indication in the monograph of any attempt to establish the possible role of the co-formulants, even when other studies (*in vitro* or in animals) report negative effects for the active substance and positive effects for the formulated products.

Sixteen *in vivo* studies in somatic cells and two *in vivo* studies on germ cells were reported on rodents treated orally with dose levels of up to 5,000 mg/kg bw or via

intraperitoneal injections. All studies conducted according to internationally validated guidelines and some non-GLP published studies gave negative results, while two non-GLP studies were positive in mice treated intraperitoneally with dose levels in the range of the intraperitoneal LD_{50} for mice, one study presenting major flaws. Conflicting results were obtained regarding DNA adduct formation; induction of DNA strand breaks was observed in mice treated intraperitoneally with doses close to or in excess of the LD_{50}.This induction may be caused by secondary effects of cytotoxicity. No genotoxic effects on germ cells have been detected in rats or mice treated orally at dose levels up to 2,000 mg/kg bw.

b) Oxidative stress and use of scientific literature

The available studies and reports on the oxidative stress potential of glyphosate, and its causal link, if any, to the occurrence of tumours, are extremely limited. The possibility that glyphosate could cause oxidative stress was indeed discussed during the EFSA peer review: oxidative stress was recorded only in one study in rats administered with pure glyphosate, in combination with cytoxicity and degenerative effects in the targeted organ. Thus, in consideration of the extremely limited database and because of the lack of evidence for carcinogenic potential of glyphosate, no further consideration regarding the mode of action was necessary.

EFSA agrees with the statement in the open letter regarding the relevance of scientific literature, e.g. for understanding the mechanism of action. The EU regulatory system requires an assessment of scientific peer-review data published in the previous 10 years to be presented in the dossier, and EFSA has developed a guidance document for ensuring a proper implementation of this requirement (EFSA, 2011); in addition, the regulation allows the submission of additional data to the RMS; additional data can also be submitted during the public consultation. Scientific peer-reviewed publications support several recommendations in the EFSA conclusion, such as the proposal for considering specifically the genotoxicity of the formulated products during the MS evaluations.

c) Conclusion

Considering a weight of evidence approach, taking into account the quality and reliability of all available data, it is concluded that glyphosate is unlikely to be genotoxic *in vivo* and does not require hazard classification regarding mutagenicity according to the CLP Regulation. It is noted that unpublished studies that were the core basis of the EFSA evaluation were not available to the IARC experts as reported in the IARC monograph 112 on glyphosate.

V. Active substance versus formulations

In the summary of the open letter a distinction is made between the assessment of the active substance and the assessment of the formulations. "*The most parsimonious scientific explanation of the cancers seen in humans and laboratory*

animals supported by the mechanistic data is that glyphosate is a probable human carcinogen. On the basis of this conclusion and in the absence of contrary evidence, it is reasonable to conclude that glyphosate formulations should also be considered probable human carcinogens." IARC did not try to differentiate whether the effects were linked to the active substance, other ingredients (co-formulants), or combined effects of several ingredients, even when the evidence suggested negative effects for glyphosate and positive effects for a formulated product. The IARC monograph states that formulated products contain other ingredients, and mentions specifically polyethoxylated tallowamine, a co-formulant considered of potential concern and recently assessed by EFSA (EFSA, 2015d).

VI. Summary

EFSA considers that the arguments brought forward in the open letter do not have an impact on the EFSA conclusion on glyphosate. The arguments expressed in the open letter reflect a misunderstanding of the evidence used for the EFSA evaluation.

As reported in the EFSA Conclusion (EFSA, 2015a), there is very limited evidence for an association between glyphosate-based formulations and non-Hodgkin lymphoma, and overall evidence is inconclusive for a causal or otherwise convincing associative relationship between glyphosate and cancer in human studies. There is no evidence of carcinogenicity in either rats or mice due to a lack of statistical significance in pair-wise comparison tests, lack of consistency in multiple animal studies and slightly increased incidences only at dose levels at or above the limit dose/MTD, lack of pre-neoplastic lesions and/or being within historical control range. The statistical significance found in trend analysis (but not in pair-wise comparison) per se was balanced against the former considerations. Considering a weight of evidence approach, taking into account the quality and reliability of all available data, it is concluded that glyphosate is unlikely to be genotoxic in vivo and does not require hazard classification regarding mutagenicity according to the CLP Regulation.

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