May 28, 2017

Jean Claude Juncker
President, European Commission
European Commission
Rue de la Loi, 200
1049 Brussels
Belgium

By email only
(Cc to Jyrki Katainen, EC Vice President for Jobs, Growth, Investment and Competitiveness; Vytenis Andriukaitis, EU Commisioner for Food Safety and Health; Michael Flüh, DG SANTE; Bernhard Url, Executive Director, EFSA; Giovanni La Via, Chair, ENVI Committee; EFSA Panel on Plant Protection Products and their Residues; Andreas Hensel, President, BFR; Chris Wild, Director, IARC; Wendy Cleland-Hamnett, Acting Associate Director, US EPA Office of Chemical Safety and Pollution Prevention, Jose Tarazona, Pesticides Unit, EFSA)

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

Dear President Juncker,

Executive Summary: The European Food Safety Agency (EFSA) and the European Chemical Agency (EChA) have completed their assessments of the carcinogenic potential of glyphosate and concluded that the evidence does not support a classification for glyphosate. The raw data for the animal cancer studies for glyphosate have been released, and a reanalysis of these data show eight instances where significant increases in tumor response following glyphosate exposure were not included in the assessment by either EFSA or EChA. This suggests that the evaluations applied to the glyphosate data are scientifically flawed, and any decisions derived from these evaluations will fail to protect public health. I ask that the evaluations by both EFSA and EChA be repeated for all toxicological endpoints and the data underlying these evaluations be publicly released.

On November 27, 2015, my colleagues and I wrote to Commissioner Andriukaitis[1] regarding the European Food Safety Agency (EFSA) and German Federal Institute for Risk Assessment (BfR) reviews of glyphosate. At the time, we had serious concerns regarding the scientific evaluation in the BfR Addendum[2] and believed it was misleading with regard to the potential for glyphosate to cause cancer in humans. On 13 January, 2016, we received a response[3] from Dr. Bernhard Url, Director of EFSA. Since that time, both EFSA[4] and the European Chemical Agency (EChA) have completed their carcinogenic hazard evaluations for glyphosate and have concluded that the evidence does not support a classification for glyphosate.

I continue to have serious concerns about the scientific quality of the evaluations by both EFSA and EChA on a number of issues which were not adequately

addressed by Dr. Url in his response to the previous letter from me and my colleagues. These concerns will be reiterated at the end of this letter. There is, however, one topic I believe needs your immediate attention before a final decision is made regarding glyphosate re-authorisation. **Both EFSA and EChA** (in their proposal of the dossier submitter[5]) **failed to identify all statistically significant cancer findings in the chronic rodent carcinogenicity studies with glyphosate.**

On March 15, 2016, members of the European Parliament requested public access to the complete records of animal laboratory data from chronic carcinogenicity studies of glyphosate; these data were previously deemed to be confidential business information. The presence of this new information along with what was already available in the Supplemental Material from Greim et al. (2015)[6] allowed me to evaluate the data for any additional significant increases in tumor incidence that have not been reported in the evaluations by both EFSA and EChA. In these additional analyses, I found eight (8) significant increases in tumor incidence that do not appear in any of the publications or government evaluations presented by both EFSA and EChA. Table 1 summarizes those findings. Some of these tumors were also present in multiple other studies increasing the consistency of the findings across studies.

Transparency is an important aspect of the scientific process and I applaud EFSA for allowing limited access to the raw data from the animal studies of glyphosate. However, scientific rigor is required and the tumors identified in Table 1 may be interpreted as a failure by the agencies involved in these assessments to carefully review and analyze all of the available data before rendering a decision that there is no evidence that glyphosate is carcinogenic to humans. Some of these positive tumor findings may have been missed because two-sided tests[a] might have been used, but not all. In my opinion, one-sided tests[b] are more appropriate for public health evaluations.

As noted before, Monograph 112[7] from the International Agency for Research on Cancer (IARC) Monographs Programme evaluated the publicly accessible data for glyphosate and concluded that glyphosate is classifiable as probably carcinogenic to humans. IARC Working Groups routinely re-analyze 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. This is especially true for chronic studies of carcinogenicity in rodents. The IARC Working Group for Monograph 112 identified positive significant trends for tumors in two mouse carcinogenicity studies using the Cochran-Armitage linear trend test in proportions. Similarly, they identified a positive finding in one study in Sprague-Dawley rats. In their response to the IARC Monograph, the BfR re-evaluated some of the mouse data using this same statistical test.

---

[a] A two-sided test addresses the question of whether glyphosate increased or decreased the tumor incidence. In an evaluation of this type, you are only interested in increases.
[b] A one-sided test addresses the question of whether glyphosate increased the tumor incidence

Table 1: Eight additional tumor sites with significant ($p<0.05$) increases due to glyphosate exposure in the carcinogenicity studies cited by EFSA and EChA

Study **Species**	**Tumor type** **Sex; Incidences**	**p-value[c]** **(one-sided)**
Wood et al. (2009) CD-1 Mouse	Lung adenocarcinomas Males; 5/51, 5/51, 7/51, 11/51	0.028
Sugimoto et al. (1997) CD-1 Mouse	Hemangioma (any tissue) Female: 0/50, 0/50, 2/50, 5/50*	0.002
Atkinson et al. (1993) Sprague-Dawley Rat	Thyroid follicular cell adenomas and carcinomas Males; 0/50, 0/50, 0/50, 2/50, 2/49	0.034
Lankas (1981) Sprague-Dawley Rat	Thyroid c-cell Carcinomas Females; 1/47, 0/49, 2/50, 6/47	0.003
Enomoto (1997) Sprague-Dawley Rat	Kidney adenoma Male; 0/50, 0/50, 0/50, 4/50	0.004
Brammer (2001) Wistar Rat	Hepatocellular Adenoma Males; 0/53, 2/53, 0/53, 5/52*	0.008
Wood et al. (2009) Wistar Rat	Skin Keratocanthoma Males; 2/51, 3/51, 0/51, 6/51	0.030
	Mammary gland adenomas and adenocarcinomas Females; 2/51, 3/51, 1/51, 8/51*	0.007

* These groups have a significantly increased ($p<0.05$) incidence of tumors relative to the controls by the Fisher Exact Test in addition to a significantly positive trend test finding

Table 2 shows all of the statistically positive findings cited by EChA and an indication of whether these findings were known before the IARC Monograph. It appears, from my study of these documents, that BfR cited only four of these tumors prior to the IARC Monograph and identified an additional 9 positive findings after the IARC Monograph. I could find no comments in the EFSA Peer Review document[8] prior to the release of the IARC Monograph suggesting concern for these 9 positive tumor findings. Nor can I find any mention of the 8 positive tumor findings in Table 1. Thus, of the 21 positive tumor findings in Table 1 and Table 2, BfR, in their original submission, had only identified 20%.

In a recent interview on Euractiv.com[d], the EFSA spokesperson stated that "*EFSA and EU member states rely primarily on the original studies and the underlying raw data which they check themselves.*" My review of the recently available data suggests this is not the case and that, again, several important positive findings have been missed. After the IARC Monograph review and after recognizing that there were other studies with positive results in these data that were not reported by the Glyphosate Task Force, it is difficult to understand why BfR, EFSA and EChA failed to re-evaluate all of the available data using an appropriate trend test.

---

[c] The p-value presented here are from the exact Cochran-Armitage linear trend test in proportions.

[d] http://www.euractiv.com/section/agriculture-food/news/green-ngos-blame-monsanto-for-buying-science-to-save-glyphosate/

Table 2: Tumor sites discussed in the draft CLH Report[5] which were identified either before or after the IARC Monograph[9]

Study Species, Duration	Tumor type, Sex	p-value[1] (HC)	IARC[2]	BfR[3]	Reason Not +[4]
Stout and Ruecker, (1990) Sprague-Dawley Rat 24 months	Pancreas islet-cell adenomas, Males[5]	0.147	yes	yes	a,b,c[6]
	Hepatocellular adenomas, Males	0.015	yes	no	b,c[6]
	Thyroid c-cell adenoma, Females	0.049	yes	no	b,c[6]
Lankas (1981) Sprague-Dawley Rat 26 months	Pancreas islet-cell tumors, Males[5]	0.315	yes	yes	a,b,c[6]
	Testes interstitial cell tumors, Males	0.009	yes	yes	a,c[6]
Wood et al. (2009) CD-1 Mice, 18 Months	Malignant Lymphoma, Male	0.007	no	no	c[7],d,e
Kumar (2001) Swiss Albino 18 Months	Malignant Lymphoma, Males[5]	0.096	no	no	c[7],d,e
	Malignant Lymphoma, Females	0.070	no	no	
Sugimoto (1997) CD-1 Mouse 18 Months	Malignant lymphoma, Males	0.016	no	no	c[7],d,e,f
	Renal adenoma, Males	0.062 (0.005)	no	no	c[7],f,g,h
	Hemangiosarcoma, Males	0.062 (0.004)[10]	no	no	c[7],f
Knezevich and Hogan (1983), CD-1 Mice 24 Months	Renal tumors, Males	0.065 (0.011)	yes	yes	c[7],d,e,f
Atkinson et al. (1993) CD-1 Mice, 24 Months	Hemangiosarcoma, Males	0.004 (0.001)	yes	no	c[7],f

[1] Exact Cochran-Armitage linear trend test in proportions, one-sided; (HC) is the probability of seeing the observed trend or greater assuming the mean of the historical control data for CD-1 mice from Giknis and Clifford (2000)[10] is correct (only applied to rare tumors)
[2] Identified in IARC Monograph
[3] Identified in BfR draft RAR prior to the IARC Monograph
[4] reasons cited by EChA for exclusion of the positive statistical finding: a-non clear dose-response; b-no progression to carcinoma; c-inconsistent across studies; d-trend test and pair-wise tests not consistent; e-historical controls with high incidence; f-in the range of the historical control data; g-tumors only at doses above 1000 mg/kg/day; h-no plausible mechanism
[5] the incidence counts for these studies in the draft EChA evaluation do not match the original pathology tables; p-values presented here relate to the original pathology counts
[6] comparing Sprague-Dawley rats with Wistar rats and studies at 26 months with studies at 24 months
[7] Comparing mice in 18-month studies with mice in 24-month studies
[10] No tumors were seen in 26 historical control groups so historical control response was set at the response that provides a 5% chance that we see 26 controls with no response – 0.0026

I am concerned that other areas of the EFSA review (e.g. reproductive toxicity and endocrine disruption) may have also received inadequate evaluations. Since the industry-supported scientific evidence is not available to external scientists, I am unable to evaluate these data and determine if there are positive findings

that escaped detection. I encourage you to release these data for external analysis and review as well.

In summary, after numerous scientists from EFSA, from EChA, from BfR and from the Glyphosate Task Force have reviewed and evaluated this massive amount of data, there are still serious omissions in the way in which these data have been assessed and reported. I respectfully ask that the agencies involved in the evaluation of glyphosate conduct their own analyses of the tumor sites presented in Table 1 and amend the record of their decision as appropriate rather than simply ignoring these observations.

Even while I applaud the European Commission for a limited release of some of the information submitted by the registrants for glyphosate, it is still impossible for outside scientists to be fully confident in any reassessment of these studies. This is because important parts of the safety record are still sealed. While the raw data tables were made available upon a request by the members of the European Parliament, the materials and methods, analysis and discussion sections from these submissions are not available. These omissions make it impossible for outside scientists to judge the quality of the studies, the rigor of the methods used to analyze the data, or to determine if there are legitimate reasons in these discussions why the tumors identified in Table 1 were excluded.

Finally, in our previous letter, several major concerns were raised that have not been adequately addressed in the final assessments and should again be addressed appropriately. These are:

- the classification of the human evidence as "very limited" is not a valid characterization under the CLP guidelines and fails to properly address the strength of the available evidence;
- both EFSA and EChA dismissed positive findings because they fell inside of the range of the historical controls (this is an improper use of historical control evidence);
- both EFSA and EChA compared findings across different strains and different study durations to conclude that studies were inconsistent (this is not scientifically justifiable);
- both EFSA and EChA characterize the evidence for genotoxicity as negative, yet a careful review of the evidence released by EFSA and the open scientific literature suggest there are many guideline and non-guideline studies demonstrating genotoxicity.

I firmly support the principle that scientific evidence should be used to help guide societal decisions about health risks to humans. However, the individual scientific studies must be carefully summarized and reviewed if their findings are to serve as a true guidance. The glyphosate hazard classification appears to have been a good example of how lack of transparency regarding the scientific evidence that underlies important public health decisions can erode public trust and raise concerns. I respectfully request that you instruct the appropriate agencies to review the evidence submitted herein and ask that you refrain from making any decisions on glyphosate until these positive findings are included.

I also request that, in the interest of scientific transparency, EFSA should release all of the raw data in all areas of toxicology for all pesticides so scientists interested in repeating the evaluations by EFSA and EChA can do so.

Thank you for your time and I look forward to your response.

Sincerely,

Christopher J. Portier, Ph.D.
Thun, Switzerland
Former Director US National Center for Environmental Health
Former Director US Agency for Toxic Substances and Disease Registry
Former Associate Director, US National Institute of Environmental Health Sciences
Former Associate Director US National Toxicology Program
Fellow, American Statistical Association
Fellow, International Statistics Institute

Disclosures: The opinions expressed here and the analyses done to support those opinions are mine alone and were conducted without any compensation. In my capacity as a private consultant, I am an expert witness for a US law firm involved in glyphosate litigation. I also work part-time as a Senior Contributing Scientist for the Environmental Defense Fund (EDF) on issues not related to glyphosate or other pesticides.

References

1. Portier, C.J., et al. *Open Letter: Review of the Carcinogenicity of Glyphosate by EFSA and BfR*. 2015 [cited 2016 1/18/2016]; Available from: http://www.efsa.europa.eu/sites/default/files/Prof_Portier_letter.pdf.
2. (BfR)., G.F.I.f.R.A., *Final Addendum to the Renewal Assessment Report: Glyphosate*. October, 20154322.
3. Url, B. *Response to Open Letter: Review of the Carcinogenicity of Glyphosate by EFSA and BfR*. 2016 1/13/2016; Available from: http://www.efsa.europa.eu/sites/default/files/EFSA_response_Prof_Portier.pdf.
4. European Food Safety Authority, *Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate*. EFSA Journal, 2015. **13**(11): p. 4302.
5. German Federal Institute for Occupational Safety and Health, *Proposal for Harmonized Classification and Labeling: Glyphosate*, F.O.f. Chemicals, Editor. 2016: Dortmund, Germany.
6. Greim, H., et al., *Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies.* Crit Rev Toxicol, 2015. **45**(3): p. 185-208.
7. Guyton, K.Z., et al., *Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate.* Lancet Oncol, 2015. **16**(5): p. 490-1.
8. European Food Safety Authority. *Peer Review Report on Glyphosate*. October, 2015; Available from: http://registerofquestions.efsa.europa.eu/roqFrontend/outputLoader?output=ON-4302.
9. IARC Working Group, *Glyphosate*, In: *Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos*. 2015, IARC Monogr Prog. V. 112. p. 1-92.
10. Giknis, M. and C. Clifford, *Spontaneous Neoplastic Lesions in the CrI:CD-1(ICR)BR Mouse*. 2000, Charles River Laboratories.

THEY FOUND 80 MORE CASES OF TUMORS CAUSED BY GLYPHOSATE IN A STUDY.