20 October 2015

Mr. Vytenis Andriukaitis
Commissioner Health & Food Safety
European Commission
Rue de la Loi / Wetstraat 200
1049 Brussels
Belgium

By email only

(Cc to Mr. Ladislav Miko, Action Director-General, DG Health & Food Safety, and Bernhard Url, Executive Director, EFSA)

Open letter:
EFSA peer review of the renewal assessment report (RAR) on glyphosate by the BfR

Dear Commissioner Andriukaitis,

We are writing to you as we are concerned about the ongoing peer review of the renewal assessment of the active substance glyphosate in the context of Regulation (EC) No 1107/2009 concerning the placing of plant protection products on the market in the European Union. In March 2015, the WHO Agency for Research on Cancer (IARC) announced its classification of glyphosate as "probably carcinogenic to humans". The corresponding monograph was published in July 2015.[1] The Commission requested the European Food Safety Agency (EFSA) in April 2015 to consider the findings by IARC as regards the potential of carcinogenicity of glyphosate or glyphosate containing products in the ongoing peer review. We welcome this request.

However, since March there has been much debate on the question of how and why the German competent authority, the Federal Institute for Risk Assessment (BfR), acting for the rapporteur Member State Germany, came to a very different conclusion than IARC. BfR continues to consider that glyphosate would not be carcinogenic, most recently at a hearing in the German Parliament on 28th of September.

Several experts had a closer look at BfR's risk assessment report – see e.g. the written statements for the hearing[2] and a recently published report[3]. One of these experts was a member of the so-called "JMPR Expert Taskforce on Glyphosate". This task force was established to recommend to JMPR (Joint FAO/WHO Meeting on Pesticide Residues) how to proceed, taking into account the strong divergence between JMPR's evaluation of glyphosate, which is comparable to BfR's conclusions, and

[1] http://monographs.iarc.fr/ENG/Monographs/vol112/
[2] http://www.bundestag.de/bundestag/ausschuesse18/a10/anhoerungen/anhoerung_glyphosat_28_09_2015/386986
[3] http://blog.campact.de/2015/09/studien-zur-krebsgefahr-von-glyphosat-verschwiegen/

the recently published IARC assessment. In September 2015, the task force came to the conclusion that a full re-evaluation of glyphosate on the FAO/WHO level would be necessary, noting that many studies, mainly from the published peer-reviewed scientific literature, were not considered in the former JMPR reports (2004 and 2011) on glyphosate[4]. Leading author of both JMPR reports was a staff member of BfR[5].

The BfR risk assessment report constitutes the basis for the EU risk assessment of glyphosate. However, a considerable list of open questions regarding the quality and reliability of BfR's risk assessment arose from the work of these experts (see appendix).

We are convinced that it is indispensable to address all open questions thoroughly before any further decision is taken concerning the re-approval of glyphosate. Therefore, we ask you to ensure that EFSA fully addresses these issues listed in the appendix in the context of its current peer review – and that clear answers to these questions are made publicly available.

If additional time was needed for that, this should not be a problem, as the current authorization of glyphosate was recently extended to the end of June 2016. As such, there is enough time to fully consider all open questions without any need for further delays regarding the re-approval decision.

In this context, we consider that two aspects are of particular concern: genotoxicity and human evidence. IARC found "strong evidence" for genotoxic effects of glyphosate – while BfR found no evidence at all for such effects "under normal exposure scenarios". Given that genotoxic substances are normally considered to be non-threshold substances, it is of crucial importance to properly assess the potential genotoxicity of glyphosate.

Secondly, BfR recently stated that it also found "limited evidence" for cancer-causing effects in humans – only to dismiss these findings arguing that epidemiological studies concern the formulation instead of the active substances alone and would therefore not be relevant. However, we would consider this to be incompatible both with the letter of the law as well as the mandate you have given to EFSA. According to Article 4(5) of the Regulation on Plant Protection Products, for the approval of an active substance, the approval criteria need to be satisfied for at least one or more representative uses of at least one plant protection product containing that active substance. And in your request to EFSA, you clearly refer to the potential of carcinogenicity of glyphosate or *glyphosate containing products* to be assessed.

We therefore urge you to ensure that all relevant data with regard to glyphosate and the use of glyphosate containing products, including epidemiological data, are fully considered by EFSA in its peer review.

Moreover, we are greatly concerned that the Commission asked EFSA in its request from April 2015 to consider "whether a **firm causality** can be established between the phenomena observed in IARC's assessment and the application of glyphosate containing plant protection products consistent with good plant protection practice and having regard to realistic conditions of use" (own emphasis added).

We consider that the request for a "firm causality" not only has no basis in Regulation (EC) No. 1107/2009, but could moreover undermine the letter and the spirit of the law. The legislator clearly decided that an active substance that is carcinogenic shall only be approved, if it is not or has not to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogen category 1A or 1B. According to that Regulation, a substance may be classified as Category 1B based

[4] http://www.who.int/foodsafety/areas_work/chemical-risks/jmpr/en/
[5] http://apps.who.int/pesticide-residues-jmpr-database/pesticide?name=GLYPHOSATE

on animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity. There is no requirement whatsoever to prove that the effects found in animal experiments also occur in the field, let alone establish a "firm causality" between the carcinogenicity found in animal experiments and the application of the glyphosate containing plant protection product in the field.

The classification alone triggers the regulatory consequences. An approval of a carcinogen is only possible if the exposure of humans to that active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, or pursuant to the derogations laid down in Article 4(7), but not based on any other considerations.

We urge you to clarify that there is no need for EFSA to establish a "firm causality" between the application of glyphosate in agriculture and cases of cancer in the population in order to recommend a classification in category 1B ("presumed to have carcinogenic potential for humans, classification is largely based on animal evidence") **according to the CLP regulation. IARC, as one of the most trusted names in Cancer Hazard Evaluation, found "sufficient evidence" for glyphosate causing cancer in experimental animals and "limited evidence" for cancer causing effects in humans. At this level of hazard assessment any request for a "firm causality" as a potential prerequisite for classification or further consequences is inadequate.**

Yours sincerely,

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Appendix

A. Genotoxicity of Glyphosate

IARC Monographs Working Group concluded: "There is strong evidence that glyphosate causes genotoxicity. The evidence base includes studies that gave largely positive results in human cells in vitro, in mammalian model systems in vivo and in vitro, and studies in other non-mammalian organisms."[6] These conclusions were derived independently for glyphosate active substance and glyphosate formulations. BfR, in contrast, concluded: "Taking a weight of evidence approach, it may be concluded that there is no *in vivo* genotoxicity and mutagenicity potential of glyphosate or its formulations to be expected under normal exposure scenarios, *i.e.*, below toxic dose levels."[7]

BfR relied for their conclusion mainly on unpublished regulatory studies, predominantly showing no genotoxic effects, and rated most published studies "not relevant", while IARC, considering only the publicly available, mostly peer-reviewed literature, states that the majority of reported tests for genotoxicity found such effects (see table 1).

	Tests in unpublished regulatory studies (always reporting one test/endpoint per study)		Tests in published, peer-reviewed studies (partly reporting several tests/endpoints in one study)	
	no genotoxic effects	genotoxic effects	no genotoxic effects	genotoxic effects
BfR RAR	34	2	15	39
IARC Monograph	-	-	10	23
Total of tests	34	2	25	62
% showing effects	6% (2/36)		71% (62/87)	

Table 1: Number of genotoxicity tests showing (no) effects referenced in the BfR RAR and the IARC Monograph, respectively.[8]

In this context we would like to know

1. how EFSA evaluates the genotoxic potential of glyphosate;
2. how EFSA assesses BfR's selective approach;

[6] IARC Monograph 112, p. 77 (http://monographs.iarc.fr/ENG/Monographs/vol112/)
[7] BfR Renewal Assessment Report, version 18 December 2013, Volume 1, p. 56 (accessible via EFSA: http://dar.efsa.europa.eu/dar-web/provision/request/subid/562)
[8] excluding equivocal results; compiled by Dr. Peter Clausing, see also http://blog.campact.de/wp-content/uploads/2015/10/Glyphosat-Studie_Campact_PAN_korrigiert.pdf

3. whether EFSA has any evidence of unpublished regulatory studies which indicate genotoxicity that are withheld by the applicant, and if yes, how it intends to deal with this[9];
4. whether EFSA considers it appropriate to dismiss an important part (results of the micronucleus test) of a high quality study published in a peer-reviewed journal and only mention the less important results (SCGE assay) in the RAR[10] as it happened with the paper of Koller et al. (2012)[11] and whether it would be important to evaluate the RAR concerning further omissions of this type.

B. Human and animal evidence for carcinogenicity and toxic effects to reproduction of glyphosate

IARC Monographs Working Groups found "limited evidence for the carcinogenicity of glyphosate in humans and sufficient evidence for the carcinogenicity of glyphosate in animals". BfR agrees that there is "limited evidence" in humans, but stresses at the same time that epidemiological data rely on glyphosate containing formulations instead of the pure active ingredient. Regarding the animal evidence, BfR does not suggest any classification for carcinogenicity.

In this context we would like to know

1. whether EFSA agrees with BfR and IARC that there is "limited evidence" for the carcinogenicity of glyphosate in humans and what conclusions are drawn from this assessment;
2. whether EFSA agrees that meta risk-ratios of 1.3 and 1.5 in two meta-analyses on data regarding non-Hodgkin lymphoma and occupational exposure to glyphosate indicate that Glyphosate-exposed individuals (farmers) may have a higher risk of getting non-Hodgkin lymphoma than non-exposed individuals[12];
3. whether EFSA shares BfR's view that hairy cell leukemia is a different endpoint than non-hodgkin lymphoma and that therefore data on both should not be pooled[13];
4. whether EFSA considers Klimisch's "Systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data"[14] appropriate for the assessment of epidemiological studies;
5. whether EFSA considers it appropriate to dismiss published, peer-reviewed studies because of their condensed presentations (according to the rules of the publishing journals) or whether authorities like BfR should get in touch with the authors of important publications to clarify details which were not included in their papers[15];

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[9] the applicant might be tempted to withhold unpublished regulatory studies which indicate genotoxicity since such studies are relatively cheap to repeat and the long-term price for a classification as genotoxic is high as it may prevent authorization or result in strong restrictions in the use of a pesticide – the conspicuous difference in the share of tests that indicate genotoxicity in the unpublished and the published literature (6% vs. 71%, see table 1) suggests that this may have happened in the case of glyphosate

[10] see RAR, version 31 March 2015, Volume 3, Table 6.4-29 as cited in Clausing (2015) p. 13; download at: http://blog.campact.de/wp-content/uploads/2015/10/Glyphosat-Studie_Campact_PAN_korrigiert.pdf; missing in RAR, version 18 December 2013, Volume 3, Table 6.2-28

[11] http://www.ncbi.nlm.nih.gov/pubmed/22331240

[12] see IARC Monograph 112, p. 30

[13] http://bfr.bund.de/cm/343/einschaetzung-des-bfr-zu-epidemiologischen-studien-ueber-kanzerogene-effekte-von-glyphosat-in-der-eu-wirkstoffpruefung.pdf

[14] http://www.ncbi.nlm.nih.gov/pubmed/9056496

[15] "To avoid missing relevant studies, the relevance criteria should not be too restrictive." (Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009, EFSA Journal 9(2):2092, p.13) http://www.efsa.europa.eu/de/efsajournal/pub/2092

6. whether EFSA considers it appropriate that BfR classified the studies by De Roos et al. (2003)[16] and Eriksson et al. (2008)[17], which were identified as significant evidence by the IARC Monographs Working Group, as "not relevant";
7. whether EFSA agrees with BfR's view that "unequivocal evidence"[18] is necessary before conclusions can be drawn regarding an active substance which might have consequences regarding its risk management;
8. whether EFSA agrees that Arbuckle et al. (2001)[19] found a substantial increase of spontaneous abortion after pre-conception glyphosate exposure – and how this relates to BfR's statement that this study did not demonstrate any toxic effects of glyphosate to reproduction[20];
9. whether EFSA shares BfR's evaluation that the mouse carcinogenicity study by Wood et al. (2009) does not show a significant increase in tumor incidence. It should be noted that the applicable OECD Guideline implies that both pairwise comparison as well as trend tests should be applied before making a judgement[21];
10. whether EFSA believes that BfR's conclusion of no carcinogenicity from the Wood et al. (2009) study is "fully covered by historical control data"[22] although the BfR itself states that "the quality and regulatory value of the historical data (i.e. the same data referred to in volume 1) is very much compromised"[23];
11. how EFSA assesses the detailed comments of Prof. C. Portier on the substantial differences in the evaluation and reporting of four regulatory animal studies by IARC and BfR, respectively, in his written statement for the hearing in the German parliament[24].

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[16] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1740618/

[17] http://www.ncbi.nlm.nih.gov/pubmed/18623080; see also the detailed comments of Prof. C. Portier in his written statement for the hearing in the German parliament (http://www.bundestag.de/bundestag/ausschuesse18/a10/anhoerungen/anhoerung_glyphosat_28_09_2015/386986)

[18] http://bfr.bund.de/cm/343/einschaetzung-des-bfr-zu-epidemiologischen-studien-ueber-kanzerogene-effekte-von-glyphosat-in-der-eu-wirkstoffpruefung.pdf

[19] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1240415/

[20] http://bfr.bund.de/cm/343/einschaetzung-des-bfr-zu-epidemiologischen-studien-ueber-kanzerogene-effekte-von-glyphosat-in-der-eu-wirkstoffpruefung.pdf; see also the comments of Prof. E. Greiser in his written statement for the hearing in the German parliament http://www.bundestag.de/bundestag/ausschuesse18/a10/anhoerungen/anhoerung_glyphosat_28_09_2015/386986

[21] OECD GUIDANCE NOTES FOR ANALYSIS AND EVALUATION OF CHRONIC TOXICITY AND CARCINOGENICITY STUDIES, citing US EPA's Proposed Guidelines for Carcinogen Risk Assessment (1996) (p. 62: "Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result.") http://www.oecd.org/officialdocuments/displaydocument/?cote=env/jm/mono(2002)19&doclanguage=en

[22] RAR version 31 March 2015, Volume 1, p. 65 as cited in Clausing (2015) p. 13; download at: http://blog.campact.de/wp-content/uploads/2015/10/Glyphosat-Studie_Campact_PAN_korrigiert.pdf

[23] RAR, version 31 March 2015, Volume 3, Annex B.6, p. 509 as cited in Clausing (2015) p. 13; download at: http://blog.campact.de/wp-content/uploads/2015/10/Glyphosat-Studie_Campact_PAN_korrigiert.pdf

[24] http://www.bundestag.de/bundestag/ausschuesse18/a10/anhoerungen/anhoerung_glyphosat_28_09_2015/386986; see also the comments of Prof. I. Rusyn on "high doses/concentrations" in animals studies

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