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

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BfR relied for their conclusion mainly on unpublished regulatory studies, predominantly showing no genotoxic effects, and rated most published studies "not relevant", while IARC, considering only the publicly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	Tests in unpublished regulatory studies (always reporting one test/endpoint per study)		Tests in published, peer-reviewed studies (partly reporting several tests/endpoints in one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 whether EFSA has any evidence of unpublished regulatory studies which indicate genotoxicity that are withheld by the applicant, and if yes, how it intends to deal with this[9];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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