

**Expert Report on the Presentation and
Assessment of five Mouse Carcinogenicity
Studies as Related to the Renewal of Approval
of the Active Ingredient Glyphosate**

by

Dr. Peter Clausing, PAN Germany

.....
Hamburg – 29th February 2016

recommends trend tests for the assessment tumour frequencies in a flow diagram (OECD 2009b, p. 123).

Antecedents: Prior neglect and external pressure

In line with Regulation (EC) No. 1107/2009 the applicant for the (re)-approval of a pesticide active ingredient – in the case of glyphosate the Glyphosate Task Force (GTF) – can select by itself the Reporting Member State (RMS), i.e. the country whose authorities are required to assess the dossier submitted by the applicant. The GTF selected Germany and with regard to the assessment of toxicological information, including information on carcinogenicity it was the responsibility of the Federal Institute of Risk Assessment (BfR for its German designation).

The dossier submitted by Monsanto Europe S.A. on behalf of the GTF dated “May 2012” concludes that glyphosate has “no oncogenic potential” (GTF 2012, p. 525). The BfR in its Renewal Assessment Report (RAR) agreed with this conclusion, stating: “Classification and labelling for carcinogenicity is not considered appropriate by the RMS” (RAR, Volume 1, 2015, p. 65).

On 20 March 2015 the IARC announced that it considers glyphosate “as probably carcinogenic to humans” (carcinogen group 2A according to the IARC nomenclature, which is similar the CLP-category 1B; IARC 2015a). On 29 July 2015 the IARC published its complete monograph on glyphosate, which was elaborated by 17 international experts (IARC 2015b). Thereafter, the EFSA commissioned and the BfR performed a comparative analysis of IARC’s monograph and BfR’s RAR resulting in an Addendum to the RAR dated 31 August 2015 (Addendum 2015).

Admitting the facts after re-visiting the data

In the following we will focus on the five mouse carcinogenicity studies which are part of the Dossier/RAR. However it should be noted that the Addendum also dealt with carcinogenicity studies in rats (admitting that two out of nine studies exhibited significant carcinogenic effects) and with mechanistic evidence for carcinogenic effects which was recognised by the IARC. In line with the IARC, the BfR in its Addendum acknowledged: “From the available data on glyphosate there is some indication of induction of oxidative stress from testing in human cell cultures and in mammalian (*in vivo*) experimental systems. In particular, the IARC statement that there are indications of oxidative stress in the blood plasma, liver, brain and kidney of rats upon exposure to glyphosate can be supported” (Addendum, p. 79).

Keeping in mind that there is supportive evidence from rat studies and studies on the mechanism by which glyphosate can induce cancer, we focus on mouse studies, because of the CLP (1272/2008) definition, that the demonstration of carcinogenicity in “two or more independent studies in one species” is sufficient evidence to classify a compound as a “presumed human carcinogen” (see Introduction).

In its Addendum, the BfR recognises that five valid long-term feeding studies in mice demonstrate a significant increase in tumours related to glyphosate exposure. This is a

dismissed, because this was "... fully covered by historical control data" (RAR Volume 1, p. 65).

In relation to the significant increase in haemangiosarcoma, the BfR simply states: "The background incidences for haemangiosarcoma in male CD-1 mice provided by Charles Rvier Laboratories ... were up to 6/50 (12%) ... Therefore the observed incidences for haemangiosarcoma were spontaneous and unrelated to treatment" (Addendum, p. 92). This means, the BfR considers the significantly increased incidence in the study of 1997 with Crj:CD-1 mice as insignificant, because of a background incidence observed in CrI:CD-1(ICR)BR that was "up to 12%" without specifying how many of the 51 studies exhibited such a high incidence. Besides the deficiency of comparing different strains, it should be noted that the OECD recommends to use the median and interquartile ranges (OECD 2012, p. 135). By using the arithmetic mean and the simple range of historical data (Addendum, p. 91) the BfR did not follow the recommendation of the OECD.

In summary, the BfR's argument that a high background incidence invalidates the significant findings of the five mouse carcinogenicity studies is based on an entirely inappropriate use of data. In addition, the presentation of data is contradictory between different parts and versions of the RAR.

Excessive toxicity

Another argument used in the Addendum to dismiss the significant findings of animal carcinogenicity is "excessive toxicity" (p. ii) or "high-dose phenomenon" (p.36). Again, it is worth comparing the argument of the RMS with the recommendations given by the applicable Guidance and Guidelines.

The BfR refers to a top dose of 1,000 mg/kg that should not be exceeded in animal studies. Here it should be noted that a top dose of 1,000 mg/kg is mentioned in the OECD Guideline for Chronic Toxicity Studies (OECD 2009b), but not in the OECD Guideline for Carcinogenicity Studies (OECD 2009a). In other words, no top dose limit is defined for carcinogenicity studies, although they may be limited to 1,000 mg/kg when combined with a chronic toxicity study.

The BfR also refers to a recommendation that depression of body weight gain (as an indication of toxicity) should not exceed 10% as compared to the control group. Referring to the studies from 1983 and 1997, it argues that "excessive toxicity" has had a confounding effect here, based on the observation that "the body weight gain was decreased by more than 15% compared to controls, but mortality/survival was not affected" (Addendum, p. ii).

First, it should be noted that the exact wording of the OECD Guidance No. 116 is that "the top dose should ideally provide some signs of toxicity such as slight depression of body weight gain (not more than 10%), without causing e.g., tissue necrosis or metabolic saturation". There is no mention of "necrosis" or "metabolic saturation" in the summaries of the long-term studies in mice presented in the RAR of 31 March 2015. Also, in the light of biological variability, a 15% depression of body weight is a moderate departure from the ideal of "not more than 10%".

References

- [CLP] 1272/2008: 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.
- EFSA (2015): Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate. EFSA Journal 2015;13(11):4302.
- GTF (2012): Glyphosate & the IPA-, K-, NH₄-, and DMA-salts of glyphosate. Document M, Point 5: Toxicological and toxicokinetic studies, 1027 pp.
- IARC (2015a): Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. Lancet Oncology, 20 March 2015, [http://dx.doi.org/10.1016/S1470-2045\(15\)70134-8](http://dx.doi.org/10.1016/S1470-2045(15)70134-8)
- IARC (2015b): IARC monograph No. 112. Glyphosate. <http://monographs.iarc.fr/ENG/Monographs/vol112/index.php>
- OECD (2002): OECD Environment, Health and Safety Publications. Series on Testing and Assessment No. 35 and Series on Pesticides No. 14. Guidance Notes for Analysis and Evaluation of Chronic Toxicity and Carcinogenicity Studies. [http://www.oecd.org/officialdocuments/displaydocument/?cote=env/jm/mono\(2002\)19&doclanguage=en](http://www.oecd.org/officialdocuments/displaydocument/?cote=env/jm/mono(2002)19&doclanguage=en)
- OECD (2009a): OECD Guideline for the Testing of Chemicals No. 451, Carcinogenicity Studies. http://www.oecd-ilibrary.org/environment/test-no-451-carcinogenicity-studies_9789264071186-en;jsessionid=16odl65wcetn2.x-oecd-live-03
- OECD (2009b): OECD Guideline for the Testing of Chemicals No. 452, Chronic Toxicity Studies. http://www.oecd-ilibrary.org/environment/test-no-452-chronic-toxicity-studies_9789264071209-en;jsessionid=16odl65wcetn2.x-oecd-live-03
- OECD (2012): Guidance Document 116 on the Conduct and Design of Chronic Toxicity and Carcinogenicity Studies, Supporting Test Guidelines 451, 452 and 453, 2nd Edition Series on Testing and Assessment No. 116. [http://www.oecd.org/officialdocuments/displaydocument/?cote=ENV/JM/MONO\(2011\)47&doclanguage=en](http://www.oecd.org/officialdocuments/displaydocument/?cote=ENV/JM/MONO(2011)47&doclanguage=en)
- Portier et al. (2015): Open letter: Review of the Carcinogenicity of Glyphosate by EFSA and BfR. <http://images.derstandard.at/2015/11/30/glyphosate.pdf>
- RAR Addendum (2015): Glyphosate Addendum 1 to RAR, 31 August 2015. Renewal Assessment Report on Glyphosate, Public version.
- RAR Volume 1 (2015): Renewal Assessment Report, Glyphosate. Report and Proposed Decision, 31. March 2015, 190 pp.
- RAR Volume 3 (2015): Renewal Assessment Report Glyphosate Volume 3; Annex B.6, Toxicology and metabolism, dated 31 March 2015.
- Regulation 1107/2009: <http://eur-lex.europa.eu/legalcontent/EN/TXT/PDF/?uri=CELEX:32009R1107&from=DE>

Taddesse-Heath, L.; Chattopadhyay, S.K.; Dillehay, D.; L.; Lander, M.R.; Nagashfar, Z.; Morse III, H.C.; Hartley, J.W. (2000): Lymphomas and high-level expression of murine leukemia viruses in CFW mice Journal of Virology 74:6832-6837

Hamburg, 29th February 2016



Dr. Peter Clausing

Pestizid Aktions-Netzwerk e.V. / PAN Germany
Nernstweg 32
D-22765 Hamburg
Phone: +49 (0)40-3991910-0
www.pan-germany.org

peter.clausing@pan-germany.org,

Mobile: +49-176 7801 2705