

# The Carcinogenic Hazard of Glyphosate: BfR's "Weight of Evidence Approach"\*

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\* Originally published in German in:  
Umweltmedizin – Hygiene – Arbeitsmedizin  
(Journal of Environmental and Occupational Health Sciences),  
Vol. 22, No. 1 (2017), pp. 27-34,  
ecomед Medizin, a brand of ecomed-Storck GmbH, Landsberg, Germany.  
Translation by the author.



Hamburg - March 2017





more clearly structured summary with almost identical contents, which also was written by the BfR, and was submitted in spring 2016 to the European Chemicals Agency (ECHA). From this document it is clear that a total of 2 carcinogenicity studies in rats and 5 studies in mice demonstrated significantly increased tumour incidences after glyphosate administration. More precisely, 11 significantly increased incidences for 6 different tumour types were identified in these 7 studies. These were haemangiosarcoma, malignant lymphoma, and renal tumours in mice and pancreas carcinoma, liver adenoma, and C-cell adenoma of the thyroid in rats.

Here, we focus on the ECHA dossier which – as mentioned above – will lead to a revival of the controversy surrounding glyphosate during the second half of 2017 at the latest. However, the data presented in the dossier are congruent with those of the RAR. For the sake of clarity, our analysis will concentrate on one tumour type – the malignant lymphoma in mouse studies. An analysis with similar results could for instance also be presented for the renal tumours observed in the mouse studies. The data are summarized in Table 1. Information about statistical significance has been derived from the ECHA dossier (BAuA 2016).

**Table 1:** Incidences of malignant lymphoma in males of mouse carcinogenicity studies of glyphosate; number of animals (n) = 50 per group and sex, except for the study of 2009 (n=51) and 1983 (n=48-50); p-values<0.05 are considered significant. It should be noted that with a one-tailed error probability (i.e. testing only for a significant increase of the incidence) the calculated p-value would be divided in half; for pair-wise comparisons the p-values displayed refer to the high dose-group; for the trend test, the value refers to the entire study. In cases of trend tests, the Cochran-Armitage-trend test was used. Data from the ECHA dossier (BAuA 2016).

Year of study	Mouse strain	Doses (mg/kg body wt.)* Tumour incidence	Statistical method and p-value, all non-trend tests were pairwise comparisons
2009	CrI:CD1	0 – 71 – 234 – 810 0 – 1 – 2 – 5	Chi-Square-Test, p = 0.067 Trend-Test, p = 0.0037
2001	HsdOLA:MF1	0 – 15 – 151 – 1460 10 – 15 – 16 – 19	Z-Test, p = 0.002 Fisher's Exact Test, p = 0.077 Trend-Test, p = 0.0655
1997	Crj:CD1	0 – 165 – 838 – 4338 2 – 2 – 0 – 6	Fisher's Exact Test, p = 0.269 Trend-Test, p = 0.0085
1993	CD1, not further specified	0 – 100 – 300 – 1000 4 – 2 – 1 – 6**	Fisher's Exact Test, p = 0.741 Trend-Test, p = 0.0760
1983	CD1, not further specified	0 – 157 – 814 – 4841 2 – 5 – 4 – 2***	No information, called significant in the narrative.

\*dietary administration, doses were calculated from concentration in food, food intake and bodyweight

\*\*according to ECHA-Dossier only incidences of lymph nodes with macroscopic changes

\*\*\* sum of lymphoreticular neoplasms, malignant lymphoma not specified















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Originally published in German in: Umweltmedizin – Hygiene – Arbeitsmedizin, Vol. 22, No. 1 (2017), pp. 27-34, ecomed Medizin, a brand of ecomed-Storck GmbH, Landsberg, Germany

**Annex:**

**Table 2:** Summary of the critique of the „weight of evidence approach” by BfR and EFSA (referring to malignant lymphoma in mouse studies). The critical assessment relates to the studies of 1997, 2001 and 2009, because – as detailed in the text – the studies of 1983 and 1993, as related to malignant lymphoma were only of limited use (1983) or completely useless (1993).

<b>Issue</b>	<b>Opinion by BfR and EFSA</b>	<b>Critique of the Opinion</b>
Contradicting statistical results	Trend-tests were mostly (but not always) significant, however for pairwise comparisons there were no significant differences.	Trend-tests are explicitly recommended for the assessment of tumour incidences by the applicable OECD guidance. Even pairwise comparisons result in statistical significance if one-sided tests as recommended by the same guidance are used.
Inconsistencies concerning the dose-response-relationship	Different tumour incidences in the control groups and similar tumour incidences at different dosages in the different studies.	This is invalid, because it ignores the fact that different strains of mice were used in the different studies.
Excessive toxicity in high-dose groups	An increase in tumour incidences occurred only after exceeding the „limit-dose“ of 1,000 mg/kg and excessive toxicity was observed.	A significant increase was also seen at 810 mg/kg. A „limit-dose“ is not defined in OECD Guideline 451 (Carcinogenicity). Excessive toxicity was not seen in any of the studies. The reduced body weight is due to reduced food consumption (as a consequence of the high glyphosate concentration in the test diet).
An infection with oncogenic viruses makes the study of 2001 unusable	According to EFSA the study is not acceptable because of a viral infection; infections with oncogenic viruses are widespread in the strain of mice used.	According to the ECHA-dossier there is no proof for this claim made in the EFSA-Conclusion. In the publication, that is cited as alleged evidence for widespread infections by oncogenic viruses in the particular mouse strain, the term widespread is not used. To the contrary the authors emphasized, that they only presented results from two laboratories with mice from the same breeder.
Tumour incidences as related to historical control data	The tumour incidences of glyphosate-treated animals were in the range of historical control data.	For the study of 1997 OECD-recommendations for historical control data (HCD) are violated, for the 2001 study the HCD actually support the tumour finding, and no usable HCD are available for the study of 2009.
No conclusive evidence for a carcinogenic mode of action	From the “sole” observation of oxidative stress and a plausible mechanisms for its formation a carcinogenic action cannot be deduced.	Because of statistically significant increases in tumour incidences in three independent studies and epidemiological evidence, although limited, for tumours of the lymphatic system it is incorrect to speak of a „sole“ observation of oxidative stress.

## Imprint

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Hamburg, 01 December 2015

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