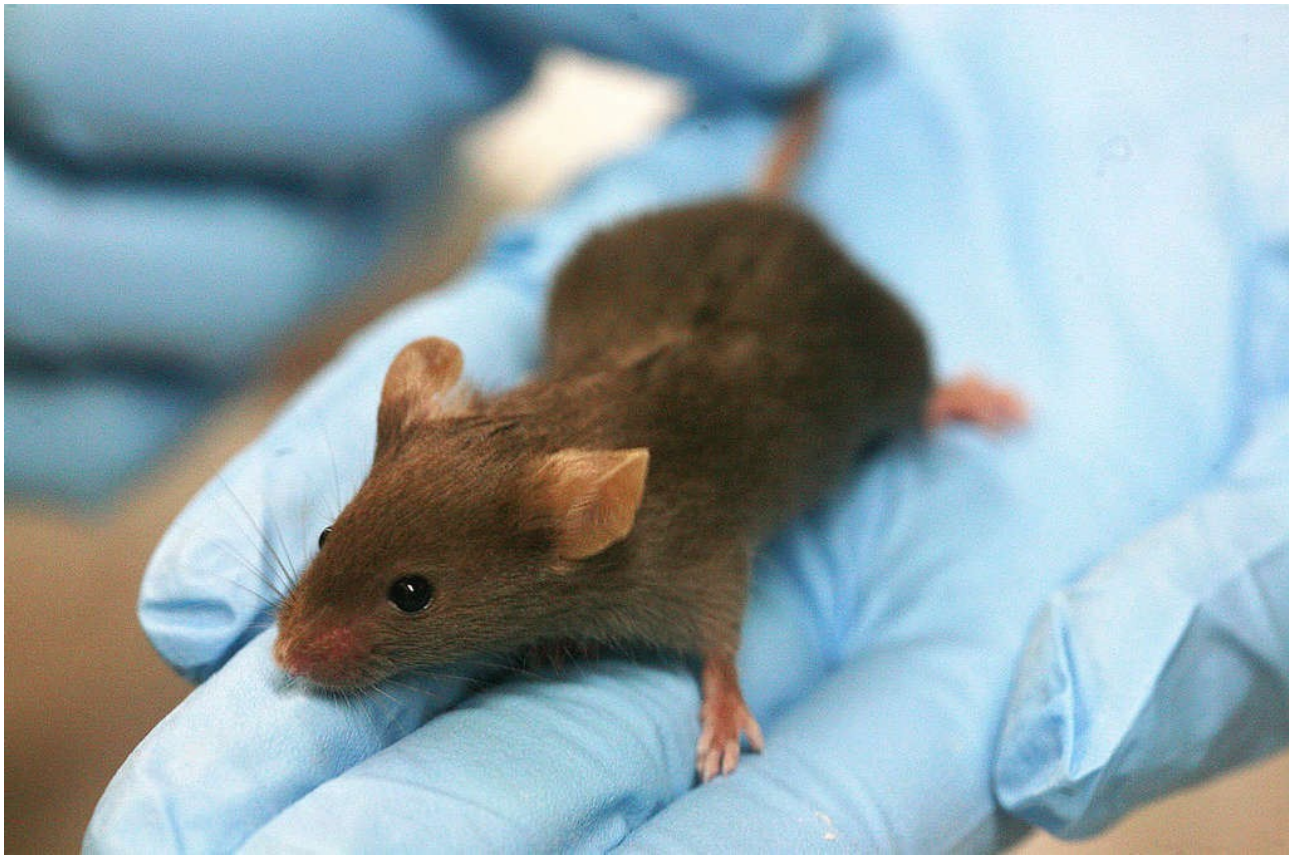
The course of the European re-approval procedure for glyphosate



DI Dr. Helmut Burtscher, GLOBAL 2000

Vienna, 20 April 2016

Carcinogenicity studies by the producers of glyphosate

To get a pesticide approved for the European market, producers have to prove that it is not carcinogenic. Among other things, they submit **long-term carcinogenicity studies in animals**[1] to the authorities. If there is no observable dose-dependent increase in malignant tumours, this is an indication that the examined pesticide is not a carcinogen. However, if there is an observable causal connection between the pesticide and the increase in malignant tumours, the pesticide must not be approved in the European Union.[2]
In May 2012 Monsanto submitted a dossier to the German licensing authorities[3] on behalf of the Glyphosate Task Force (GTF).[4] This dossier contained five carcinogenicity studies in mice.[5] In all studies malignant tumours were observed in kidneys, blood vessels, and/or lymphatic glands. The connection with the glyphosate dose is shown in the following tables and graphics.

Table 1: Number of male animals (49-51 per group) with development of tumours dependent on the glyphosate dose in five long-term carcinogenicity studies in laboratory mice

Type of tumor	study	control	low dose	moderate dose	high dose
kidney cancer	Monsanto 1983	1	0	1	3
	Arysta 1997	0	0	0	2
	Adama 2001	0	0	1	2
angiosarcoma	Cheminova 1993	0	0	0	4
	Arysta 1997	0	0	0	2
lymphoma	Arysta 1997	2	2	0	6
	Adama 2001	10	15	16	19
	Nufarm 2009	0	1	2	5

1 Four groups, each with 50 male and 50 female mice, are fed increasing doses of glyphosate during a period of 18 months: one zero, one low, one moderate and one high dose

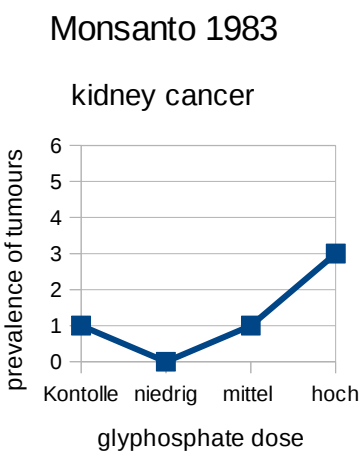
2 According to Act No. 1272/2008 EG, a substance has to be claimed carcinogen of category 1A or 1B if there a positive evidence of tumours in at least two studies

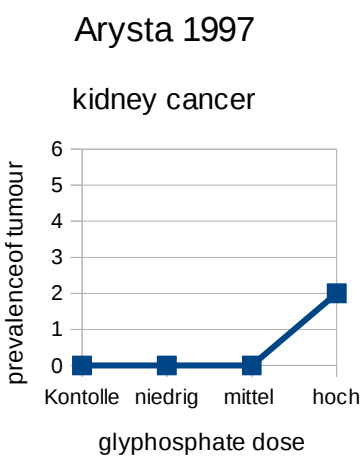
3 Thus Germany became a “Reporting Member State” (RMS)

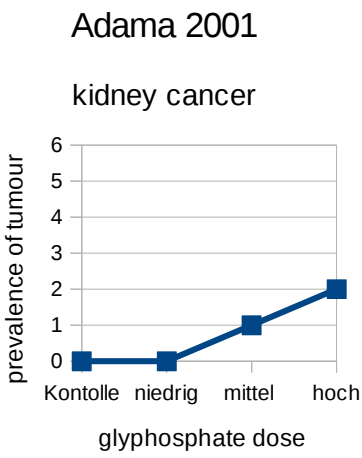
4 Coalition of producers and retailers of glyphosate http://www.glyphosat.de/impressum

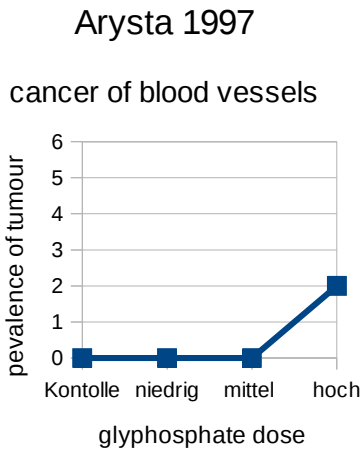
5 „Final addendum to the Renewal Assessment Report “ October 2015 (pages 1013 - 1040 and 4184 - 4200)

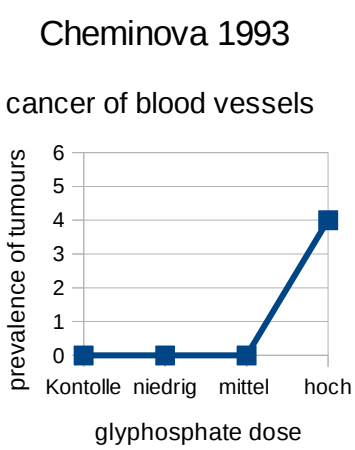
Picture 1: Dose-effect-relationship graphs (extracted from the five long-term carcinogenicity studies that had been submitted as supporting evidence for the clearance of no-objection to glyphosate). They show an increasing tendency of tumour prevalence with increasing doses of glyphosate:

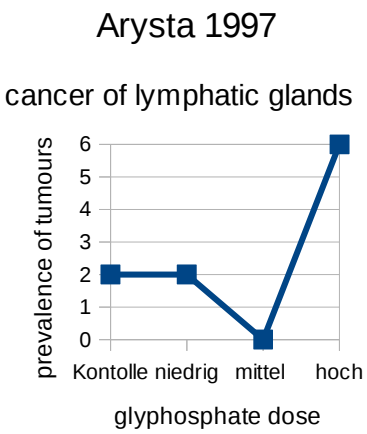


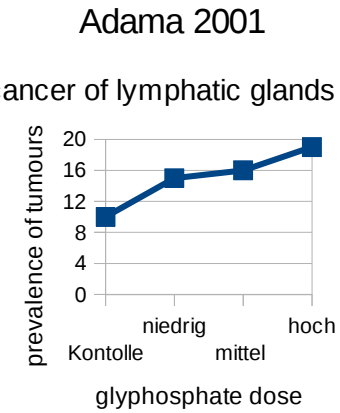


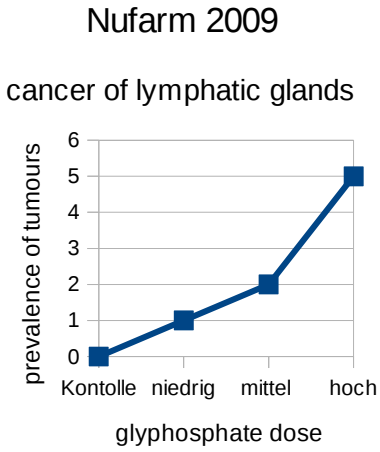












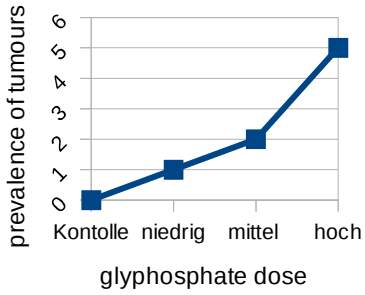
Statement of the German Federal Institute for Risk Assessment (BfR)[6] regarding the carcinogenicity studies

In addition to the documents that had been included in the first examination of activity of the substance more than 1000 new studies have been examined and evaluated. These studies show no evidence of an effect on the mice by glyphosate that is carcinogenic, harmful for the reproductive system or teratogenic. "These data do not require a change in the threshold values of the substance," Professor Dr Andreas Hensel states.

press handout by BfR (20 January, 2014)

Nufarm 2009

cancer of lymphatic glands



Comment by GLOBAL 2000

This statement is obviously contrary to the results of the long-term studies of carcinogenicity with mice which the IRA had to evaluate. However, similar statements have been made by applicants and the BfR. We now want to show this with reference to the carcinogenicity study conducted by Nufarm in 2009[7] (see picture).

Incorrect interpretation by reference to "Nufarm 2009"

Evaluation of the study by GTF[8]

Histopathology
There were no treatment-related histopathological findings observed in any dose group of either sex.

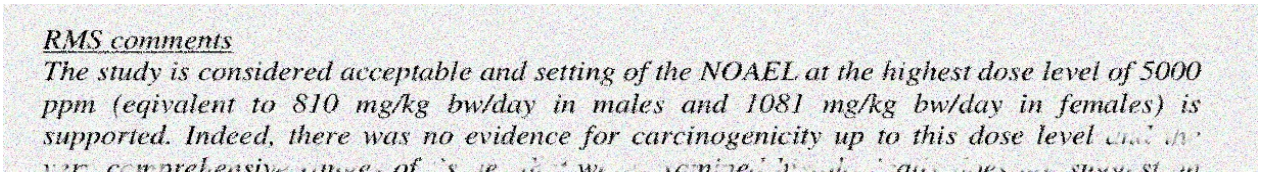
Conclusion by the Notifiers
Based on the study results the NOEL and NOAEL in mice after chronic exposure to Glyphosate technical for 18 month is 810 mg/kg bw/day for males, and 1081 mg/kg bw/day for females. It is concluded that Glyphosate technical is not carcinogenic in mice.

Comment of GLOBAL 2000

The statement by the GTF that no treatment-dependent histopathological evidence was observed is inexplicable in light of the dose-effect relationship graph shown above. In fact the histopathological evidence provided by this carcinogenicity study shows a dose-dependent and statistically significant increase in lymphoma in male mice, with the frequency of tumours as follows: control 0%, low dose 2%, mid dose 4%, high dose 10% (p=0.0037 according to Cochran-Armitage[9]).

6 The German Federal Institute for Risk Assessment (BfR) evaluated the human toxicity of glyphosate for the European Union.
7 There is a summary of this study on pages 1023-2030 in the RAR
8 RAR page 1028
9 The test of tendency of Cochran Armitage is the recommended statistical procedure for the evaluation of long-term studies according to OECD-test-guidances number 116 (published 13th of April, 2012)

Evaluation by the RMS in the first interim report[10] [11]



RMS comments
The study is considered acceptable and setting of the NOAEL at the highest dose level of 5000 ppm (eqivalent to 810 mg/kg bw/day in males and 1081 mg/kg bw/day in females) is supported. Indeed, there was no evidence for carcinogenicity up to this dose level

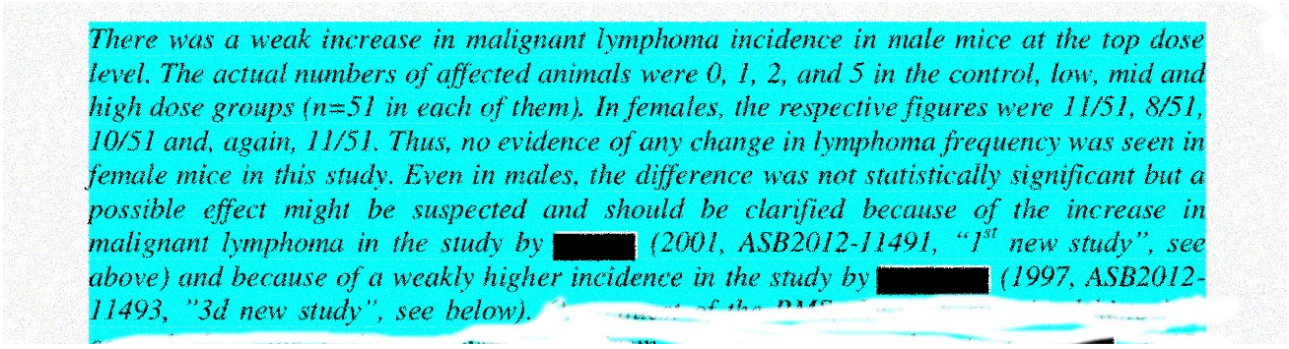
Comment of GLOBAL 2000

On the same grounds as above, this evaluation by the BfR also appears to be inexplicable.

Assessment by the BfR: final evaluation report[12]

On 31 March, 2015 – eleven days after the IARC classified glyphosate as being a probable carcinogen – the BfR published a final evaluation report.

An extract states:



There was a weak increase in malignant lymphoma incidence in male mice at the top dose level. The actual numbers of affected animals were 0, 1, 2, and 5 in the control, low, mid and high dose groups (n=51 in each of them). In females, the respective figures were 11/51, 8/51, 10/51 and, again, 11/51. Thus, no evidence of any change in lymphoma frequency was seen in female mice in this study. Even in males, the difference was not statistically significant but a possible effect might be suspected and should be clarified because of the increase in malignant lymphoma in the study by [redacted] (2001, ASB2012-11491, "1st new study", see above) and because of a weakly higher incidence in the study by [redacted] (1997, ASB2012-11493, "3d new study", see below).

Comment of GLOBAL 2000

The RMS contradicts its original evaluation of "no indications of carcinogenicity" and for the first time it admits a "slight increase" in the tumour prevalence. Nevertheless it characterizes this increase as being "not statistically significant", without explanation.[13]

10 The BfR published a draft of the evaluation report on 18th of December, 2013

11 NOAEL (No Observed Adverse Effect Level): highest dose with no observable negative effect

12 Published on 31st of March, 2015

13 The evaluation with the recommended test for tendency (according to OECD guidance 116) shows a significant result (p=0.0037)

Evaluation by the RMS in the addendum of the RAR[14]

The IARC also examined two of the five mice studies[15] that had been claimed as having negative results (no effect) by the BfR – but the IARC classified them as positive evidence of carcinogenicity.[16] Therefore the BfR had to re-evaluate this obvious discrepancy and was forced to state:

Comment of GLOBAL 2000

Obviously the BfR feels compelled to correct the evaluation that had already been revised anyway: Instead of a "slight" and "not statistically significant increase" it now detects a "dose-dependent, statistically significant increase" in malignant lymphoma.

The BfR tries to explain this as follows:[17]

ii) Differences in evaluation of individual study reports

Due to the application of different statistical approaches selected for evaluation, IARC and RMS came to diverging conclusions when evaluating cancer incidences in animal studies. IARC included a trend test (generally according to Cochran-Armitage) for statistical evaluation of the data (IARC, 2015, ASB2015-8421). In contrast, initially, the RMS relied on the statistical evaluation provided with the study reports, which was performed and documented as foreseen in the individual study plans (RAR, April 2015, ASB2015-1194). The later were mostly based on pairwise comparison of treatment groups using tests including Fishers exact test, Chi-Square test, or Z-test. As a consequence, IARC reported a positive carcinogenic response in some of these studies, while RMS did not. According to guidance documents for the evaluation of carcinogenicity studies published in support of respective OECD test guidelines (OECD 2012, ENV/JM/MONO(2011)47, ASB2015-8445 and OECD 2002, ENV/JM/MONO(2002)19, ASB2013-3754), both statistical approaches are appropriate.

Comment of GLOBAL 2000

This statement of the BfR is striking in three different ways:

1. The BfR admits that in the beginning it *trusted* the statistical evaluation submitted by the GTF.
2. With these evaluations "provided" by the applicants, the BfR justifies the discrepancy between the positive evidence of cancer found by the IARC and its own negative (no effect) results.
3. Referring to the OECD guidelines, the BfR characterises both statistical evaluations as "appropriate". It suppresses the fact that the OECD guidelines that the BfR quoted state: *"Significance in one of the methods is enough to declare the result as being significant."* However, the current OECD guideline for testing recommends the Cochran-Armitage test for trend.[18]

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14 The BfR completed its addendum to the final evaluation report on 31st of August, 2015.

15 In spite of company secrets, the access to these two older studies of Monsanto (1983) and Cheminova (1993) had been big enough for an evaluation by the experts of IARC.

16 IARC-MONOGRAPHS – 112 (pages 30-35)

17 "RMS" stands for BfR in the following excerpt as the BfR is the responsible authority in Germany.

18 OECD Guidance 116, 2009b, page 123

Summary

The example of one of five regulatory long-term studies of carcinogenicity showed how the BfR changed its evaluation of the study results step-by-step:

Originally: *"No indications for carcinogenicity up to the highest dose level"*[19]

Later: *"Slight increase in the incidence of malignant lymphoma, but not statistically significant."*[20]

Finally: *"Statistically significant increase of malignant lymphoma, which could be considered as treatment-dependent.*[21]

Also the evaluations of the remaining four mice studies passed through comparable metamorphoses. In its interim report of December 2013 the BfR stated that with one exception,[22] all graphs showed **no indications for carcinogenicity.** In the addendum of 31 August 2015, the IRA admits a significant increase in kidney tumours in the studies of Monsanto 1983, Arysta 1997 and Adama 2001; significant increases in angiosarcoma in the studies of Cheminova 1993 and Arysta 1997; and significant increases in lymphoma[23] in the studies of Arysta 1997, Adama 2001, and Nufarm 2009.[24]

In spite of these results the IRA sticks to its original recommendation to classify glyphosate as being non-carcinogenic.

How the IRA explains this recommendation has been analysed by the toxicologist Dr Peter Clausing and summarised for GLOBAL 2000. The analysis can be downloaded here:

https://www.global2000.at/glyphosat-zulassung-wir-zeigen-monsanto-bfr-und-efsa

19 Interim report of the RAR, 18th of December, 2013
20 Final version of RAR, 31st of March, 2015

21 Addendum to RAR, 31st of August, 2015 (pages 4192 - 4200)
22 Lymphomas in the study of Adama (2001) are significant in pairwise comparison but not if using the test for trend

23 An increased risk for lymphoma (group of Non Hodgkin lymphoma) is linked in epidemiological studies to glyphosate exposure of farmworkers.
24 Addendum to RAR, 31 August, 2015 (pages 4192 - 4200)