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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

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Introduction and legislative background

In the European Union (EU) the approval for the herbicide active ingredient glyphosate expires in June 2016. The re-approval for the EU market crucially depends on whether or not the EU will recognize glyphosate as a carcinogenic hazard. The final decision will be with the Directorate General Health and Food Safety (DG SANTE) of the European Commission. If DG SANTE classifies glyphosate as a "presumed human carcinogen", then – according to applicable EU legislation (Regulation 1107/2009; Annex II, 3.6.3) – it cannot be re-approved, unless human exposure is “negligible”.

The classification as a "presumed human carcinogen" (category 1B) hinges on the assessment whether there is “sufficient evidence” from experiments “to demonstrate animal carcinogenicity" (Regulation on classification, labelling and packaging [CLP] 1272/2008, Annex I; 3.6.2.1). The definition of the term ‘sufficient’ has been adopted from the WHO’s International Agency for Research on Cancer (IARC, cf. CLP Regulation 1272/2008, Annex I; 3.6.2.2.3). and is as follows: “A causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols” (emphasis added).

This regulation further states that the “(c)lassification of a substance as a carcinogen is a process that involves two interrelated determinations: evaluations of strength of evidence and consideration of all other relevant information to place substances with human cancer potential into hazard categories” (3.6.2.2.2.). It goes on to state that “(s)trength of evidence involves the enumeration of tumours in human and animal studies and determination of their level of statistical significance” (Annex I; 3.6.2.2.3.).

When seeking (re-)approval of pesticide active ingredients in the EU, the reports and result summaries of carcinogenicity studies performed in compliance with OECD Test Guideline No. 451 or 452 (OECD 2009a, OECD 2009b) have to be submitted as part of a dossier. In these two test guidelines, reference is made to OECD Guidance Documents No. 35 (OECD 2002) and No. 116 (OECD 2012) which support the design, conduct and assessment of the results of chronic toxicity and carcinogenicity studies. With regard to Guidance Document 116, reference is made to the draft version which is available since 2009. Its final version was published on April 13th, 2012.

Different versions of statistical tests can be used for data assessment. These tests essentially belong to one of two test types – pairwise comparisons and trend tests. In pairwise comparisons the data of the individual groups treated with the test compound are separately compared with the data of the concurrent control group. In trend tests, in particular the Cochran Armitage Trend Test, the data trend (i.e. increasing or decreasing values) of all treated groups is compared simultaneously with the data of the concurrent control group.

Guidance Document No. 35 refers to the Environmental Protection Agency of the United States (U.S. EPA) and emphasizes: “Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result” (OECD 2009a, p. 62). Guidance Document No. 116 continues to cite this sentence from U.S. EPA, and furthermore explicitly

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

radical departure from the 31 March 2015 version of the RAR in which the BfR reported only one mouse study (from 2001) as showing a significant increase in the incidence of tumours, i.e. in malignant lymphoma (see Table 1).

In the RAR of March 2015 the BfR argued that the finding of increased malignant lymphoma in the 2001 mouse study was irrelevant because the specific study was conducted in a mouse strain (Swiss albino) that is characterized by a high spontaneous incidence of this tumour, and that the other four mouse studies which employed different mouse strains (from the CD-1 group) did not show this effect.

Furthermore, in the RAR of 31 March 2015, renal tumours were observed in three studies but not identified as treatment-related, as well as haemangiosarcoma in two studies (see Table 1). In its Addendum, the BfR concedes that "initially, the BfR relied on the statistical evaluation provided with the study reports, which was performed and documented as foreseen in the individual study plans" (emphasis added, Addendum p. 37).

Table 1: Significant increase in tumour incidence in male mice (indicated by +) using pairwise testing (RAR of March 2015) compared with the Cochran Armitage Trend Test (Addendum). Since 2012, this trend test is the method of statistical evaluation explicitly recommended by the OECD.

Year	Top dose (mg/kg bw)	Renal tumours		Haemangiosarcoma		Malignant lymphoma	
		BfR March	BfR August	BfR March	BfR August	BfR March	BfR August
1983	4.841	-	+				
1993	1.000			-	+	-	-
1997	4.843	-	+	-	+	-	+
2001	1.460	-	+			+@)	-*)
2009	810					-	+

bw = body weight; @)statistically significant based on the pairwise Z-test as performed by the authors of the study report; *) close to statistical significance (p=0.0655)

In the same Addendum, after applying the trend test, the BfR reports a significantly increased incidence of one or even several tumour types for male mice in each of the five studies.

Insisting on the old conclusion in spite of the new facts

While admitting statistically significant increases of tumour incidences in all five mouse studies (Table 1), the BfR dismisses all these findings and concludes that they are unrelated to treatment (Addendum, p.90-93). This is a remarkable turnaround, in particular because in the 31 March 2015 version of the RAR, BfR's main argument for the irrelevance of the increased number of malignant lymphomas in the study of 2001 was the presumed lack of statistically significant effects in the other four studies.

In the abstract of the Addendum (p. iii) the BfR becomes entangled in contradictions. While admitting the statistically significant increases as mentioned above, it argues that "(i)t should be avoided to base any conclusion only on the statistical significance of an increased tumour incidence identified in a single study without consideration of the biological significance of the finding" (emphasis added). With this statement the BfR ignores the fact that it was five

different studies with up to three different tumour types which showed statistically significant increases. In addition, while admitting that "there is some indication of induction of oxidative stress from testing in human cell cultures and in mammalian (*in vivo*) experimental systems" and that "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), the BfR does not hesitate to claim in the Addendum's abstract that "the mechanistic and other studies do not provide further evidence for a carcinogenic mechanism" (Addendum, p. iii).

Historical controls

In its attempt to support the dismissal of the significant tumour findings in these five studies the BfR argues that these findings are all irrelevant because they are covered by so-called historical control data**.** In other words, it is claimed that tumour incidence data of control groups from earlier studies invalidate the statistically significant increases in the five mouse studies in question.

To fully understand the futility of this argument it is necessary to keep in mind the recommendations given by the applicable guidance (OECD 2012) on this issue.

For historical control data this Guidance No. 116 (OECD 2012) states on p. 135 (emphasis added): "In any discussion about historical control data, it should be stressed that the concurrent control group is always the most important consideration in the testing for increased tumour rates. The historical control data can, though, be useful provided that the data chosen are from studies that are comparable with the study being investigated. It is widely recognized that large differences can result from disparities in factors such as pathology nomenclature, strain, husbandry, pathologists. It has been suggested that historical control data should only be used if the concurrent control data are appreciably 'out of line' with recent previous studies and that only historical data collected over the last 5 years should be used."

In an extremely strong violation of these important principles, the BfR presents historical control data of 51 studies collated by Charles River Laboratories between 1987 and 1996 (year of study initiation) which means that they are disconnected from the actual studies by time and/or location. Good practice would have been to use historical control data for the same strain of mice, used within the same laboratory, collected over the last 5 years prior to the study, and ideally assessed by the same study pathologist.

Details of the Charles River pool of historical control data compared to the date of the actual studies, as far as available, are presented in Table 2. The BfR uses these data as its crucial argument in an attempt to invalidate findings of significantly increased tumour incidences.

From Table 2 it can be derived that in addition to the disconnected location of study conduct:

- the significant findings of the study from 1983 are dismissed with "historical" data collected after the study was conducted.
- the significant findings of the studies from 1997 and 2001 using the strains Crj:CD-1 and Swiss Albino, respectively, are dismissed with historical data from Crl:CD-1(ICR)BR
- the significant findings of the study from 2009 are dismissed with historical data from a period ending more than 7 years before study initiation

Possible further mismatches cannot be assessed due to the lack of details in RAR and Addendum[1].

Table 2: Study data (as far as available) of the five valid mouse carcinogenicity studies used in the RAR (RAR Addendum 2015) as compared to the Charles River historical control pool.

Study	Strain	Study initiation	Study location
Charles River Historical Control data	*Crl:CD-1(ICR)BR*	*Between 1987 and 1996*	*Not disclosed in Addendum. Pool of 51 studies total is suggestive of data from various laboratories*
1983	CD-1, substrain not mentioned in RAR of 2015	Before 1983	Not disclosed in RAR of 2015
1993	CD-1, substrain not mentioned in RAR of 2015	Before 1993	Not disclosed in RAR of 2015
1997	Crj:CD-1	1995	Institute of Environmental Toxicology, Tokyo, Japan
2001	Swiss Albino	1997	Rallis Research Ctr., Rallis, India
2009	Crl:CD-1(ICR)BR	2005	Harlan Laboratories, Shardlow, UK

It should be noted that for the 2001 study valid historical control data (same strain, same laboratory) were available which actually confirmed the validity of the observed significant increase of the incidence of malignant lymphoma as described in detail in the RAR of March 2015 (Volume 3, B 6.5.2.). There it is stated (emphasis added): "The incidence was statistically significantly elevated as compared to the actual control groups in this study, was above the mean values of the (relatively small) historical control and, for males, outside the historical control range." Concealing this fact and using an absolutely inappropriate data base the BfR now bluntly states the untruth by saying: "Also in the study with Swiss mice, which have considerably higher background incidences for malignant lymphomas, the observed incidences were within the historical control range." (Addendum p.92, emphasis added).

A similar contradiction can be found within the 31 March 2015 version of the RAR itself, related to the study from 2009. There, it was described that historical control data were requested from the laboratory that conducted this study, but the historical control data supplied were unusable. In Volume 3 it is stated: "However, the quality and regulatory value of the historical control data is very much compromised ..." RAR of March 2015 (RAR, Volume 3, p. 509). In contrast, in Volume 1 of the RAR it is stated that the observation of "slightly higher incidences in top dose males" (in fact this was a significant increase) was

[1] The gaps highlighted in this assessment underscore the importance that all study reports used for regulator decisions are made publicly available as demanded by civil society (e.g. http://www.pan-europe.info/sites/pan-europe.info/files/public/resources/campaigns/pesticides/2015_10_29ngo_letter_glyphosate.pdf)

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 Crl: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%".

More importantly, for the study from 1997 it is documented in the RAR of 31 March 2015 that the observed decrease in body weight gain was related to a decrease in food consumption. In fact, the reduction of food consumption and the depression of body weight gain were even greater in the females of this study which did not exhibit any significant increase of any type of tumours. In addition, it is well-known that body weight and spontaneous tumour incidences are positively correlated (cf. OECD 2012, p. 133-134). This means, if the body weight is reduced due to lower food consumption, it may result in a lower incidence of tumours. The conclusion is that the increased tumour incidences observed in the high dose group of the 1997 study could have been even higher (and not lower!) if the body weight gain had not been reduced in the glyphosate treated groups.

Finally it should be noted that a significant increase of tumour incidences was also observed in studies with top doses of 1000 mg/kg (study from 1993) and 810 mg/kg (study from 2009).

In conclusion, the argument of "excessive toxicity" has no factual basis in the studies reported.

Old distortions repeated and new ones added by the EFSA

On 12 November 2015 the EFSA published its opinion on the RAR (EFSA 2015). In the part dealing with the mouse carcinogenicity studies it discusses in detail the study of 2001, i.e. the one which exhibited a statistically significant increase of malignant lymphoma using the statistical method of pairwise comparisons. Furthermore, the EFSA repeats arguments presented earlier by the BfR concerning the presumed lack of statistical significance in the other studies (see above), echoes the BfR statements claiming that carcinogenic effects were only seen at high dose levels and that historical control data are sufficient to dismiss the findings.

The 2001 study

On page 10 of its Conclusion, the EFSA acknowledged that this "study with Swiss albino mice showed a statistically significant increased incidence of malignant lymphomas at the top dose of 1460 mg/kg bw per day" (EFSA 2015). But subsequently the EFSA dismissed this observation, claiming that the increased incidence of malignant lymphomas

(a) "occurred at a dose level exceeding the limit dose of 1000 mg/kg bw per day recommended for the oral route of exposure in chronic toxicity and carcinogenicity studies";

(b) "was not reproduced in four other valid long term studies in mice"; adding that

(c) "(t)he large majority of the experts had considered it highly unlikely that glyphosate would present carcinogenic potential due to the generally recognised high background incidence of malignant lymphomas in this strain"; and that

(d) "(t)he study was re-considered during the second experts' teleconference (TC 117) as not acceptable due to viral infections that could influence survival as well as tumour incidence – especially lymphomas".

Here it is contended that the following reasons these EFSA claims are false:

Claim (a): Dose level exceeding the limit dose

This false claim is discussed in detail together with the considerations on the high dose level of the other studies (see paragraph on Excessive Toxicity above.)

Claim (b): Incidence of malignant lymphomas not reproducible in other studies

This is a false claim. As it can be seen in Table 1 a significant increase in malignant lymphoma was identified in the majority of the studies (3 out of 5) when the appropriate statistical method, i.e. trend test, is used. In addition to the statistical significance *per se* the higher incidence of malignant lymphoma increased dose-dependently in two of the three studies (Table 3). This is important to note, because such a dose-dependence supports the biological relevance of the observations of carcinogenic effects.

Table 3: Percent incidence of malignant lymphomas in male mice in the three studies with statistical significance. Note: CD-1 mice were used in the studies of 1997 and 2009, and Swiss albino mice in the study of 2001.

Year	*Control*	*Low-Dose*	*Mid-Dose*	*High-Dose*
1997	4 %	4 %	0 %	12 %
2001	**20 %**	**30 %**	**32 %**	**38 %**
2009	**0 %**	**2 %**	**4 %**	**10 %**

Claim (c): No carcinogenic potential due to high background incidence

This is false claim. In this particular study the relatively high background incidence has to be put into perspective by the historical control data for this particular mouse strain and this particular laboratory. It should be noted that this is the only the five studies which in fact has valid historical control data, and that these control data support the finding of a glyphosate-induced increase in malignant lymphoma instead of invalidating them.

As stated in the RAR, the observed significantly increased incidence of malignant lymphoma in males of the high dose group was not only above the mean value of historical controls, but even “outside the historical control range” (RAR Volume 1, p.63).

In line with applicable OECD guidance “that the concurrent control group is always the most important consideration in the testing for increased tumour rates” (OECD 2012, p. 135), the high background incidence does not invalidate the even higher and in the top dose statistically significantly higher incidence in the glyphosate-treated groups.

Finally, using the Cochran-Armitage-Trend Test, a significant increase in malignant lymphomas was also observed in the two studies that used different mouse strains (Crj:CD-1, Crl:CD-1(ICR)BR) which have a clearly lower background incidence.

Claim (d): Study not acceptable due to viral infections

This is a false claim. The wording used in the *EFSA Conclusion* (“study was … not acceptable due to viral infections …”) is suggestive of a proven viral infection in this study, which supposedly contributed to the high spontaneous rate of malignant lymphoma. However, this is not true. In the RAR (Volume 1, p.63) it is clearly stated: “No information is available on possible abundance of such viruses in the mouse colonies from which animals

used in the glyphosate studies were obtained." Instead, reference is made to the paper by Taddesse-Heath et al. (2000) who in general "emphasized the contribution of widespread infections with murine oncogenic viruses to the high, remarkably variable incidence of tumours of the lymphoreticular system." RAR (Volume 1, p.63)

No evidence is provided in the RAR that the mice used in the 2001 study were infected by oncogenic viruses. The EFSA statement cited above is clearly misleading aimed at discrediting the findings of the 2001 study.

Lack of consistency in multiple animal studies

The EFSA contends that "(n)o evidence of carcinogenicity was confirmed … due to … lack of consistency in multiple animal studies" (EFSA 2015, p11). This claim is not supported by evidence.

As it can be easily derived from Table 1, it was possible to replicate the following findings:

(a) a significant increase in malignant lymphoma in three out of five studies (in two studies with a clear dose-dependence);

(b) renal tumours in three out of five studies; and

(c) haemangiosarcoma in two out of five studies.

This leads to the conclusion that in fact the results were consistent.

Slightly increased incidences only at dose levels at or above the limit dose/Maximum Tolerated Dose

This is a false statement. This statement is not true even if one would accept the wrong claim by the EFSA that there is a "limit dose" of 1,000 mg/kg body weight for carcinogenicity studies. A significantly increased incidence of malignant lymphoma ($p<0.01$) was also seen at 810 mg/kg in the 2009 study (Table 1).

Most importantly however, there is no "limit dose" defined in the OECD guideline for carcinogenicity studies (OECD 2009a, OECD 2009b). OECD guidance No. 116 refers to both, carcinogenicity studies (Guideline No. 421, OECD 2009a) and chronic toxicity studies (Guideline No. 422, OECD 2009b). In this guidance the term "limit dose" is not used, but a top dose of 1,000 mg/kg is mentioned as an option: "As indicated in the Test Guidelines, a top dose not exceeding 1,000 mg/kg body weight/day may apply except when human exposure indicates the need for a higher dose level to be used." (OECD 2012, p. 66). Pointing to "Test Guidelines" (in plural) includes Guideline No. 422 (Chronic toxicity studies) where the term "limit dose" is used and defined at 1,000 mg/kg. From that it becomes clear that EFSA's reference to the term "limit dose" and to a 1,000 mg/kg-limit in the context of carcinogenicity is wrong.

For investigating the carcinogenic potential of a compound, Guideline No. 421 (OECD 2009a, p. 5) recommends a concept designated the Maximum Tolerated Dose (OECD 2012, p. 53). According to this concept "the highest dose level should normally be chosen to elicit evidence of toxicity, as evidenced by, for example, depression of body weight gain (approximately 10%)" (OECD 2009a, p. 5). In addition to making reference to a "limit dose", the EFSA claims that the Maximum Tolerated Dose (MTD) was exceeded. This claim is

explained in Addendum 1 to the RAR. Referring to the observation of an increased incidence of renal tumours it is stated there: “A confounding effect of excessive toxicity cannot be excluded at the highest dose of 1460-4841 mg/kg bw/d. In both studies in CD-1 mice but not in Swiss albino mice, the body weight gain was decreased by more than 15% compared to controls, but mortality/survival was not affected (Addendum 1, 2015, p.ii).” What EFSA and the BfR neglect is that the concern with regard to a decreased body weight gain is because it could mask carcinogenic effects rather than exaggerating them: “It is now recognised that there is a positive correlation between body weight and the occurrence of certain tumours in rodent species and strains used in safety assessment or for hazard identification; … Moreover, the lower the body weight, the less sensitive the animal may be to agent-induced toxicity, including cancer.” (OECD 2012, p. 64). Finally, it should be noted, that the decreased body weight gain – at least in the study where the data were available (study of 1997, Volume 3, p. 522) – was obviously caused by a lower food consumption casting further doubt on the “excessive-toxicity”-argument.

Summary and conclusion

The Glyphosate Task Force provided data for the re-approval of glyphosate in the European Union, claiming that glyphosate has “no oncogenic potential”. The submitted dossier included the reports on five mouse-studies that had not been evaluated by the appropriate statistical test, as recommended in the OECD Guidance 116.

The German Federal Institute of Risk Assessment (BfR), i.e. the authority in charge of the Renewal Assessment Report for glyphosate agreed with this conclusion, stating: “Classification and labelling for carcinogenicity is not considered appropriate by the RMS“. When the WHO’s International Agency for Research on Cancer (IARC) announced that it considers glyphosate “as probably carcinogenic to humans”, a conclusion which subsequently was supported by IARC’s monograph on glyphosate, the BfR and the EFSA used various arguments to dismiss the finding of carcinogenic effects of glyphosate in their own Renewal Assessment Report. In the document presented here, the handling of the results of mouse carcinogenicity studies by the BfR and the EFSA has been analysed as an emblematic example. The evidence provided above shows that the arguments used by the BfR and the EFSA have neither a formal nor a scientific basis. Bold distortions of facts by these two institutions have been identified in their attempt to defend their wrong conclusion that glyphosate does not show carcinogenic effects in five long-term mouse studies and, therefore, does not pose a carcinogenic hazard. This attempt includes the use of the inadequate methods of statistical data analysis, and the presentation of distorted or falsified facts to defend this inadequate use. Besides others, these distortions or falsifications refer to historical control data, excessive toxicity, presumed viral infections of study animals, and lack of reproducibility between different studies.

The distortions or falsifications become obvious, because of contradictions within the different parts of the Renewal Assessment Report itself and by cross-referencing the claims made by BfR and EFSA against applicable guidelines, guidance and legislation. This leads to the conclusion that the two authorities in complicity with the Glyphosate Task Force deny a proven carcinogenic hazard facilitating glyphosate’s re-approval in the European Union.

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

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

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

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

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