ATTACHEMENT 1

Evidence why the increase in malignant lymphoma is <u>NOT</u> "equivocal"

All five guideline compliant mouse carcinogenicity studies exhibited a statistically significant increase in tumour incidences. Here, we concentrate on malignant lymphoma, because

(a) there was a statistically significant increase in this tumour type in three of the five studies while studies with non-significant findings are invalid (4th study) or questionable (5th study);
(b) this finding was supported by "limited evidence in humans", i.e. non-Hodgkin lymphoma;
(c) in general, the findings were supported by mechanistic evidence (oxidative stress, genotoxicity).

Nonetheless, the evidence for glyphosate-induced malignant lymphoma was characterized as "equivocal" (Dossier p. 73), allegedly because of:

1. partly contradictory study outcomes, depending on the statistical method applied;
2. inconsistent dose response in the individual studies;
3. a highly variable tumour incidence as suggested by historical control data;
4. a possible role of oncogenic viruses that should not be ignored;
5. doubts about human relevance, if occurring only as a high-dose phenomenon.

Before addressing these five items it is important to take note of an important error committed by the Dossier's authors with regard to the use of the data on malignant lymphoma of the Atkinson et al. (1993) study. They missed or ignored the fact that the incidences reported for the Atkinson study were limited to the "histological examination of lymph nodes with macroscopic changes" (see footnote in Table 31, page 68). Therefore it is misleading and totally inappropriate to use these data. This is particularly important, because it is one of the two studies not showing a significantly increased incidence in malignant lymphoma, compared to a significant increase in male mice of three other studies. It cannot be excluded that, using a proper histopathological assessment, the Atkinson et al. (1993) study too would show a dose-dependent, statistically significant increase of malignant lymphoma.

<u>Item 1:</u>

The statement "<u>contradictory</u> study outcomes" is wrong and misleading for several reasons.

First, the incidence of malignant lymphoma was higher in glyphosate treated groups of all five studies. In addition, in Table 31 the findings for the 1993 study by Atkinson et al. carry the footnote "based on histological examination of lymph nodes with macroscopic changes". Such an incomplete histopathological assessment is inacceptable and **renders the Atkinson et al. (1993) study as non-compliant with applicable guidelines as far as malignant lymphoma are concerned.** Therefore, it is wrong to refer to the Atkinson et al. (1993) study at all and it is futile to claim: "In the study by Atkinson et al. (1993, TOX9552382), in contrast, there was no dose response and the incidence in the control group was similar to that at the top dose level" (Dossier, p. 68). Besides the incomplete assessment (because of limiting histopathology to macroscopic findings) the data presentation is

wrong, i.e. when only lymph nodes with macroscopic changes have been assessed, the ones with histopathologically identified lymphoma should not be put into relation to the 50 animals per group, but to the number of animals with macroscopic changes in lymph nodes. Also, it should be noticed that Table 30 (page 67) contains the remark "Equivocal evidence of enlarged/firm thymus" for the Atkinson et al. (1993) study. No comment is given for the histopathology of this macroscopic finding which is another indication of incomplete histopathological assessment which would render this study as inacceptable.

The other study with no significant increase in malignant lymphoma (Knezevich and Hogan 1983) should be scrutinized concerning the histopathological terminology to clarify whether "lymphoblastic lymphosarcoma" with or without leukemia (Dossier, p. 68, Table 32) are equivalent to "malignant lymphoma" or not. An evaluation based on "assumptions" (cf. Dossier, p. 71) should not be accepted. While according to modern terminology tumours of lymph nodes, spleen and thymus are subsumed under the term "lymphoma", such tumours were e.g. separated into "lymphoma" and "thymoma" in the past. Because it is not clear to which organs the "lymphoblastic lymphosarcoma" and whether a distinction between "lymphoma" and "thymoma" was made, the summary data of this study cannot be used unless it can be clarified from the descriptions in the original report and its raw data.

Finally, the statement "partly contradictory study outcomes, depending on the statistical method applied" is misleading and appears to be a "constructed" contradiction. This statement refers to the use of trend tests as compared to pairwise comparisons (all studies) and the use of the Z-test as compared to Fisher's exact test for the studies by Kumar (2001) and by Wood et al. (2009). In the Dossier itself, in a different paragraph (p. 71), it is explained that "significance in either kind of test (i.e., trend test or pair-wise comparison) was sufficient to reject the hypothesis of a chance event", citing from OECD Guidance 116 (OECD 2012). Therefore, the malignant lymphomas that were found statistically significant by the trend tests in the three studies must not be considered as "chance events". Moreover, the trend test is more suitable when one expects a dose-response relationship. In the case of the Kumar study (2001) the incidence of malignant lymphoma of male mice was assessed with three different statistical methods: (a) the Z-test which yielded a significant increase of $p = 0.002$ for the high-dose, (b) the "more usual" Fisher's exact test which yielded $p = 0.077$, and (c) the Cochran-Armitage trend test across all groups which had a p of 0.065. According to Table 34 of the Dossier, the Wood et al. (2009)-study was assessed using the Chi-square-test ($p = 0.067$), Fisher's exact test ($p = 0.056$), three different versions of the Z-test ($p = 0.0220$, $p = 0.0219$, $p = 0.067$) and the Cochran-Armitage trend test ($p = 0.0037$). Formally, some calculations reached statistical significance and others not. Nevertheless, when a $p = 0.05$ was applied as the criterion in these two studies, the p-values were close to significance. However, this presumed contradiction in the statistical analyses disappears completely, when the recommendation described in paragraph 384 of OECD Guidance 116 (OECD 2012) is taken into consideration, where it says: "In a carcinogenicity study, … a one-sided test may be considered more appropriate, ...". Using one-sided tests, all three methods (Z-test, Fisher's exact test and Cochran-Armitage trend test) yield statistical significance. Moreover, when discussing statistical relevance *vs.* biological significance, it is often forgotten that this applies in both directions. As paragraph 292 of OECD guidance 116 explains: "Similarly, declaring a result non-significant … should not be interpreted as meaning the effect is not biologically important ..." (OECD 2012). With increases of malignant lymphoma in glyphosate-treated males of all five mouse studies and indications of an association between glyphosate use and the incidence of non-Hodgkin lymphoma, this effect certainly should be considered biologically important.

Item 2:

It is wrong to state that the dose response in the individual studies is inconsistent.

Strain-specific differences in tumour incidences in general and in malignant lymphoma in particular are a well-known phenomenon. This is even acknowledged in the RAR. Therefore it is scientifically unjustified to draw conclusions of "inconsistency" from a direct comparison of the tumour incidence of studies using different strains, even when the top doses are comparable as for the Wood et al. (2009) and the Kumar (2001) study (cf. Dossier p.71). The authors of the Dossier seem to have missed that the incidences of malignant lymphoma in the control groups of these studies were different too. The important and consistent outcome of these two studies is a dose-dependent, statistically significant increase in malignant lymphoma.

Item 3:

It is misleading and unjustified to question the study results because of "a highly variable tumour incidence as suggested by historical control data".

First of all "it should be stressed that the concurrent control group is always the most important consideration in the testing for increased tumour rates" (OECD 2012, paragraph 398). Keeping this in mind, the main purpose of using historical control data is to facilitate an evaluation in the light of variable results. In this regard, it is important to emphasize that the only historical control data compliant with the recommendations of OECD guidance 116 (OECD 2012, p. 135-136) are those for the Kumar (2001) study which actually support the observation of a significant increase of malignant lymphoma in male mice. There is just one other study with "reliable historical control data on malignant lymphoma incidence from the performing laboratories" (Dossier, p. 71) - that of Sugimoto (1997). However, the presentation of the historical control data of that study in the Dossier is not compliant with the recommendation by OECD guidance 116 which recommends the use of the median and interquartile range of historical control data. These data are not presented. In addition, the upper range of the incidence (19.23%) can be suspected as a "rogue outlier" (OECD 2012, paragraph 400). Median and interquartile range are not presented for the Kumar (2001) study either, but in this case it does not play a role, because the incidences of the glyphosate-treated groups were at or above the upper range of the historical control data anyway.

Variation of tumour incidences between different laboratories, different strains and the known possibility of a background drift over time are the reasons why it is recommended to use data collected over the five last years, from the same strain and the same laboratory (OECD 2012, ECHA 2015). Therefore it is futile to compare the high-dose incidences of the Atkinson et al. (1997) and the Wood et al. (2009) study with the Charles River historical control database derived from studies in 11 different laboratories, using animals of four different breeding facilities, and performed over a period of 13 years (Dossier, p. 73). It is highly disturbing that the authors seem to have no problem doing this, while two pages before (Dossier, p. 71) they "of course" question the relevance of the valid historical control data of the Kumar (2001) study which are compliant with OECD criteria (!) "since it was based on observations in only five studies employing in total 250 untreated control animals per sex."

Item 4:

The call not to ignore "a possible role of oncogenic viruses" is not based on study-related evidence and only weakly supported by literature.

In the Dossier it is admitted for the study by Kumar (2001) that "in the study report itself, there was no evidence of health deterioration due to suspected viral infection" (p. 72). Later it is attempted to discredit the observation of an increased incidence of malignant lymphoma with a "possible role of oncogenic viruses" (p. 73). One single paper (Tadesse-Heath et al. 2000) pointed out the relationship between lymphoma and the infection with oncogenic viruses. However the paper explicitly refers to CFW (=Swiss Webster) mice "from one source observed by two laboratories" (Tadesse-Heath et al. 2000, p. 6832). The word "widespread" does not occur in this publication. At the end of their paper the authors state: "It should be noted that the several strains of outbred and inbred Swiss Webster mice designated as CFW in use in the United States and in Europe should not be considered to be identical. We have examined only one population for the highlymphoma–high-MuLV-expression phenotype" (Tadesse-Heath et al. 2000, p. 6836). Therefore, it should be scrutinized how the authors of the Dossier came to the conclusion that Tadesse-Heath et al. "emphasised the contribution of widespread infections with murine oncogenic viruses to the high but remarkably variable incidence of tumours of the lymphoreticular system in this species" (Dossier p. 72). Also, the Dossier refers to Wogan and Pattengale (1984) who came to the conclusion that "since it is possible that many other species, including man, carry undetected oncogenic virus which may act with chemicals to increase tumour burdens, considerations of viral carcinogenesis do not totally resolve the questions concerning the significance of mouse lymphoma in safety testing, except to point out that the prevalence of oncogenic viruses in mice may make them highly susceptible to the induction of lymphoma, leukaemia, and perhaps other neoplasms" (Dossier, p.72). Such a prevalence, however, is unknown in the case of the Kumar (2001) study, where "there was no evidence of health deterioration due to suspected viral infection" (Dossier, p. 72). Therefore, the exclusion of the Kumar (2001) study because of a suspected viral infection has no factual basis.

Item 5:

Doubts about "human relevance, … if occurring only as a high-dose phenomenon" are unjustified

The simple reason is that the occurrence of malignant lymphoma was not a high-dose-only phenomenon. As explained above, there are three studies remaining concerning malignant lymphoma[1] which all showed a significantly increased incidence. Two of these studies exhibited a statistically significant dose-dependent increase across all dose-group. Moreover, the top-doses of these two studies were at 810 mg/kg body weight (Wood et al. 2009) and at 1460 mg/kg body weight (Kumar 2001). In other words, the top dose of the Wood et al. (2009) study was below and that of Kumar (2001) was only slightly above the 1.000 mg/kg considered as a "limit dose" in OECD Guideline 422. Therefore, the claim that malignant lymphoma were "occurring only as a high-dose phenomenon" (Dossier, p. 73) is false and is not supported by evidence.

[1] One of the two studies not showing an effect is unacceptable with regard to the quality of the histopathological evaluation of malignant lymphoma, while the other one needs scrutiny with regard to tumour classification.

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ATTACHMENT 2

"Limited evidence in humans" needs to be taken into consideration

In the Dossier (p. 96) it is stated: "The DS concluded in accordance with IARC (2015) *'There is limited evidence in humans for the carcinogenicity of glyphosate.',* considered as "the best description", because "Evidence suggesting lack of carcinogenicity", "Inadequate evidence of carcinogenicity", and "Sufficient evidence of carcinogenicity" where not considered suitable.

This "limited evidence" (in accordance with IARC's assessment) should not be discussed in isolation, but needs to be seen as supportive of the evidence provided by the animal studies. Similar tumours associated with glyphosate exposure were seen in mice (malignant lymphoma) and in humans (non-Hodgkin lymphoma, NHL), though epidemiological data where considered as "limited evidence" by both, the IARC and the DS. No room was given in the Dossier for an overarching evaluation of human data together with animal data which both point into the same direction. However, this would have been the appropriate attitude for a "weight of evidence approach".

In an attempt to weaken the "limited evidence" classification for human data, the Dossier refers to the United States' Agricultural Health Study (AHS) as "the largest and most convincing study" where no effect of glyphosate was demonstrated. However, this largest and most convincing study "had only 92 cases of NHL in the unadjusted analysis as compared to 650 cases in a pooled case-control study from the USA" according to Portier et al. (2016), which actually demonstrated a statistically significant association between glyphosate use and increase NHL incidence (De Roos et al. 2003). Another critique was that the median follow-up time in the AHS was only 6.7 years, a period unlikely to be long enough to account for cancer latency (Portier et al. 2016). Furthermore, in the RAR, all case-control studies were classified as "not reliable" because, for instance, allegedly information on glyphosate exposure, smoking status and/or previous diseases was not assessed. However In most cases, this is contrary to what is actually described in the publications (cf. Portier et al. 2016). For detailed examples of unjustified dismissals of these studies see Greiser (2016).

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ATTACHEMENT 3

Mechanistic evidence / Oxidative stress

The IARC assessed that the carcinogenicity found in animal studies on glyphosate is supported by strong mechanistic evidence, i.e. genotoxic effects and oxidative stress. In the following, the oxidative stress part is discussed. The Dossier (p. 93) refers to the Addendum of the RAR and states that "it was concluded in the addendum that from the sole observation of oxidative stress and the existence of a plausible mechanism for induction of oxidative stress through uncoupling of mitochondrial oxidative phosphorylation alone, genotoxic or carcinogenic activity in humans cannot be deduced for the active substance glyphosate and glyphosate based formulations."

As explained in Attachments 1 and 2 of this comment, the "deduction" of carcinogenicity is not based on the "sole observation" of oxidative stress. Rather this observation is considered as supportive evidence of the demonstrated increase of tumour incidences, in particular of malignant lymphoma, in animal experiments. Similar to the evidence derived from epidemiology, findings of oxidative stress caused by glyphosate should be part of an overarching assessment and of an appropriate weight of evidence approach. Such publications help to fill the knowledge-gap that exists, because the measurement of oxidative stress parameters is not part of carcinogenicity bioassays or any other guideline-driven study designs.

In the RAR, publications on oxidative stress caused by glyphosate or glyphosate-based formulations (GBFs) were not considered at all in the context of carcinogenicity. Therefore the statement, "For detailed mechanistic information on e.g. oxidative stress please refer to the addendum to the RAR or to the RAR …" (Dossier p. 93) is misleading. Only after the IARC monograph (IARC 2015) was published this item was addressed in the Addendum to the RAR. However, in the Addendum only the studies referenced in the IARC monograph were taken into account. No additional studies were considered. But according to the Guidance for the application of CLP criteria "the mode of action and its relevance for humans" belongs to the "more important" additional considerations as part of the weight of evidence approach (ECHA 2015, p. 374, see also Dossier, p. 96). Therefore, the fact that the Dossier ignored further evidence of oxidative stress after exposure to glyphosate or GBFs represents an important omission.

The 22 references listed below, including seven studies in rats and mice or their tissue/cells, that have not been addressed in the Addendum to the RAR need to be taken into consideration. In these studies oxidative stress for the active substance glyphosate or GBFs after various routes of exposure and different doses or concentrations in rats, mice, tadpoles and fish were investigated. Some of these studies used glyphosate and GBFs in parallel, enabling a direct comparison.

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