

## **Assessment of the BfR concerning epidemiological studies on carcinogenic effects of glyphosate in the context of the EU active substance review**

BfR background information No. 034/2015, 28 September 2015

Within the context of the EU active substance review of glyphosate, the Federal Institute for Risk Assessment (BfR) has comprehensively reviewed and evaluated more than 1,000 studies, documents and publications. These include epidemiological studies on the assessment of the carcinogenicity of glyphosate. Based on these studies, the BfR arrives at a similar assessment to that of the other 27 pesticide assessment authorities of the European Union and equivalent authorities in other countries, as well as the International Agency for Cancer Research (IARC). The evidence for the carcinogenicity of glyphosate in humans based on the epidemiological studies is considered to be "limited". This assessment was published as "background information" on 22 September 2015 (<http://www.bfr.bund.de/cm/343/bfr-hat-die-epidemiologischen-studien-zu-glyphosat-umfassend-geprueft.pdf>).

Although this assessment by the BfR is currently undisputed in international scientific expert circles, the studies that contain alleged indications of a cancer risk to humans are now outlined in more detail below in response to the increasing number of inquiries received by the BfR.

### **1 Current situation**

Discussion is currently ongoing in the press and the public arena regarding the relevance of several epidemiological studies on the possible carcinogenic effects of glyphosate (study by DeRoos et al., 2003, study by Hardell et al., 2002, and study by Arbuckle et al., 2001).

The BfR has reported in detail on these studies in the revised renewal assessment report (RAR). This report includes the full, unaltered abstract, in other words the summary and the conclusion of the study authors. In addition, the report of the BfR also comments that, in individual cases, the submitted original scientific papers on the implementation of the epidemiological studies fail to include important technical information that is necessary in order to be able to assess the robustness of the conclusions. This does not mean, however, that these studies were therefore excluded from the overall assessment of glyphosate or that the study findings were not taken into consideration for this reason.

The first draft of the BfR report with commentary that is currently the subject of debate has been revised twice in the meantime and supplemented with an addendum to the report by the IARC (2015). The assessment of the epidemiological studies on the carcinogenicity of glyphosate in humans by the BfR is generally in line with the IARC assessment.

So that a comparison of the epidemiological studies could even be made, the BfR, in its' statement concerning the IARC report, used the same criteria given in the IARC report. In addition, it also employs the rules set out in the relevant guidelines, for example the so-called STROBE criteria (<http://www.strobe-statement.org>).

### **2 Scientific assessment**

#### *Assessment of the study by DeRoos et al., 2003*

The RAR reported in detail on the study by DeRoos et al. (2003), and the entire abstract of the study was included. In addition, however, a brief commentary pointed out that various confounding factors had not been taken into consideration.

The study by DeRoos et al., 2003 is an analysis of data merged from 3 individual studies (Zahm et al., 1990; Hoar et al., 1986; Cantor et al., 1992). However, the publication does not report on the procedure for the combination and evaluation of the widely varying data sets:

The study by Zahm et al. investigates a totally different substance, namely 2,4-dichlorophenoxyacetic acid (2,4-D for short), which is not chemically related to glyphosate. This study is therefore completely unsuitable for an assessment of glyphosate.

The study by Hoar et al. does not focus on the active substance glyphosate but only names "herbicides" in general as the factor under investigation.

Although the study by Cantor et al. reports on smoking habits of the subjects, it does not report on other possible confounding factors listed in the commentary of the BfR on the study by DeRoos et al., 2003 (such as the use of prescribed medications).

Despite all these technical limitations, the study by DeRoos et al. was not excluded from the assessment. Contrary to speculation in the public arena and the press suggesting that this was not the case, the study was included as an important element in the BfR assessment of the carcinogenicity of glyphosate in humans and reviewed once again in 2015 in response to the report of IARC (2015). This assessment arrived at the conclusion that the study does not provide any "unequivocal evidence" for a connection between glyphosate exposure and *non-Hodgkin lymphoma*. In addition, it was confirmed once again that the study has limitations in terms of reporting, in particular with regard to the description of study design, analysis and findings.

The assessment by the BfR largely corresponds to the IARC assessment (2015). Both IARC (2015) and the BfR summarise their assessment as follows: "low power of the study to assess risk of NHL associated with glyphosate" and "not controlled for exposure to other pesticides" (IARC 112).

#### *Assessment of the study by Hardell et al., 2002*

The study by Hardell et al. (2002) was also outlined in detail in the RAR, together with comments on the limitations of the study. It was noted that the study report does not contain any details on duration of exposure, exposure concentration, patient history and lifestyle factors.

The study merges two studies that examined different toxicological endpoints (NHL, hairy cell leukaemia). In this particular case, the merging of the studies is questionable not only from a biological point of view. This practice of combining different toxicological endpoints without adequate substantiation is not an accepted statistical method and is also criticised by the BfR from a toxicological perspective.

Nevertheless, the listed limitations did not lead to the exclusion of the study from the assessment. In agreement with the IARC assessment (2015), the BfR established that the study was of limited predictive power. Even after a repeat review by the BfR in 2015, the study was assessed as "not reliable" and as not relevant for the link between glyphosate and NHL.

The study by Hardell et al., 2002 incorporates the following primary studies: Hardell and Eriksson, 1999; and Nordström et al., 1998.

The study by Nordström et al. (1998) states that the affected persons were asked about their working history and for information about various exposures and leisure time activities.

However, this information is inadequately explained in the study. It is not possible to assess whether the study findings might have been influenced by chance, bias or confounding factors.

The study by Hardell and Eriksson (1999) states that the respondents were asked about previous working conditions, smoking habits, prior illnesses and dietary habits. However, the findings are not reported in the publication, nor does the study indicate the extent to which these or other factors, bias or chance might have influenced the results.

In agreement with the assessment of IARC (2015), the BfR comes to the conclusion that the study has limited power to detect an effect.

#### *Assessment of the study by Arbuckle et al., 2001*

The study by Arbuckle et al. (2001), which does not concern the issue of carcinogenicity, is described and commented on in detail in the RAR.

Among other things, this report includes the full unaltered abstract, so that readers can take note of the conclusions of the study authors in their original form. In connection with the study description, the report also outlines criticism of this study by another group of scientists<sup>1</sup>.

Moreover, the publication of Arbuckle et al. (2001) is cited at various points of the RAR as other studies also refer to it.

This study is not mentioned in the summary as it did not provide any evidence for toxic effects of glyphosate on reproduction in humans.

This means that the trivial description "pregnancy poison" sometimes used in connection with glyphosate is not proven by this study, is not scientifically justifiable and is also misleading.

In addition to the aforementioned studies, the following studies on the carcinogenicity of glyphosate were also discussed in the public arena and in the press:

#### *Assessment of the study by Orsi (2009):*

In agreement with the IARC, the BfR cannot identify any connections between glyphosate and NHL. In the summary of their findings, the authors themselves did not consider any positive association between tumours of the lymphatic system including NHL and glyphosate exposure to be worthy of mention.

#### *Assessment of the studies by Brown (1990, 1993):*

The BfR agreed with IARC that the study was insufficiently robust to serve as evidence of the effects of glyphosate. The authors came to the following conclusion: "This study, where over half of the subjects were farmers, found little evidence of an association between risk of MM and farming. These data also do not provide strong support for an association with specific agricultural chemicals."

In line with the stipulations of EFSA, the studies were not outlined in the first draft of the RAR as they were published before 2000. They were discussed in the Annex to the RAR in the comparison with the IARC assessment.

#### *Assessment of the study by Cocco (2013):*

The comprehensive epidemiological study by Cocco et al. (2013, published online in advance in 2012) investigated a possible influence of occupational use of pesticides on the

incidence of lymphomas in general and on B-cell lymphomas and their various sub-types in a total of 6 European countries. An increased risk for the development of chronic lymphatic leukaemia (CLL) was determined for the active substance class of organophosphates (OR 2.7; i.e. 2.7-fold increase in risk with a confidence interval of 1.2 – 7).

Alongside a number of other active substances, the authors consider glyphosate to belong to the group of organophosphates. From a chemical and toxicological point of view, however, there are fundamental differences between glyphosate and organophosphates, which are known to act as cholinesterase inhibitors.

As the data on CLL refer to organophosphates overall and as glyphosate is not assessed as an individual substance, this analysis has no predictive power for the active substance glyphosate.

In a further evaluation, exposure to glyphosate was only considered in connection with B-cell lymphomas. The analysis included 4 cases of disease with prior exposure as well as 2 non-diseased control persons who had also been exposed. These case numbers are too low to allow robust evaluation. Although there was a 3.1-fold increase in risk, the confidence interval of 0,6 to 17.1 was extremely wide.

### 3 Literature

Interested parties can request the full list of references by sending a mail to [bfr@bfr.bund.de](mailto:bfr@bfr.bund.de).

**More information on this topic is available on the BfR website:**

[http://www.bfr.bund.de/de/a-z\\_index/glyphosat-126638.html](http://www.bfr.bund.de/de/a-z_index/glyphosat-126638.html)

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i Williams, A.L.; Watson, R.E.; DeSesso, J.M. (2012): Developmental and Reproductive Outcomes in Humans and Animals After Glyphosate Exposure: A Critical Analysis. J. Toxicol. Env. Health, Part B, 15, 39-96.