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New meta-analysis of glyphosate-based plant protection products does not alter the assessment of the active substance

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If used properly and for its intended purpose, glyphosate is not carcinogenic. This was the conclusion arrived at by the German Federal Institute for Risk Assessment (BfR) and numerous other national and international authorities. A new meta-analysis in which already published studies are evaluated collectively does not alter the assessment of the BfR.

In the meta-analysis, Luoping Zhang, University of California, Berkeley, and her team pursued the question of whether people who used plant protection products containing glyphosate (such as farmers and gardeners) had an increased risk of contracting Non-Hodgkin Lymphoma (NHL), a form of lymph node cancer. To this end, the scientists evaluated updated data from the "Agricultural Health Study" (AHS), a large-scale cohort study, and five case-control studies.

The researchers' analysis concluded that people who had the greatest exposure to plant protection products containing glyphosate contracted NHL more often than persons with lower or no exposure. This result is supported, in the view of the authors, by previous experiments with animals and "mechanistic" studies in which the causes were sought. It is suggested that there is a "compelling" link between the uptake of glyphosate-based plant protection products and an increased risk of NHL.

The BfR has a different opinion. Although the meta-analysis with its reference to glyphosate-based plant protection products is interesting from a scientific point of view, it involves great uncertainty: It could not be determined with sufficient accuracy in the studies how much glyphosate the study participants were actually exposed to. It should also be taken into account that according to the current state of knowledge, farmers in the USA can come in closer contact with plant protection products containing glyphosate (e.g. because larger areas are treated or because it is often sprayed from aircraft).

Several of the case-control studies used by Zhang and colleagues found an increase in the NHL risk. These studies should only be given very limited consideration, however, when assessing the active substance glyphosate, as no distinction can be made between glyphosate and the various co-formulants contained in the products that were spread. Furthermore, it was not taken sufficiently into account in several studies that the farmers were possibly exposed to other plant protection products too.

Even though the meta-analysis presents a weak connection between the uptake of glyphosate-based plant protection products and the risk of NHL, this result involves considerable uncertainty in the corresponding studies. When all of the findings are viewed together, therefore, a causal connection between exposure to (contact with) the active substance glyphosate and the occurrence of NHL has still not been substantiated, in the view of the BfR.

In concurrence with the International Agency for Research on Cancer (IARC), the BfR established "limited evidence" of a connection between exposure to glyphosate-based plant protection products and Non-Hodgkin Lymphomas (NHL) in an overall assessment of the epi-

demiological data made in August 2015¹. In the conclusion of the peer reviews and final expert meeting, this connection was evaluated as providing “very limited evidence” in the assessment of the European Food Safety Authority (EFSA). In addition to the CLH dossier (harmonised classification and labelling), the European Chemicals Agency (ECHA) conducted its own assessment of the epidemiological studies and confirmed that several case-control and meta-studies show a weak connection between exposure to glyphosate-based plant protection products and NHL. The Risk Assessment Committee (RAC) of the European Chemicals Agency (ECHA) concluded in 2017, however, that the criteria for classification as carcinogenic are not satisfied in the overall view of epidemiological examinations².

The publication “*Exposure to Glyphosate-Based Herbicides and Risk for Non-Hodgkin Lymphoma: A Meta-Analysis and Supporting Evidence*”³ by Luoping Zhang et al. (2019), presents an analysis of already published epidemiological studies⁴. Zhang and colleagues (2019) analysed the connection between the occurrence of NHL and high exposure to glyphosate-based herbicides (GBH) in the Agricultural Health Study (AHS). High exposure to GBH is understood here to be exposure which is high in a group comparison. Zhang et al. (2019) identify high exposure in the AHS study on the basis of the cumulative exposure of users. As the BfR does not have any comparable information on applications in the European Union (EU), a comparison with the customary exposure of users in the EU is not currently possible. The AHS recorded data from plant protection product users in the US states Iowa and North Carolina. It is assumed that exposure was representative of these regions of the USA and the study period. The BfR does not have any reliable information, however, on whether the quantities of GBH used in the USA and Europe are comparable. The BfR is assuming that the treated area per user is higher in the USA than in Europe and that other application techniques (e.g. per aircraft) are also used.

Based on the data from five case-control studies from Sweden, France, Canada and the USA, as well as the newly updated results of the US-American AHS (Andreotti et al., 2018), the analysis conducted by Zhang et al. shows an increase of approx. 41% in the relative risk of the occurrence of NHL with high as opposed to lower GBH exposure (statistical uncertainty range: 13% to 75%). The strength of this connection is of the same magnitude as in previously published meta-analyses (Chang & Delzell, 2016; IARC, 2015; Schinasi & Leon, 2014) and equates to roughly 6 additional NHL cases a year per 100,000 highly exposed persons (e.g. farmers, uncertainty range: 2 to 11 cases).

Because several scientifically justifiable analysis scenarios were considered, it was possible to reduce the uncertainty of the estimation compared to previous meta-analyses. A reduction of the uncertainty when recording exposure and cases of disease in the underlying studies is not possible by means of the study by Zhang et al. (2019). Separate review of the analysed studies is not suitable for showing a connection between exposure to GBH and NHL. A comprehensive assessment of the study by Andreotti et al. (2018) in the context of all existing epidemiological studies based on the meta-analysis by Zhang et al. (2019) therefore complements the estimation of the BfR of 27 November 2017 of the separately reviewed publication by Andreotti et al. (2018).

The BfR estimates, therefore, that high GBH exposure could pose a moderately elevated risk of NHL. The causality of this connection cannot be substantiated by the available data, however. This is due to various reasons, such as the imprecise recording of exposure and the

¹ Addendum 1 to RAR of 31.08.2015.

² RAC Opinion on glyphosate of 15.03.2017.

³ <https://www.toxicologia.org.ar/wp-content/uploads/2019/02/1-s2.0-S1383574218300887-main.pdf>

⁴ Andreotti et al., 2017, *J Natl Cancer Inst*, 110, 509; De Roos et al., 2003, *Occup Environ Med*, 60, e11; Eriksson et al., 2008, *Int J Cancer*, 123, 1657; Hardell et al., 2002, *Leuk Lymphoma*, 43, 1043; Orsi et al., 2009, *Occup Environ Med*, 66, 291; McDuffie et al., 2001, *Cancer Epidemiol Biomarkers*, 10, 1155.

extent of exposure through the incorrect use of GBH and possible parallel exposure to other herbicides (which were not recorded in the same way in all studies).

It must also be taken into consideration that the EU active substance assessment as well as classification and labelling in line with the CLP regulation relate to the technical active substance. In the epidemiological studies, however, exposure to GBH was recorded as a matter of course. For this reason, no reliable statement can be made on the basis of the epidemiological studies as to whether the effects in question were caused by the active substance glyphosate or by co-formulants in the formulations, and/or enhancement of the glyphosate effects through co-formulants (the BfR already remarked in Addendum 1 to the RAR (2015) that sometimes significantly higher toxicity of GBH was detected compared to the pure active substance).

To reduce the great uncertainties of the epidemiological data requires the acquisition of additional data within the scope of an independent epidemiological study under user conditions in Europe. The BfR recommends the planning, funding and conducting of a study of this kind in Europe so that reliable statements can be made. This epidemiological study should contain an as precise as possible characterisation of exposure to plant protection products as it exists in Europe.

On the basis of the provisional estimation, the BfR concludes that the existence of a connection between exposure to GBH and NHL has become more plausible compared to the previous estimation, although the causality of the connection has still not been substantiated. To satisfy the criteria of the CLP regulation for classification as carcinogenic, however, these findings would have to be supported by other studies. Viewed overall, therefore, it would not be appropriate at the moment from a German point of view for the European authorities responsible for classification and labelling to look into the matter once again.

Moreover, the BfR suggests that the comparability of the authorised forms of use of GBH, including the quantities used and frequency of use in the USA and Europe, be reviewed. It could perhaps then be evaluated on this basis to what extent the above-mentioned estimations of additional NHL cases among highly exposed users can be transferred to the situation in the EU.

More information on this topic at the BfR website:

https://www.bfr.bund.de/en/a-z_index/glyphosate-193962.html

About the BfR

The German Federal Institute for Risk Assessment (BfR) is a scientifically independent institution within the portfolio of the Federal Ministry of Food and Agriculture (BMEL) in Germany. It advises the Federal Government and Federal Laender on questions of food, chemical and product safety. The BfR conducts its own research on topics that are closely linked to its assessment tasks.

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