Frequently asked questions regarding the different assessments of the carcinogenic effect of glyphosate by BfR and IARC

BfR FAQ, 11 December 2015

Following the Pesticides Peer Review *Experts*' *Meeting* at EFSA in February 2015 as part of the procedure for the renewed evaluation of the plant protection product glyphosate, the International Agency for Research on Cancer (IARC) of the World Health Organisation (WHO) classified the active substance as "probably carcinogenic to humans (Group 2A)".

Due to the assessment approach used, the assessment of IARC is not in line with the assessments of BfR, EFSA and the competent national, European and other international institutions including the WHO/FAO Joint Meeting on Pesticide Residues (JMPR). WHO itself has set up an “ad hoc expert task force" to clarify the reasons for the different assessments of the data by its own committees, IARC on the one side and JMPR on the other. This is known as a scientific divergence procedure within WHO, which has not yet been completed.

Following a renewed review of its assessment of the health risk, the Federal Institute for Risk Assessment (BfR) came to the conclusion that, based on current knowledge, no carcinogenic risk to humans can be concluded if glyphosate is used in the proper manner and for the intended purpose. The experts from the authorities of the 28 EU member states and the European Food Safety Authority (EFSA) also reviewed all documents. The outcome of the final expert discussion formed the basis for the EFSA Conclusion, which is in agreement with the assessment of BfR.

BfR has prepared questions and answers on the different assessments of the carcinogenic effect of glyphosate by BfR and IARC.

What are the reasons for the differing assessments of IARC and BfR?
IARC uses its own system for the classification of carcinogenic properties established in 1971 and adopted in 1987/1988, whereas a new "Globalised Harmonised System" has been introduced in the EU which is legally implemented in the CLP Regulation (*Regulation on Classification, Labelling and Packaging of Substances and Mixtures*).

IARC carries out a purely hazard-based analysis that is not designed to serve as a recommendation for governments and authorities. Hazard-based classification of carcinogens describes the cancer-causing property of an active substance. However, this kind of classification does not address the probability of cancer actually being caused if such an effect depends on the intake quantity of the substance in question.

In contrast, BfR conducts a risk-based assessment in the approval procedure for pesticide active substances. This takes into consideration not only the hazard-based analysis of a substance but also the estimated exposure, in other words the actual intake quantity of the substance, and uses this information to calculate the risk of cancer. In the EU, legally binding hazard-based classification is performed according to a separate procedure based on the CLP Regulation by the European Chemicals Agency (ECHA). BfR has initiated an assessment procedure for glyphosate based on the CLP Regulation.

What is the view of BfR on the IARC assessment?
The Federal Institute for Risk Assessment (BfR) reviewed the monograph of IARC on the health assessment of glyphosate published at the end of July 2015 and summarised the content in an addendum for the re-assessment of glyphosate within the framework of the EU active substances programme. Following a comprehensive review by experts from the authorities of the 28 EU member states and the European Food Safety Authority (EFSA), a majority of the experts determined in the final scientific assessment that, based on current knowledge, no carcinogenic risk to humans can be derived if glyphosate is used for the intended purpose and properly applied. In addition, classification as carcinogenic according to the criteria of the CLP Regulation was not considered necessary.

What were the reasons that led IARC to conclude that glyphosate probably causes cancer?
With regard to the question of a possible carcinogenicity of glyphosate, IARC evaluated epidemiological studies on humans as well as published industry studies on rats and mice, and mechanistic studies using the active substance as well as various unnamed pesticides containing glyphosate, all of which are publicly available. Based on the available epidemiological studies, IARC comes to the conclusion that there may be limited evidence for a statistically significant correlation between exposure to pesticides that also contain glyphosate and an increased risk of non-Hodgkin lymphoma.

IARC points to studies based on animal experiments using glyphosate and conducted by the industry as "sufficient evidence" for the probably carcinogenic effect of this pesticide active substance. IARC did not have access to the original studies. All competent authorities who had access to the original studies came to the conclusion that no carcinogenic risk to humans can be derived from the studies. These authorities also included the US-EPA and the JMPR panel of the WHO.

The results from these animal experiments were known to BfR and had already been included in the Renewal Assessment Report (RAR) within the framework of the EU active substances programme, based on the original studies to which IARC did not have access.

- Joint FAO/WHO Meeting on Pesticide Residues (JMPR) (2016)
  http://www.who.int/foodsafety/areas_work/chemical-risks/jmpr/en/

Does the assessment of IARC concern only the active substance glyphosate, as is currently being re-evaluated in the EU approval procedure?
No, IARC performed a joint assessment of the active substance and its main metabolite as well as various pesticides containing glyphosate. In the EU, on the other hand, pesticides containing glyphosate will only be assessed in the second phase - the zonal authorisation procedure - once the active substance has been approved. It was established that many of the studies and publications on possible carcinogenicity and genotoxicity that are currently the subject of discussion in the scientific world as well as the epidemiological studies did not use the active substance glyphosate in isolation (i.e. as a pure substance) but only as part of a formulation, in other words in the form of a commercially available product containing various other components. As the toxicity of the co-formulants may be higher than that of the active substance glyphosate, and as the exact composition of the test substance is frequently not described in articles in scientific journals, the informative value of the studies that used products containing glyphosate is generally low with regard to the active substance review within the framework of the EU approval procedure.

In its assessment report, did the BfR evaluate the same studies and sources as IARC?
With regard to the long-term studies on rodents that IARC viewed as providing sufficient evidence in animals, three findings from animal studies funded by the industry were included in the IARC assessment. These studies have already been assessed by the US-EPA and the JMPR panel at the WHO, and the result of the assessment was that no carcinogenic risk to humans is to be expected from glyphosate.

All findings to which IARC refers without access to the original data and using its own statistical methods, which are not covered by GLP and the test plans outlined in the OECD guidelines, were assessed by BfR in the RAR of April 2015 and in the addendum to the assessment report of 31 August 2015, together with numerous other carcinogenicity studies on rats and mice based on the original data, which are not publicly available.

With regard to the data on epidemiology, which was assessed by IARC as providing limited evidence in humans, BfR had already taken the corresponding core studies into account in the revised RAR of April 2015. In the addendum on the assessment of the IARC monograph of August 2015, BfR assessed further studies cited by IARC. In terms of the epidemiological conclusions, on which BfR generally agrees with IARC, these additional studies did not result in any change in the overall assessment.

In addition, the RAR contains numerous OECD-compliant studies that were not available to IARC. In particular, these were studies on mutagenicity that were conducted using the pure active substance in line with the legal data requirements. Studies that were either conducted using pesticides of unknown composition, that were tested on fish or plants, or the methodology of which was not clearly comprehensible or validated were not included in the original RAR.

In the addendum to the assessment report forwarded to the competent European authorities and meanwhile published by EFSA, BfR and the other EU member states fully reviewed all of the studies cited by IARC that were not previously contained in the RAR.

Is it in line with OECD guidelines if completed studies are evaluated using a different statistical method from that defined during the planning of the study?
A guidance document of the OECD (Guidance Document 116) stipulates that the statistical methods used for the evaluation of the data must be selected during the planning phase, in other words before the study begins. Pairwise statistical comparisons or trend tests are proposed for this purpose. For reasons of transparency, the addendum of BfR reviewed not only the statistical tests used in the original studies but also the trend test favoured by IARC in terms of its statistical results. However, according to the guidance document, statistical significance does not generally indicate biological relevance.

Did BfR overlook something in its assessment of the carcinogenicity of glyphosate?
No. The general public, the scientific community, political decision-makers, industry and non-governmental organisations already made their comments on the assessment documents considered up to November 2013 during the public and expert consultations on glyphosate organised by EFSA. When the IARC findings were made known following the conclusion of the EFSA expert discussion, the EU Commission issued an additional mandate to EFSA that the findings of the IARC should be taken into consideration in the approval procedure for glyphosate and extended the assessment period accordingly. As a result, all the findings listed in the IARC monograph were reviewed, described and conclusively discussed in the final assessment report of EFSA and in the addendum of BfR. This means that, in the EFSA Conclusion, the experts from the authorities of the EU member states and the European

Food Safety Authority (EFSA) did not overlook any relevant findings that were published up to July 2015 in their assessment of the carcinogenicity of glyphosate, and that they therefore complied with the legal requirements in the approval procedure for the active substance.

How does BfR view the "Open Letter" of some scientists to the EU Commissioner for Health and Food Safety?
The Open Letter was not signed by IARC itself. It was written by Christopher Portier, who was involved in the compilation of the IARC monograph on glyphosate as an invited specialist but not as a member. The initiator and author of the letter is an active member of the Environmental Defense Fund, a non-governmental organisation based in the USA. In other words, the letter is addressed to the EU Commissioner responsible for the further procedure not in the name of IARC, but by Christopher Portier together with other scientists who followed his call. It is the view of BfR that the letter does not contain any new scientific information that was not already assessed by EFSA and the European member states within the framework of the EU active substances programme.

The statements on the carcinogenicity of glyphosate made in the letter contradict the assessments of the competent national and international institutions including the WHO/FAO Joint Meeting on Pesticide Residues (JMPR). Following a review of all available studies by these institutions, the health assessment of the pesticide active substance glyphosate arrived at the conclusion that, based on the current data, a carcinogenic risk to humans is unlikely if glyphosate is used in the proper manner and for the intended purpose. This is also the assessment to date of the Environmental Protection Agency (EPA) in the USA and the competent Canadian authority (Canada Health).

BfR recommends principally that discussions on scientific studies, also and in particular controversial discussions of this kind, be conducted on a scientific level and in a transparent manner. The scientific publication process is an indispensable integral part of scientific work. Hypotheses or commentaries on studies can only be included in the process of scientific discourse if they have been published and if the conclusions drawn are transparent and comprehensible.

As the scientific assessment of the active substance glyphosate has been completed by the competent EU authority and the competent authorities of the member states, and as all articles and letters published thereafter did not provide any new findings, the responsible political bodies in the EU can now reach a decision based on the scientific assessment.

Do the differing conclusions challenge the quality of the scientific assessment of glyphosate by BfR?
No, the fact that separate committees assess issues differently due to divergent information and assessments of epidemiological data and experimental studies is a part of scientific work and the daily routine of scientific risk assessment processes.