Frequently asked questions on the assessment of the health risk of glyphosate

BfR FAQ, 1 March 2016

Glyphosate is one of the most widely used active substances in pesticides worldwide. Like any other active substance in a pesticide, glyphosate is regularly re-assessed within the framework of the EU evaluation of active substances to determine the risk to health and the environment as well as its efficacy. Germany is the Rapporteur Member State for the Community evaluation and assessment of glyphosate. In the re-assessment procedure, the BfR was commissioned to assess the health risk of the active substance and one representative formulation. For the purpose of health assessment, the BfR has reviewed and evaluated over 1,000 studies, documents and publications. The scientific assessment procedure for the active substance glyphosate has now been completed at the European level. The European Food Safety Authority (EFSA) has submitted its Conclusion on the risk assessment to the European Commission and the member states of the European Union, thereby initiating the decision-making process in the area of risk management. EFSA published the evaluation of the public and expert consultations (Peer Review Report), the BfR addendum on assessment of the IARC monograph and the revised assessment report including the corresponding supplements (Renewal Assessment Report) on its website at www.efsa.europa.eu.
The documents are available on:
http://registerofquestions.efsa.europa.eu/roqFrontend/ListOfQuestionsNoLogin?1

In response to the public debate, BfR has prepared the following questions and answers on glyphosate and pesticides containing glyphosate and their health assessment.

What is glyphosate?
Glyphosate (chemical name N-(Phosphonomethyl)glycine) is one of the most widely used active substances in pesticides worldwide to prevent unwanted plant growth in crop cultures or to eliminate plants or parts of plants. These substances are referred to as herbicides or, colloquially, as “weed killers”.

How does glyphosate work in plants?
Glyphosate suppresses the enzyme 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase, which is essential in plants for the biosynthesis of the amino acids phenylalanine, tyrosine and tryptophan. This enzyme does not occur in animals or human beings.

What is glyphosate used for?
Glyphosate is used in agriculture and horticulture to combat weeds before sowing. Where genetically modified plants with resistance to glyphosate are cultivated, the substance is also used after sowing outside the European Union in order to combat competitive weeds.

What properties have toxicological studies on glyphosate revealed?
Following oral administration, around 20% of glyphosate is absorbed from the gut and almost completely excreted within 7 days. The acute toxicity (one-time application) of glyphosate was low via oral, dermal or inhalative routes of exposure in animal experiments and in all tested species. Glyphosate was not irritating to rabbit skin and proved negative in all tests for skin sensitisation. However, glyphosate acid is irritating to the eyes.

With repeated administration of glyphosate in doses above the NOAEL (no observed adverse effect level), changes were observed in the salivary glands along with effects on liver and appendix; in addition, irritant effects on the mucous membrane were observed in the gastrointestinal tract and in the urinary bladder as well as cataracts of the eyes. In all studies,

a definite NOAEL, in other words a maximum dose at which no damaging effects to health occurred, could be determined.

Is there a risk that glyphosate may be carcinogenic to humans?
After reviewing all studies, documents and publications available to date, including the glyphosate monograph of the International Agency for Research on Cancer of the WHO (IARC), BfR comes to the conclusion that, based on current scientific knowledge, no carcinogenic risk to humans is to be expected from glyphosate if it is used in the proper manner for the intended purpose. With one exception (Sweden), experts from the EU member states and the recently published ESFA Conclusion also support this assessment in the ongoing procedure of the EU active substance review for the renewed approval of glyphosate as an active substance in plant protection products.

Does glyphosate cause deformities?
Studies on rats and rabbits showed that glyphosate is not to be classified as reprotoxic or developmentally toxic based on the legal provisions of the CLP in Europe. Anomalies occurred in the offspring in isolated cases following the administration of very high doses to pregnant rabbits. However, since these effects were limited to doses at which the rabbits already exhibited clear symptoms of poisoning and mortality, these findings were - in line with internationally accepted assessment principles - not considered to indicate any risk for developmental disorders in humans.

It is not only the experts in the EU who agree in the EFSA Conclusion that glyphosate is detrimental to neither the reproduction nor the development of mammals including humans. This view is shared by the Joint Meeting on Pesticide Residues (JMPR) of the WHO and the Environmental Protection Agency (EPA) in the US.

Why is glyphosate not assessed as detrimental to development by the assessment authorities?
According to the legal requirements, testing for developmental toxicity properties of active pesticide substances must be carried out on two mammalian species (rats, rabbits); this is why the largest database exists for these species with regard to transferability of findings to humans. The test substance is normally administered to the females orally, although, in the case of human exposure, there is sufficient indication of exposure via the skin or by inhalation. The internationally binding test guidelines stipulate that the highest dose should only cause slight toxic effects in the mother animals, as an embryonic or foetal toxic effect can also occur as a result of maternal toxicity, reduced water or feed intake, stress, specific nutritional deficiencies or other unspecified factors. Special consideration must therefore be given to the potential impact of these factors on the development of the progeny - because it is critical for the assessment of the findings and for classification under the hazardous substance regulations whether the toxic effect on the embryo or foetus occurs at a dose with or without pronounced maternal toxicity.

How are the glyphosate studies with clawed frogs and chickens to be interpreted?
Even if it is possible in principle to detect certain developmental toxicity effects of chemical substances in experiments on frog or chicken embryos, these are nevertheless not validated as test systems in the human toxicological testing of active ingredients of pesticides and other chemicals. This means that they have not been verified with regard to the informational value, practicability and reproducibility of the results, nor have they been recognised by the EU and other international organisations (such as the OECD). For this reason, the findings of such studies are of only limited use for the purpose of health risk assessment.

As regards the studies conducted by Professor Carrasco (University of Buenos Aires) with frog or chicken embryos, it must be taken into account that the test substances were administered directly to the progeny, i.e. by mixing them into the culture medium or through injection into the chicken eggs. The guidelines for toxicity testing of chemicals stipulate, however, that the test substance must be administered to the females orally, via the skin or by inhalation; i.e., the offspring is exposed through the passage of the test substance through the placenta.

Is glyphosate the only ingredient in pesticides containing glyphosate?
Pesticides are marketed in different formulations. These formulations consist of the active substance and various co-formulants. Glyphosate is used in pesticides not only in aqueous formulations but also in combination with co-formulants that act as surfactants. The herbicidal effect of glyphosate is systematically reinforced by the addition of these surfactants. They are designed to promote the penetration of glyphosate into the plants and are in some cases more toxic than the active substance itself. The overall effect of all ingredients of pesticides is only assessed after completion of the approval procedure for the active substances. This effect is assessed separately for each pesticide in an authorisation procedure conducted by the various member states.

What is the assessment of the toxicological properties of certain co-formulants in pesticides containing glyphosate?
Certain surfactants like POE tallowamines (polyethoxylated alkylamines) have a higher toxicity than glyphosate, primarily due to their irritant effect. The cases of poisoning in humans that have become known following accidental or intentional (suicidal) oral intake of larger amounts of herbicides containing glyphosate and the higher toxicity of some pesticides in laboratory animals compared to the active substance are attributed to the effects of these substances. The Federal Office of Consumer Protection and Food Safety (BVL), which is responsible for the authorisation of pesticides in Germany, called on the licence holders of the relevant pesticides to replace the POE tallowamines with other surfactants, and these substances have already been replaced.

Is it permissible for glyphosate residues to be detected in foods?
The European Commission has set maximum residue levels for glyphosate in foods as is the case with other active substances in pesticides. The maximum residue levels always refer to an active substance/crop combination and take account of the type of application. The amount of permitted residues is determined on the basis of residue trials conducted in accordance with the rules of good agricultural practice. The health-related limit or reference values may not be exceeded based on the stipulated maximum residue levels even in the case of frequent consumers of certain foods. Consequently, different maximum residue levels are defined for glyphosate depending on the crop and type of application. The maximum residue concentration for its use to combat weeds in cereal crops, for example, is 0.1 mg per kilogram of harvest yield for buckwheat and rice. If glyphosate is used for pre-harvest treatment (desiccation), then a maximum residue concentration of 10 mg per kilogram of harvest yield applies for wheat and rye.

Can glyphosate be ingested by humans via foods of animal origin like milk and dairy products?
There is no evidence to date that glyphosate migrates from feed into the milk of cows. In a cow-feeding study in which glyphosate and the metabolite AMPA (aminomethylphosphonic acid) were administered, the levels found in milk were very low even in the highest dose, which was far higher than the concentrations to be expected in feed under real-world conditions.

What is the significance of glyphosate and its metabolite AMPA (aminomethylphosphonic acid) being found in the urine of humans and animals?
Glyphosate is an approved active substance in herbicides and agents used for desiccation (pre-harvest treatment), and residues in foods and feed are therefore admissible if they are below the permitted maximum residue level. This means that humans and animals may ingest small amounts of glyphosate via food and feed. As glyphosate is rapidly excreted once again by the body, it is to be expected that traces of the active substance can be detected in the urine of humans and animals. The glyphosate concentrations detected in urine to date do not, however, indicate that the exposure of users or consumers to glyphosate represents any risk to their health.

On this matter, BfR has published an overview based on evaluation of studies in Europe and the USA in which urine samples were analysed for glyphosate residues (http://link.springer.com/article/10.1007%2Fs00003-014-0927-3#page-1).

Due to the residues in their feed, farm animals may excrete higher amounts of glyphosate in their urine than humans. This is the finding of tests on German and Danish dairy cows. The low volume of data that is currently available shows here as well, that the estimated intake was well below the concentrations that caused effects in toxicological studies and that therefore no risk to health is assumed to exist.

On the question of glyphosate detected in urine, we also refer you to the response to the parliamentary question in the German Bundestag parliament on 1 July 2013.
http://dip21.bundestag.de/dip21/btd/17/142/1714291.pdf

Can glyphosate accumulate in the body and migrate into breast milk?
Based on current scientific knowledge, BfR assumes that, due to the physical and chemical properties of glyphosate, in particular its solubility, there is no accumulation in fatty tissue that would lead to the migration of this active substance into breast milk. Despite many studies, there are no validated indications of accumulation in the organism. The National Breastfeeding Commission and BfR note that breast milk is still the best nutrition for infants. Mothers should not feel unsettled and should continue to nurse their babies.

In a notification from the "Bündnis 90/Die Grünen" parliamentary party, it is reported that increased glyphosate values were found in samples of urine and breast milk. What is BfR's assessment of these measurements?
On 25 June 2015, the "Bündnis 90/Die Grünen" parliamentary party reported that a laboratory had found the active pesticide substance glyphosate in 16 breast milk samples and described the findings as "a matter of grave concern". A large number of mothers were understandably worried about this study.

The test laboratory used the so-called ELISA test as a detection method to analyse the 16 breast milk samples for the presence of glyphosate. The glyphosate concentrations in the samples were reported to have been between 0.21 and 0.43 ng/mL. However, the manufacturer of the ELISA test specifies a sensitivity of only 75 ng/mL for the detection of glyphosate in milk using this method. Moreover, the positive findings in breast milk were not confirmed by independent analysis. BfR therefore expressed doubts regarding the reliability of the results and commissioned its own study in order to achieve valid findings. Neither did the available data indicate whether the test had been validated in advance for all analysed matrices (breast milk, urine). This would have been necessary to allow any robust statements.

The levels measured in breast milk are therefore neither an indication for accumulation of the active substance in the body nor for a risk to health.

Why is BfR conducting its own study to test breast milk for glyphosate?
After it was reported in the media that glyphosate had been found in 16 breast milk samples, concerned mothers contacted BfR to obtain information on the risk posed by glyphosate concentrations in breast milk. BfR expressed scientific doubts regarding the reliability of the findings and commissioned a study of its own to achieve valid results.

How are the studies from the USA published in 2014 that detected glyphosate in breast milk to be viewed?
To the knowledge of BfR, this information is based on a single study with a sample that was not representative, conducted on behalf of two US non-governmental organisations (“Moms Across America” and ”Sustainable Pulse”) by a laboratory in St. Louis using the ELISA technique and published by Honeycutt and Rowlands (2014) on the Internet. The study analysed milk samples from ten nursing mothers. Three samples exceeded the detection limit of 75 micrograms (µg) per litre (L) specified by the laboratory, and the highest value was said to be 166 µg per L. These preliminary data are neither representative nor adequately validated or plausible.

How is it possible to monitor, based on the statutory provisions, whether pesticides are used in the proper manner and for their intended purpose?
Every assessment of risks is generally based on use of a product or substance for the intended purpose or on foreseeable use. It goes without saying that misuse, negligent use or incorrect use can result in risks that cannot be assessed. This is why the government has put various checks in place in the area of pesticides. Monitoring of use for intended purpose is not the job of BfR as a risk assessment authority, however. This is the responsibility of the competent management authorities. In this case, the German Plant Protection Act (PflSchG) stipulates that this is the job of the regional state authorities. In the event of non-compliance with the provisions, Art. 13 of the PflSchG provides for appropriate penalties and fines. The PflSchG also stipulates that use over large areas may only be carried out by qualified experts who can provide proof of proficiency and who regularly have to undergo suitable further training.

To ensure that use of these products in the private sphere is for the intended purpose and in the proper manner, the PflSchG stipulates mandatory advice for customers by dealers selling pesticides. The supervisory authorities monitor trade compliance with this stipulation. In addition, the guidelines for use and the full assessment reports can be found on the website of the Federal Office of Consumer Protection and Food Safety (BVL).
http://www.bvl.bund.de/DE/04_Pflanzenschutzmittel/01_Aufgaben/02_ZulassungPSM/02_Zulassungsberichte/psm_zulassungsberichte_node.html

Why were the ADI and the AOEL adjusted in the context of the renewal procedure for glyphosate?

ADI stands for Acceptable Daily Intake and indicates the amount of a substance that a consumer can ingest daily over an entire lifetime without any recognizable health risk. The ADI value is used to assess the chronic risk.

AOEL stands for Acceptable Operator Exposure Level and represents the exposure level for operators during the application of plant protection products below which no recognizable health risk is to be expected.

In the context of the renewal procedure for glyphosate, numerous toxicological studies were submitted and evaluated, which exceeded by far the required number of animal experiments and were not available for the first approval. The ADI and AOEL values were derived during the re-evaluation of glyphosate by taking into consideration all available studies and information.

Why was an Acute Reference Dose (ARfD) derived during the renewal procedure of glyphosate?

The acute reference dose (ARfD) is defined as the quantity of a substance in food that a consumer can ingest in the course of one day spread over one or more meals without any appreciable health risk. Thus, the ARfD represents a threshold value for the health risk assessment with respect to short-term exposure for consumers.

In the context of the renewal procedure for glyphosate, all available toxicological studies were reviewed in terms of harmful effects after a single or short-term exposure. It was observed that in the developmental toxicity studies serious effects can occur in the rabbit dams at relatively low doses (mortality and post-implantation loss from 100 mg/kg bw/day). For this reason, an ARfD of 0.5 mg/kg bw was derived. This value is based on a NOAEL (No Observed Adverse Effect Level) of 50 mg/kg bw, that is, the dose at which no toxic effects were observed, and an assessment factor of 100.

Which consequences does the additionally derived ARfD have for the health risk assessment?

While the assessment of the chronic health risk for consumers is based on the average concentrations of substances in food ingested daily over a lifetime (chronic exposure), the acute health risk is calculated additionally for exposure to substances for which an ARfD has been derived. For this, the more critical case of a singular consumption of high amounts of food with maximum residue level is considered (acute exposition). Accordingly, the previous health risk assessment for glyphosate was expanded to enable a comprehensive chronic and acute health risk assessment.

How much glyphosate do consumers ingest through food?

BfR is currently in the process of assessing the German food monitoring data from the past six years in order to be able to make statements about average user exposure to pesticide residues. The assessments have not been completed and therefore results are not yet available. BfR intends to publish the data as soon as the project is completed.

The assessments conducted so far have shown that across all food categories which have been tested as part of the food monitoring programme over the last six years, just under 1400 samples have been tested for glyphosate. To make a reliable statement about the exposure of the German population to glyphosate, this number of samples is to be regarded as too low. Overall, residues were detected in less than 4 % of the tested samples. Based on these 24 findings, glyphosate exposure amounts to less than 1 % of the ADI value. ADI

stands for “Acceptable Daily Intake” and indicates the amount of a substance which a consumer can absorb on a daily basis without appreciable health risks. The ADI value is used to assess the chronic risk of consumers.