

New data on health aspects of Glyphosate? A current, preliminary assessment by BfR

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Glyphosate is an herbicide active substance used in different plant protection products. The Federal Ministry of Food, Agriculture and Consumer Protection (BMELV) has asked the Federal Institute for Risk Assessment (BfR) to provide an opinion regarding the health risks associated with plant protection products containing glyphosate. A publication by a non-governmental organisation (NGO) and a request by the European Commission for Germany's commentary in its role as rapporteur for the active substance within the European plant protection product authorisation procedure on this report initiated this request.

BfR concludes that the NGO report in question contains little new factual information while its relevant aspects in regard to the health assessment of the active substance glyphosate have already been examined by various international panels. On the contrary, the central expert debate actually reflects fundamentally different approaches to the health risk assessment of chemicals. According to BfR, such paradigm shifts must first be subjected to an expert review process and international panel discussions in order to assess their necessity.

The present Opinion served as information to the European Commission and was thus drafted and will only be published in English on the BfR website.

1. Subject of the assessment

In its responsibility as Rapporteur Member State for glyphosate in preparation of Annex I inclusion in 2002, Germany was asked by the Commission to express its preliminary opinion on the facts listed in the recently published report "Roundup and birth defects. Is the public being kept in the dark?" by Robinson et al. (released in June, 2011 by an organization called "Earth Open Source")¹. The Federal Ministry of Food, Agriculture and Consumer Protection (BMELV) has thus asked the Federal Institute for Risk Assessment (BfR) to provide an opinion regarding the health aspects of risks associated with plant protection products containing glyphosate.

2. Results and conclusions

There are only little new facts in this report on suspected adverse health effects of glyphosate and related plant protection products. Most data has been considered in the risk assessment by national and international bodies and linked to the existing authorisations of plant protection products with glyphosate. However, it is interpreted by Robinson et al. (2011) in a way that tackles more general questions of the risk assessment. The report is on "Roundup and Birth defects" but what the authors in fact suggest is a fundamental change in the approach to be taken in the toxicological hazard assessment of chemicals.

With regard to glyphosate and Roundup, we see a need to include all new facts into the planned re-evaluation under the AIR2 process². Therefore, a time-consuming re-evaluation of old studies and a detailed evaluation of the little new facts is not included in this prelimi-

¹ <http://www.scribd.com/doc/57277946/RoundupandBirthDefectsv5>

² AIR 2 Project: Renewal of the Inclusion of Active Substances in Annex I to Council Directive 91/414/EEC

nary opinion. Nonetheless, the Robinson report is a challenging document raising a lot of questions that should be taken very seriously. An adequate response to the criticism and the many accusations in the report would require a general discussion of the established paradigms for the toxicological evaluation of chemicals, including the postulated shortcomings in the legal system, the recourse to independent science, the Commitology system, GLP, the alleged insufficiency of the toxicological approach. These general discussions should be initiated by the Commission before we start with the re-evaluation of glyphosate within the AIR2 project.

3. Rationale

The recently published report "Roundup and birth defects: Is the public kept in the dark?" is a challenging critical summary of adverse health (mainly teratological and reproductive) findings that are attributed by the authors to the compound glyphosate and/or to herbicides such as Roundup that contain glyphosate as active ingredient. The authors are apparently concerned about the extensive and long-lasting use of glyphosate in plant protection products world-wide and in particular about its growing application amounts because of the introduction of glyphosate-resistant genetically modified plants such as soybean, corn, or cotton. The main accusation in the report is that the manufacturers and the regulatory authorities had been aware of glyphosate causing birth defects in laboratory animals since long (presumably from the 1980ies) but failed to inform or even misled the public and did not take this knowledge seriously enough in regulatory practice and decisions.

The comprehensive report has been reviewed by the German Federal Institute for Risk Assessment (BfR). In the given timeframe, it is not possible to address all the points and questions that are brought up in the report and to respond adequately and precisely to the many accusations therein. For this purpose, much more time would be needed because the 359 references will have to be checked and many studies and publications to be (re-)reviewed. Here, only the more general aspects of the report can be discussed. Instead, it is suggested to deal with all these concerns in detail during the re-evaluation process of glyphosate in preparation of the regulatory decision on renewal of the Annex I decision. Since this is one of the main issues of criticism in the report.

3.1. Glyphosate

With regard to toxicology of the active substance, there is no new in vivo data referred to in the report. Clearly, a selection from the huge database on glyphosate has been made to support the authors' views. For the reader, it will not become apparent from the report that the recent evaluations on glyphosate by, e.g., the EU (2002) or the JMPR of WHO and FAO (2004) are based on a compilation of many studies from different sources. In contrast to many other compounds, all toxicological endpoints are covered for glyphosate by more than one acceptable study and all have been taken into consideration following a "weight of evidence" approach. Thus, we are aware of at least five 2-year and one 1-year feeding studies in rats on which the assessment of chronic toxicity and carcinogenicity is based. In contrast, for most other compounds, only one study of this type is usually available. All these long-term studies provided consistent evidence that glyphosate was not carcinogenic but, due to differences in the strains employed, in dose selection and dose spacing and in the parameters under investigation and taking also into account the normal biological variability, the NO-AELs/LOAELs were not the same. This is one of the reasons to explain that there were actually concurrent proposals for setting the ADI as described in the report under sub-section 3.4. Of course, when submitting their dossiers, the different notifiers for glyphosate had proposed reference values that were based on their own experimental data or otherwise available data.

When the DAR was prepared, we found it more reliable to consider all the studies although one main notifier at that time had demanded to use only its own data that in fact would have given a higher ADI.

Indeed, the report contains a lot of in vitro data that was not part of the 1998 DAR from Germany and was not considered for Annex I inclusion in 2002 but simply because of the fact that most of these papers had not been published at the time when the DAR and the addenda were prepared (1997 – 2000). A part of them has been subject to evaluation by the German authorities since then with the conclusion that it was not necessary to revise the general toxicological assessment of glyphosate. The relation between in vitro and in vivo data is discussed under 3.4 below. By the way, it is one of the main objectives of the periodical renewal of Annex I inclusion to review new data.

3.2. Roundup

Usually, adverse health effects of plant protection products are mainly triggered by the active substances that have been developed to control different pests, i.e., that are poisonous to organisms (weeds, fungi, insects etc.). In most cases, co-formulants will only cause irritation or sensitization that the active ingredient might not exhibit or will enhance absorption. Glyphosate is rather unique because the active substance is really less toxic than at least some products. To our knowledge, this is due to certain surfactants from the chemical class of polyethoxylated (POE) tallowamines (see below). First evidence of such effects has been compiled by the German authorities in its 2000 addendum to the DAR in which many of the concerns that are mentioned now in the Robinson report (see its sub-section 12.1) have been addressed. Later on, our point of view was further substantiated by the publications of Dallegrove et al. (2003, 2007, cited in the report on different sites) on developmental and reproduction toxicity of a certain Roundup formulation from the Brazilian market revealing lower NOAELs and LOAELs in rats than the respective studies with the active ingredient.

It must be emphasized that product data is considered in the evaluation process for Annex I inclusion to a limited degree only. It is sufficient to demonstrate a safe use for a representative formulation. Evaluation of the plant protection products is a member state issue. Composition of plant protection products may differ round the world, even if they are sold in different countries under the same trade name. Thus, without any data on products and exposure, Germany or the EU are in fact not able to evaluate, e.g., the risks of Roundup applications on genetically modified crops in South America.

3.3. Tallowamines

As mentioned above, tallowamine surfactants from the (POE) class can enhance toxicity of plant protection products containing glyphosate as compared to the active ingredient. In 2010, the BfR produced a separate toxicological evaluation on one of these substance with the CAS number 61791-26-2 including setting of reference values (0.1 mg/kg bw/(day) for ADI, AOEL and ARfD; inhalative AOEL of 0.0166 mg/kg bw/day) that are lower than those which were established in the EU for glyphosate (ADI 0.3 mg/kg bw, AOEL 0.75 mg/kg bw/day, ARfD and inhalative AOEL not needed). In Germany, expected exposure is additionally compared to these reference values if plant protection products containing this surfactant are under evaluation for granting approval. This extended risk assessment has been also performed for those which were already on the market.

3.4. General comments

The crucial point in the report is the use that is made of existing knowledge. Its interpretation in the report is, to a very large extent, deviant from that of the EU, of national authorities or of internationally recognized regulatory bodies such as the JMPR. The reason behind these striking differences seems to be another understanding of general principles of toxicology by the authors. Toxicological evaluation and risk assessment of pesticides and other state-regulated chemicals must be carried out in line with certain assumptions, rules and principles that will allow transient and consistent, science-based regulatory decisions that must be able to stand legal proof if challenged. These principles have evolved over decades, are internationally accepted and applied by regulatory agencies world-wide. In the report, however, serious criticism is expressed on a number of them. A few examples are given in the following compilation. It is obvious that an evaluation of any compound under strongly amended presumptions and principles will bear different results.

- Usually, valid studies in intact laboratory mammals are considered of superior quality and reliability as compared to in vitro data. In vitro data are mostly used in two different ways: (1) for screening purposes before, e.g., major investments in the further development of a new compound are made; (2) to elucidate the mode or mechanism of action behind adverse effects that were observed in standard toxicological studies in laboratory animals. For chemicals with less stringent and regulatory requirements than for pesticides, they can be also used to indicate a need for performing so-called "higher tier" studies, i.e., experiments in mammals in vivo. We agree that some of the in vitro results with glyphosate or Roundup from recent years might have triggered the conduct of in vivo studies but a negative outcome in the latter should have convinced regulators world-wide that the suspected effects will not occur in intact animals. In case of glyphosate, all these "higher tier" in vivo studies were available (because of the general data requirements for pesticides) long before the more recently obtained in vitro data suggested the possibility of certain adverse effects. Throughout the report, however, such in vitro findings are used to outweigh or overwhelm the negative in vivo results.
- With regard to the in vivo studies, the authors do not agree with the assumption that there is a dose-response for adverse effects (see, e.g., sub-section 3.1, p. 13), i.e., that there is a threshold for the occurrence of uppermost toxic effects and that effects usually will progress and become more pronounced with increasing dose or duration of exposure. Instead, they appear to advocate the low dose concept that is indeed subject to ongoing scientific discussion but reflects a minority view among toxicologists.
- The authors deny the relevance of historical control data (if used in an appropriate way) for interpretation of adverse findings such as the incidences of tumors or malformations (3.1, p. 14).
- Regulatory agencies world-wide share the assumption that studies are more reliable and reproducible when performed under GLP conditions and according to an internationally agreed design (such as OECD test guidelines). In section 4 of the report, the authors try to demonstrate why such studies are incredible ("tyranny of GLP", p. 22, second paragraph) and results from so-called "independent research" should be given more weight. Concerning glyphosate, it should be taken into account that experimental data has been produced by different companies producing this com-

pound. It is hardly conceivable that all this research has been flawed by “industrial bias”. Turning away from GLP and test guidelines would produce a high level of inconsistency in available data making the regulatory system more intransigent and would produce endless discussion between authorities, notifiers, and other stakeholders.

- Usually, studies using the oral, dermal and inhalative routes are considered to reflect the expected human exposure. In contrast, the authors strongly advocate in section 6 the highly artificial injection route.

An adequate response to the criticism and the many accusations in the report would require a general discussion of the established paradigms for the toxicological evaluation of chemicals. These general discussions should be initiated by the Commission before we start with the re-evaluation of glyphosate within the AIR2 project.