EFSA Statement regarding the EU assessment of glyphosate and the so-called "Monsanto papers"

Background

On 29 May 2017, EFSA received a request from the European Commission to produce a statement concerning the EU assessment of glyphosate following allegations made in the so-called "Monsanto papers". The requestor asked EFSA to provide responses to the following points:

- What impact the allegations about Monsanto ghostwriting scientific review articles would have on the overall EU assessment of glyphosate, if they were confirmed;
- The role of the scientific review articles in question, including the type of publication, amount of available information, transparency of industry support for some articles;
- The legal provisions on the assessment of open scientific literature in the EU legislation on pesticides and their implementation in the EU peer review;
- The steps taken during the assessment to ascertain the reliability of guideline studies and those from the open literature.

In line with the request from the European Commission, this statement outlines the EU legislative framework concerning the submission of open scientific literature for the assessment of active substances and explains how such literature is considered during the peer-review process by Member State and EFSA experts. The statement continues with information about the steps that Member State and EFSA experts take to ascertain the reliability of guideline studies and information from the open scientific literature that are submitted by applicants for the risk assessment. The statement ends with specific information about the role of the two scientific review papers that are mentioned in the "Monsanto papers" and that were considered in the EU assessment of glyphosate, concluding that even if the allegations were confirmed that these review papers were ghostwritten, there would be no impact on the overall EU assessment and conclusions on glyphosate.

EU legislative framework regarding the submission and assessment of publications from the open scientific literature in the peer review of active substances.

The EU legislative framework governing the authorisation of pesticides was adopted by the European Parliament and the Council in 2009 and is Regulation (EC) No. 1107/2009. Commission Regulation (EU) No 1141/2010 lays down the detailed rules for the procedure of the renewal of the approval of a second group of active substances (AIR II) of which glyphosate was part. The Regulations (EC) No 1197/2009 and (EU) No 1141/2010 contain provisions regarding the information applicants must provide in their dossier to the regulatory authorities involved in carrying out the risk assessment.
Regarding publications from the open scientific literature, Article 8(5) of Regulation (EC) No. 1107/2009 requires applicants to submit scientific peer-reviewed open literature on the active substance and its metabolites dealing with side-effects on health, the environment and non-target species published within the last 10 years before the date of submission of the dossier.
According to Article 8(5) of Regulation (EC) No. 1107/2009, the search of the scientific peer-reviewed open literature has to be conducted "as determined by EFSA".

This requirement is elaborated through an EFSA guidance document[1] on the submission of scientific peer-reviewed open literature. The guidance document provides a definition of scientific peer-reviewed open literature and instructions for the applicant on how to minimise bias in the identification, selection and inclusion of peer-reviewed open literature in dossiers, according to the principles of systemic review (i.e. methodological rigour, transparency, reproducibility).

How Member State and EFSA experts implement the legal provisions on scientific open literature in the peer review process.

The legal provisions concerning the open scientific literature that the applicant must submit as part of its dossier are implemented in a consistent, structured and transparent way during the peer-review process. The steps linked to the provisions on scientific open literature in the case of the renewal of approved active substances are outlined below:

1. The Rapporteur Member State (RMS) checks that the supplementary dossier, complementing the original dossier submitted for the first approval, contains the results of the search of the open scientific literature conducted according to the EFSA guidance.
2. The RMS prepares a Renewal assessment Report (RAR) that includes an appraisal, conducted in accordance with the EFSA guidance document mentioned above, of all open scientific literature. In addition to the information provided by the applicant in the dossier, the RMS shall consider information submitted by third parties according to Art. 14 of Commission Regulation (EU) No 1141/2010, and may include additional information from the open literature that is available to it.
3. The RMS shares the RAR with EFSA, Member States and the European Commission and EFSA begins the peer-review of the RMS report.
4. EFSA organises written consultations with Member State experts. Comments are sought on all scientific information included in the applicant's dossier and reported in the RMS RAR, including the appraisal of the open scientific literature.
5. In parallel, EFSA launches a public consultation on the RMS RAR.
6. Following the public and Member State consultations, EFSA requests additional information from the applicant.
7. The comments and the additional information provided by the applicant are appraised by the RMS which, if needed, updates the RAR.
8. Based on the comments received during the consultations and the RMS responses EFSA selects the scientific topics requiring further discussions, and organises peer-review meetings with Member State experts.
9. EFSA scientific staff draft the EFSA Conclusion and EFSA holds a final consultation of the final draft with Member State experts before publishing its Conclusion.
10. Minutes of all meetings and all comments from public and Member State experts during the peer-review process are published on EFSA's website alongside the final Conclusion. This includes detailed information about how Member State and EFSA experts appraised open scientific literature.

[1] EFSA (European Food Safety Authority), 2011. Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009. EFSA Journal 2011;9(2):2092, 49 pp. doi:10.2903/j.efsa.2011.2092

How Member State and EFSA experts ascertain the reliability of guideline studies and open scientific literature during the peer-review process.

In line with EU legislation on pesticides, the EU assessment of active substances is based primarily on an analysis of the findings and raw data contained within regulatory guideline studies and on studies published in the open scientific literature. The EU legislation for pesticides offers the applicant the opportunity to provide its views in the dossier that it must submit to regulatory bodies and at different steps of the peer review process. It is the role of Member State and EFSA experts to verify the applicant's proposals, which they do by evaluating the findings and raw data of the regulatory guideline studies and by appraising the studies in the open literature according to a set of uniform scientific principles. In this way, EU experts are able to reach their conclusion about the safety of the active substance in question.

Every scientific study is scrutinised for relevance and reliability by EU risk assessors based on the evidence contained within the study. Results that are considered relevant and reliable are integrated in the weight of evidence[2], which also considers consistency between studies.

Regulatory guideline studies

Regulatory guideline studies are sponsored by industry and conducted by laboratories certified and audited under 'Good Laboratory Practice' (GLP) standards, an OECD protocol designed to ensure consistency and integrity in chemical safety tests[3].

The findings of each regulatory guideline study are presented in a detailed study report, which allows EU experts to check the reliability and quality of the results and decide for themselves which aspects to use in the risk assessment. The integrity of the findings and raw data rely on the fact that the laboratories carrying out the tests are certified and audited under the GLP system.

The international guidelines (e.g. OECD) include details on the applicable principles that must be followed by the study authors and risk assessors for a study to be considered valid. The guidelines also stipulate the required level of reporting needed to allow risk assessors to check the reliability of the study. Deviations from these guidelines have to be reported and their consequences are assessed on a case-by-case basis.

The EU legislation lays out areas in which guideline studies are performed. The relevance of the study results is provided for each guideline study according to the data requirements laid out in EU legislation and the relevant guidance documents applicable to each assessment. Studies that are considered reliable are included in the weight of evidence.

Open scientific literature

The parts of an applicant's dossier containing scientific information in the open literature typically contain the following types of publications related to information on the active substance, its metabolites, or formulations containing the active substance under assessment:

1. Original studies on the hazards or other properties relevant for the risk assessment, as well as original studies and meta-analyses of epidemiological evaluations.
2. Scientific review papers on the properties of the substance under assessment, summarising and aggregating the results of original studies, such as those mentioned in the "Monsanto papers".

In addition to the studies included by the applicant in the dossier, other studies from the open literature can be incorporated by the RMS in the first RAR as well as by all involved parties during the different commenting phases of the EFSA peer-review. Article 14 of

[2] Regarding the assessment of carcinogenicity, the experts follow the weight of evidence principles established under Regulation (EC) No 1272/2008 and further developed in the ECHA Guidance on the Application of the CLP Criteria, available at https://echa.europa.eu/guidance-documents/guidance-on-clp.

[3] OECD Series on Principles of Good Laboratory Practice (GLP) and Compliance Monitoring: http://www.oecd.org/chemicalsafety/testing/oecdseriesonprinciplesofgoodlaboratorypracticeglpandcompliancemonitoring.htm

Commission Regulation (EU) No 1141/2010 also allows third parties the submission of additional studies to be considered by the RMS when drafting the RAR.
As regards the first type of publication mentioned above (original studies), Member State and EFSA experts assess the reliability and relevance of each study following the specific guidance published by EFSA. If needed, EFSA or the RMS may contact the study authors and request access to the raw data to allow for verification of the reported results. Studies from the open scientific literature that are considered relevant and reliable are included in the weight of evidence.
As regards the second type of publication mentioned above (scientific review papers), the weight of review papers is very limited in the overall risk assessment because Member State and EFSA experts have access to, and rely primarily on, the original safety studies themselves to verify the interpretation of the authors and to produce their final conclusions.
Some review papers are based exclusively on publicly available information and in other cases the authors have been given access by industry to unpublished proprietary studies to carry out their own review. These types of review papers may or may not be sponsored by industry. Most scientific journals require the authors to make a declaration on this issue before publishing a review paper,
Where review studies are based on unpublished industry studies it is clear that the author's work has been facilitated by industry as it is only through that connection that authors would be able to access unpublished results.
Occasionally, in addition to studies and reviews on the active substance under evaluation, the submitted information includes publications on related pesticides or complementary studies on the scientific state-of-the-art of the different disciplines used during the risk assessment. These type of publications represent scientific knowledge relevant but not directly related to the substance under assessment and are used as supporting information in the weight of evidence. In those regulatory scientific areas where there is a wealth of experience and up-to-date scientific guidance, such as carcinogenicity, the role of these publications is very limited and considered on an ad-hoc basis e.g. when relevant to the assessment of inconsistencies and uncertainties observed in study results.
Concluding remarks on how EU experts ascertain the reliability of studies during the peer-review process
The quality and reliability is checked for every single original study, including regulatory guideline studies; in fact EFSA dismissed several industry-sponsored regulatory guideline studies due to study deficiencies identified during the assessment. It is also not unusual for Member State and EFSA experts to disagree with industry on how the results of the studies that they submit in their dossiers should be interpreted for the risk assessment, e.g. considering that the study is valid but the conclusion proposed by the study authors is not supported by the finding; in those cases the experts use in their assessment a different interpretation of the study results than that proposed by the authors. This was also true in the case of glyphosate, EFSA identified concerns not indicated by the applicants that led it to conclude that acute health effects should not be disregarded in the setting of Maximum Residue Levels for glyphosate in food.
There is no information contained within the "Monsanto papers" or that EFSA is otherwise aware of that indicates that industry attempted to falsify or manipulate the findings and raw data of the regulatory guideline studies used in the glyphosate assessment. If new information were to become available in the future that gave EFSA reason to doubt this, the Authority, according to its standard practice, would investigate the information as a matter of priority and, if appropriate, reassess the study or studies in question and their weight in the overall conclusion, updating the assessment as needed. Regulation (EC) No 1107/2009 allows for the re-examination of a scientific assessment and the regulatory decision on authorized active substances at any time.

Details of the scientific review articles mentioned in the "Monsanto papers" and the potential impact of allegations regarding ghostwriting on the overall EU assessment of glyphosate.

Of the various scientific review articles mentioned in the "Monsanto papers", two were considered in the EU assessment of glyphosate: Kier and Kirkland (2013) and Williams et al. (2000)[4]. The review by Greim was not considered in the EU assessment, it is only mentioned in the addendum issued in August 2015 and in connection with the IARC monograph that mentions this review.
The nature of the information contained within the "Monsanto papers" and the reported allegations regarding ghostwriting were serious enough for EFSA to investigate the significance of the two identified scientific review articles in relation to the EU assessment of glyphosate.
Following this investigation, EFSA can confirm that even if the allegations regarding ghostwriting proved to be true, there would be no impact on the overall assessment as presented in the EFSA Conclusion on glyphosate. The reasons for this are as follows:

- The two review articles in question are an analysis of regulatory guideline studies already included in the applicant's dossier. The weight of these two review papers in the overall scientific assessment of glyphosate was therefore very limited because EU experts had access to, and relied primarily on, the findings of the original guideline studies and the underlying raw data to produce their own conclusions. The review papers simply served to summarise or substantiate the industry position on glyphosate that had been presented, as required by the regulatory framework, in the applicant's dossier and in the commenting rounds during the assessment.

- Notwithstanding the fact that these two review papers might have been ghostwritten by Monsanto, their provenance was evident from the Declarations of Interest and Acknowledgements in the papers themselves. For example, the Kier and Kirkland paper states that the authors were paid by the Glyphosate Task Force to carry out the review and the Williams et al. paper acknowledges that Monsanto facilitated the authors' work by providing them with original, unpublished studies. This means that Member State and EFSA experts were under no illusion about the links between the study authors and the companies that funded or facilitated their work when the experts carried out the risk assessment.

- The review papers in question represented only two of approximately 700 scientific references in the area of mammalian toxicology considered by EFSA in the glyphosate assessment.

[4] https://www.ncbi.nlm.nih.gov/pubmed/23480780 (Kier and Kirkland 2013); https://www.ncbi.nlm.nih.gov/pubmed/10854122 (Williams et al. 2000)