Information submitted in the frame of EU glyphosate active ingredient approval renewal, according to Regulation (EC) No 1107/2009, EFSA request for additional information

Title: Response to various requests for clarifying the approach used for the literature review in view of the comments/concerns raised by several commenting parties during the public consultation

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Glyphosate Renewal Group

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The applicant provides a general response to various EFSA requests for clarifying the approach used for the glyphosate literature review in view of the comments/concerns raised by several commenting parties during the public consultation.

Statement of the applicant

Detailed description of the Glyphosate Renewal Group's (GRG) approach to the review of scientific peer-reviewed open literature on glyphosate within the EU renewal process.

Scope

This position paper describes in more detail a specific part of the approach of the applicant (GRG) to provide a comprehensive dossier for the renewal evaluation of the active substance glyphosate in the European Union (EU). To ensure that all relevant research and scientific information regarding the effects of glyphosate and its metabolites on human health and the environment are included in the dossier, the GRG performed a systematic review of scientific peer-reviewed open literature, following the instructions in the established EFSA guidance. The approach followed is described in detail in this document and additional specific requests received from EFSA and other stakeholders during the public consultation are also addressed.

Introduction

- For EU (re-)approval of an active substance companies as notifiers must ensure that all relevant data requirements are addressed for the parent compound and its potential transformation products (metabolites) by studies that comply, for example, with the standards set by organisations like the Organisation for Economic Cooperation and Development (OECD)'s guidelines and that follow Good Laboratory Practice (GLP). This assures a very high level of data quality, validity and traceability during and after study conduct. While this applies for data generated by the notifier, this should also apply for publicly available scientific peer-reviewed literature. In effect, such scientific data have to be rigorously screened and be provided to the evaluating authorities. This allows decision-making on the best possible basis.
- Article 8(5) of Regulation (EC) No 1107/2009 concerning the placing of plant protection products on the market, specifies the requirement: "*Scientific peer-reviewed open literature, as determined by the Authority, on the active substance and its relevant metabolites dealing with side-effects on health, the environment and non-target species and published within the last ten years before the date of dossier submission shall be added by the applicant to the dossier*". The relevance of the public literature data is ultimately assessed by the European Food Safety Authority (EFSA).
- To this end, EFSA has published detailed guidance on the process for identifying publicly available scientific peer-reviewed open literature and for evaluating its relevance to inform the data requirements set out in Regulation (EC) No 1107/2009.
- As part of the glyphosate reapproval dossier, the GRG as the applicant carried out an extensive review of the open literature to identify articles that could be of relevance to the scientific assessment of glyphosate and its metabolites. The GRG followed the established EFSA guidance as well as the evaluating Member States' advice as discussed during a dedicated pre-submission meeting between the Assessment Group on Glyphosate (AGG, competent authorities of France, Hungary, Sweden and The Netherlands) and GRG on 11 December 2019. Minutes and presentations are publicly available on the AGG and GRG websites.
- The literature search and review were documented by the GRG in comprehensive Literature Review Reports (LRR part one covering the search period Jan 2010 – Dec 2019, LRR part two

covering the search period Jan 2020 – Jun 2020, and a third LRR dedicated to the literature review for the endocrine disrupting properties (ED) of glyphosate) and submitted as part of the dossier to the evaluating Member States. Structure and content of these reports are in compliance with the requirements of the applicable EFSA guidance. In these LRR documents the GRG's entire public literature search, selection and evaluation process of the > 12,000 retrieved scientific articles is transparently described in detail and all search results are documented in dedicated tables and made available for authority and public review. These dossier literature review reports are available for download via the "Transparency / Scientific Dossier / Public Literature" section of the GRG website: www.glyphosate.eu [1]

- The GRG's selection and assessment of literature articles was reviewed by the evaluating Member States (AGG) and EFSA as part of the renewal process.
- Following their review, the AGG and EFSA developed, in some instances, a different opinion on the GRG's literature article selection decision and requested the GRG to provide additional articles and their summaries for the AGG's and EFSA's further consideration. In this respect also comments from other stakeholders provided during the public consultation for additional potentially relevant literature articles have been accepted and the GRG was requested to provide these articles and their summaries for the AGG's and EFSA's further consideration, in case such articles had not been included in the GRG's selection. Overall, > 300 articles have been submitted by the GRG in addition to what was provided in the frame of the original dossier submission, to address specific requests by the AGG and EFSA.
- During 2022 the AGG and EFSA will evaluate all submitted information, including those data contained in the relevant and reliable scientific public literature articles, and EFSA will provide a final conclusion on the safety of glyphosate for humans and the environment in the EFSA Conclusion document that will be made available to the public.

The following sections explain the GRG's identification and selection process for scientific peer-reviewed open literature in detail and address concerns that have been raised as part of the public debate during the reapproval of Glyphosate.

Detailed description of the glyphosate public literature review process

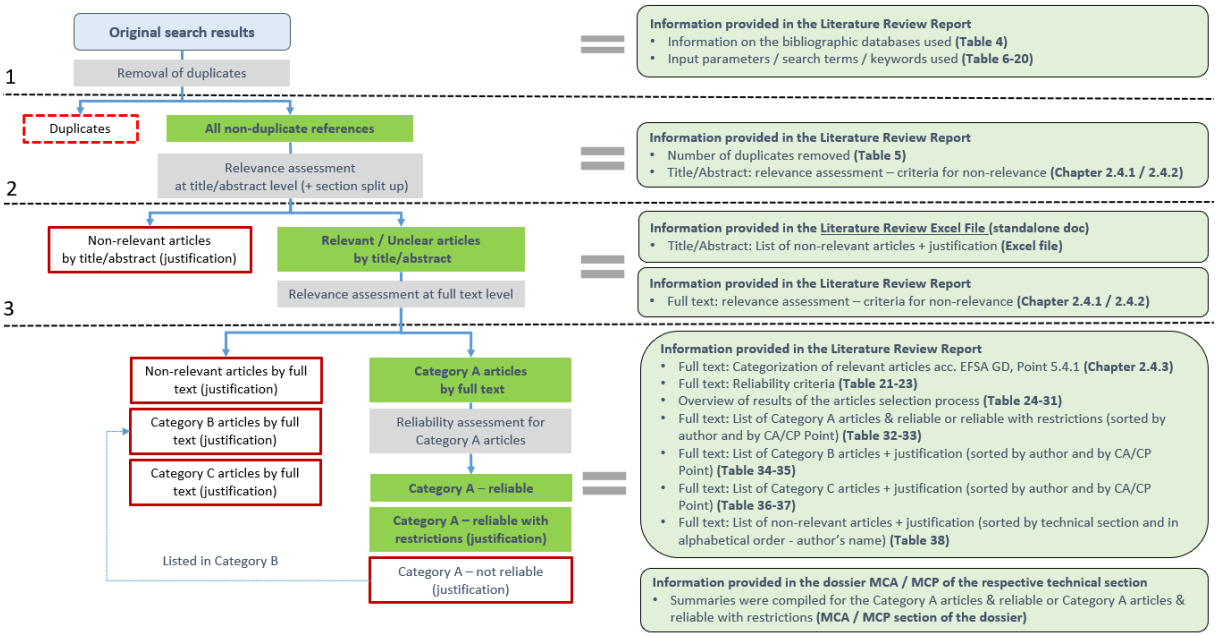
- Plant protection product (PPP) active substance approval and reapproval dossiers must include all scientific peer-reviewed open literature articles that are relevant to the assessment of the substance[2]. This evaluation must be carried out in accordance with EFSA's guidance[3] and, for glyphosate, the AGG requested a specific format for presenting the results of the search, which the GRG followed. Minutes and presentation of the dedicated public literature pre-submission meeting between the AGG and GRG are available on the AGG and GRG websites.

[1] Direct link to the public literature transparency section of the GRG website that contains the Literature Review Report documents for download: https://www.glyphosate.eu/transparency/scientific-dossier/public-literature/

[2] Regulation (EC) No 1107/2009 article 8(5).

[3] EFSA Journal 2011;9(2):2092 "*Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) 1107/2009*", and the Appendix to the EFSA Guidance Document "*Further guidance on performing and presenting the literature search*" (available online: https://efsa.onlinelibrary.wiley.com/action/downloadSupplement?doi=10.2903/j.efsa.2011.2092&file=efs22092-sup-0001-Appendix.pdf), and the EFSA supporting publication from 2019 :EN-1612 "*Administrative guidance on submission of dossiers and assessment reports for the peer-review of pesticide active substances*".

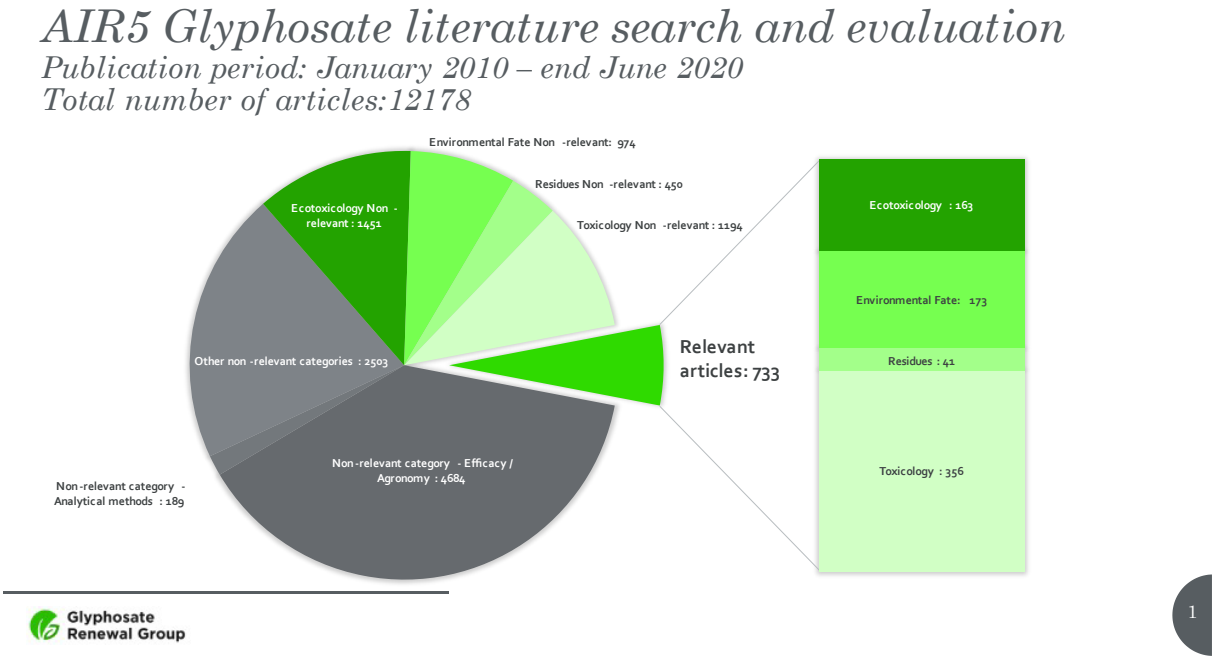
- The GRG's process of identifying and selecting scientific peer-reviewed open literature and including it into the dossier was based, according to the EFSA guidance, on a systematic, transparent and reproducible review to identify and critically appraise relevant research from publicly available literature articles. The GRG's literature search is reported in detail in the scientific peer-reviewed open literature review Reports (LRR)[4], following the EFSA guidance.
- **The decision on relevance or non-relevance of the scientific literature articles does not depend on whether or not they are conducted in accordance with Good Laboratory Practice (GLP) or according to established test guidelines.**
- After the principal relevance of information described in a literature article has been established, it is classified in one of three categories (according to EFSA guidance chapter 5.4.1.) depending on its relevance to the risk assessment:
  - **A) Studies that provide data for establishing or refining risk assessment parameters.** These studies are summarised in detail according to the OECD Guidance documents on pesticide registration and are considered for reliability assessment – as per the EFSA Guidance documents.
  - **B) Studies that are relevant to the data requirement, but which provide only supplementary information that does not alter existing risk assessment parameters.** A justification for such a decision is provided.
  - **C) Studies for which relevance cannot be clearly determined.** For each of these studies, an explanation of why the relevance of such studies could not be definitively determined is provided.
- The following flow chart illustrates the process and provides reference to chapters and tables in the LRR documents[4] that contain additional details:



[4] All Literature Review Reports included in the glyphosate renewal dossier are available for download on the GRG website in the public literature transparency section: https://www.glyphosate.eu/transparency/scientific-dossier/public-literature/
1) LRR part one covering the search period Jan 2010 – Dec 2019;
2) LRR part two covering the search period Jan 2020 – Jun 2020;
3) LRR dedicated to the literature review for the endocrine disrupting properties (ED) of glyphosate

Public literature identification and selection statistics

- The literature search was conducted by accessing 11 bibliographic databases via the service provider STN covering the period January 2010 to end-June 2020.
- The search terms covered glyphosate and its metabolites, including synonyms, in different languages and with all relevant identification (e.g. CAS numbers, IUPAC names) to maximise capturing all references related to glyphosate. Search filters relating to the four dossier-relevant technical sections (toxicology, residues, environmental fate, and ecotoxicology) were then applied in a focused search strategy. Detailed information about bibliographic databases and search terms is provided in dedicated tables of the LRR documents[4] (see flow chart above).
- After removal of duplicates, 12,178 articles in total were identified. All 12,178 articles were subsequently assessed by teams of technical experts for their relevance of informing on the dossier data requirements, by evaluating the information provided in the article title and abstract (summary).
- A total of 10,558 of the 12,178 articles were identified as "non-relevant" in this selection step. The criteria for title/abstract relevance assessment are detailed in the Appendix "criteria for relevance assessment" of this position paper, identical with the GRG's LRR documents point 2.4 "Relevance assessment".
- For the remaining 1,620 articles, identified as potentially "relevant" in the title/abstract assessment, the full text documents were purchased and reviewed by teams of technical experts in detail for their relevance following the "detailed assessment" procedure described in the EFSA Guidance document. The criteria for full article detailed relevance assessment are the same as for title/abstract relevance assessment and are described in the Appendix "criteria for relevance assessment" of this position paper, identical with the GRG's LRR documents point 2.4 "Relevance assessment".
- Of the remaining 1,620 articles, 887 were identified as "non-relevant" in the detailed assessment and were excluded from further evaluation.
- The remaining 733 articles identified as "relevant" in the detailed assessment were classified according to the EFSA Guidance Document into categories A, B, and C. The number of articles in each category were:
    - Category A: **191**
    - Category B: **523**
    - Category C: **19**
- A graphical and tabular overview of the search and evaluation statistics is provided on the next page:



January 2010 – end June 2020								
Section	**Number of articles found (after removal of duplicates)**	**Rapid assessment (title/abstract level)**		**Detailed assessment (full-text level)**				
		non-relevant articles	**potentially relevant / unclear relevance**	**non-relevant articles**	**relevant articles (category A+B+C)[c)]**	**Category A[d)]**	**Category B[e)]**	**Category C[f)]**
Efficacy / Agronomy [a)]	4684	4684						
Analytical methods [a)]	189	189						
Other non-relevant categories [b)]	2503	2503						
Ecotoxicology	1614	1039	575	412	163	12	148	3
E-fate	1147	842	305	132	173	100	73	0
Residues	491	420	71	30	41	12	19	10
Toxicology	1550	881	669	313	356	67	283	6
						0		
Total	**12178**	**10558**	**1620**	**887**	**733**	**191[g)]**	**523**	**19**

a) Efficacy / Agronomy (e.g. reporting desired effects on organisms to be controlled) and development of analytical methods (artificial measurements) do not provide information useful/required for the environmental or human safety risk assessment.
b) The category "other non-relevant categories" covers a wide range of scientific publications which are not related to glyphosate or its metabolites or are not related to exposure of humans or the environment to glyphosate or its metabolites and thus not relevant for the risk assessments.
c) Classification for relevance based on EFSA Journal 2011;9(2):2092, Point 5.4.1.
d) Category A: Articles, which provide data for establishing or refining risk assessment parameters.
e) Category B: Articles relevant to the data requirement but in the opinion of the applicant providing only supplementary information that does not alter existing risk assessment.
f) Category C: Articles for which relevance cannot be clearly determined.
g) Number of summaries presented in the AIR5 dossier (these articles are of relevance category A and reliable without or with several restrictions).

Out of the 12,178 articles identified in the GRG's public literature search, 4,802 articles were categorized by expert team judgment into the dossier-relevant technical sections (toxicology, residues, environmental fate, and ecotoxicology). Within this subset of potentially dossier-relevant articles, 733 articles were identified as relevant by expert team judgement.

- In addition to the GRG's general public literature search, an Endocrine Disruptor (ED)-specific literature search was performed to ascertain whether any scientific peer-reviewed open literature would address potential endocrine-disrupting properties of glyphosate.
- As the previous endocrine disruptor literature search, already evaluated at EU level during the AIR2 glyphosate renewal, covers the publication period between January 2014 and October 2016, a new literature search has been conducted in order to extend and update the existing search. This new ED literature search covers the publication period between November 2016 and July 2019.
- This new ED literature search is transparently documented in the Literature Review Report "Scientific peer-reviewed open literature for the endocrine disrupting properties of glyphosate", available on the GRG website[4].
- A tabular overview of the ED literature search and evaluation statistics is provided in the table below:

Table 6: Summary of the review

	Number	Justification
Total number of summary records retrieved from search.	5036	n.a
Total number of summary records retrieved after removing duplicates from all database searches. [a)]	4024	n.a.
Number of summary records excluded after rapid assessment for relevance (by title / abstract).	3640	Irrelevant information for the assessment of the ED potential of Glyphosate
Total number of full-text documents assessed in detail.	384	n.a.
Number of studies excluded from the risk assessment after detailed assessment of full-text documents (*i.e.* not relevant).	347	See table 11
Number of articles not excluded after detailed assessment. [c)]	47 (37 + 10[d)])	See tables 12 & 13
Number of articles / summaries presented in the dossier. [e)]	17	See table 14

[a)] Automatic and manual removal within databases.

[b)] EFSA GD category 5.4.1 a, b and c.

[c)] All articles belonging to the category A, B, C of the Point 5.4.1 (as stated in the EFSA Guidance Document).

[d)] Publication identified as being relevant for ED assessment in the literature assessment according to EFSA Guidance "Submission of 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

[e)] Summaries presented in the dossier: articles classified as relevant (EFSA GD, Point 5.4.1, category A) & reliable or relevant (EFSA GD, Point 5.4.1, category A) & reliable with restrictions.

The relevance assessment process

- Relevance in this context has the meaning of the contribution of the information to answer a specific question relevant to the dossier, i.e. that informs one or more data requirement(s), including hazard identification, hazard characterisation and exposure assessment, for the active substance under assessment, its relevant metabolites, or representative plant protection product, as defined by the EFSA guidance.
- The fact that 12,178 literature articles were identified by the GRG shows the extremely broad scope of the initial search for the public literature evaluation, with the goal of minimizing the risk for missing potentially relevant articles. Consequently, the broad search strategy resulted in an increased number of ultimately non-relevant articles.
- The relevance assessment process is designed to ensure that literature articles that investigate any of the four dossier-relevant areas (toxicology, residues, environmental fate, and ecotoxicology) are reliably identified.
- The assessment process is divided into three parts, in line with the EFSA guidance document on the public literature search:
    - Title/abstract relevance assessment
    - Full article detailed relevance assessment
    - Reliability assessment of the provided scientific information

Title/abstract relevance assessment

- In this first selection step, all 12,178 articles identified in the GRG's public literature search were assessed by technical expert teams for their relevance to meeting the dossier data requirements, including hazard identification, hazard characterisation and exposure assessment, for the active substance glyphosate, its metabolites, or the representative plant protection product, by evaluating the information provided in the article title and abstract (summary).
- The process by which the expert teams took the decisions on study selection is clearly and transparently reported in the LRR documents, including description of the criteria used for title/abstract relevance assessment and documentation of literature article bibliographic information in dedicated tables (see overview flow-chart above for additional details).
- Only clearly non-relevant literature articles were excluded at this stage of the assessment, for example articles dealing exclusively with topics such as the efficacy of PPPs, patents, studies not focused on glyphosate, or studies not dealing with EU relevant uses, that do not contribute to the dossier data requirements (for detailed non-relevance criteria, see Appendix "criteria for relevance assessment" of this position paper, identical with the GRG's LRR documents point 2.4 "Relevance assessment").
- **The title/abstract relevance assessment does not consider whether or not the study described in the literature article is conducted according to Good Laboratory Practice (GLP) or according to established test guidelines.**
- **For each excluded article the GRG provided a justification. Comprehensive overview tables with bibliographic details of all excluded articles, including justification why articles have not been further considered, are available on AGG and GRG websites in the form of two stand-alone pdf documents.**

Full article detailed relevance assessment

- The full text documents of literature articles not excluded in the title/abstract assessment process (1,620 articles) were purchased and reviewed in detail by technical expert teams, thus allowing in-depth insights into the nature, set-up and findings of the described scientific research. Based on the full text evaluation the technical experts were able to decide about the article's relevance for informing the dossier data requirements.
- For both assessments (title/abstract and full-text article) the same relevance criteria were applicable and a justification for their non-relevance was provided (for detailed non-relevance criteria, see Appendix "criteria for relevance assessment" of this position paper, identical with the GRG's LRR documents point 2.4 "Relevance assessment").
- **The full article detailed relevance assessment does not consider whether or not the study described in the literature article is conducted according to Good Laboratory Practice (GLP) or according to established test guidelines.**
- For each excluded article the GRG provided a justification. Comprehensive overview tables with bibliographic details of all excluded articles, including justification why articles have not been further considered, are documented in the LRR (see overview flow-chart above for additional details).
- Based on the full article detailed relevance assessment, the articles are classified as described above, according to the EFSA guidance document and assigned to either relevance category A (relevant for the risk assessment), B (supplementary information) or C (undetermined relevance).

Reliability assessment of the provided scientific information

- Reliability in this context has the meaning of a consideration on the quality of the described study data in the literature article and the extent to which critical information is provided that is necessary to understand the robustness of the test method, how the study was carried out, how it was reported and how conclusive the reported findings are.
- All category A articles (relevant for the risk assessment) were assessed for their reliability by technical expert teams and identified as either "reliable" or "reliable with restrictions". The content and findings of these "reliable" literature studies were included in a standard summary format in the dossier and contributed to the data set that informed the data requirements and risk assessment.
- In case a category A article was found to not meeting the reliability criteria, the GRG listed this article under Category B (relevant but supplementary) and provided a justification for this decision, for maximum transparency and the authorities' further consideration.
- **The reliability assessment does not depend on whether or not the experimental work described in the literature articles was conducted according to Good Laboratory Practice (GLP) or according to established test guidelines**, and articles reporting non-GLP experimental work were identified that met the reliability criteria**.**

Applicant response to comments/concerns raised by commenting parties during public consultation

EFSA requests for additional information (stop-clock): The points below are addressing aspects of EFSA's additional information requests from

- Public request # 2, 3, 11, 12, 14, 20, 21
- Mammalian toxicology # 37, 47, 58, 64
- Ecotoxicology # 67, 77, 78

- EFSA request: "*Applicant to review the literature search and clarify the approach used for the literature review in view of the comments/concerns raised by several commenting parties during the public consultation.*"
    - Applicant: The GRG's approach used for the literature review is described in detail in this position paper and the three LRR documents that are part of the glyphosate renewal dossier. Specific concerns are addressed in this chapter.

- EFSA request: "*Consider reassessment of the literature search in light of the comments received.*"
    - Applicant: The GRG followed the established EFSA guidance as well as the AGG's advice as discussed during a dedicated pre-submission meeting between the AGG and GRG on 11 December 2019. Minutes and presentations are publicly available on the AGG and GRG websites. The GRG documented the literature search and evaluation process in a transparent and comprehensive manner in the LRR documents, available for download via the "Transparency / Scientific Dossier / Public Literature" section of the GRG website: www.glyphosate.eu[5]. The LRR documents contain tables where the GRG's decision for exclusion, inclusion, relevance and reliability for each of the identified 12,178 articles is transparently documented and justifications are provided for every article. The evaluation of the public literature submitted by the GRG was a part of the first step in the dossier evaluation process. Following the AGG assessment of this literature review, it requested additional articles and summaries in cases where doubts about the GRG's selection had been raised, in order to directly evaluate information in the article and to determine if their conclusions of relevance / reliability of articles were different. These requests are documented in Volume 1 of the dRAR, under point 3.1.4 "List of studies to be generated, still ongoing or available but not peer reviewed". Subsequently, during the EFSA public consultation, numerous stakeholders submitted information on additional potentially relevant literature articles, either from the already considered search period of January 2010 – June 2020, due to a different opinion about the relevance and reliability of individual articles, or originating prior to (older) or after (more recent) the original search period. EFSA and the AGG analysed these public comments and responded to the requests for additional public literature articles in EFSA's request for additional information that the GRG received on 14 March 2022 (pre-notification received on 21 February 2022) and that the GRG addressed with submission of additional information on 14 April

[5] Direct link to the public literature transparency section of the GRG website that contains the Literature Review Report documents for download: https://www.glyphosate.eu/transparency/scientific-dossier/public-literature/

2022. In summary the glyphosate dossier evaluation is based on information from public literature articles as considered relevant by the GRG applicant, by the AGG evaluating authorities, by numerous public stakeholders and by EFSA. It is up to the AGG and EFSA to make a final decision on the relevance of the information from all these public literature articles for the risk assessment and safety conclusion of glyphosate.

- EFSA request: "*Clarifying relevance and reliability criteria.*"
    - Applicant: Relevance and reliability criteria are transparently documented in the LRR documents. These criteria have been decided upon by technical area experts and discussed with the AGG during the pre-submission meeting on 11 December 2019. Minutes and presentations are publicly available on the AGG and GRG websites. As described above, the GRG's opinion on relevance and reliability of public literature articles is a first step in the dossier evaluation process, and the AGG, EFSA and other public stakeholders sometimes had doubts about specific interpretations or a different opinion and the AGG and EFSA requested a number of additional literature articles, including their summaries, from the GRG later on during the dossier evaluation process.

- EFSA request: "*A transparent explanation should be provided with proper and well substantiated justification and solid argumentation when some publications are not considered further.*"
    - Applicant: The GRG documented the literature search and evaluation process in a transparent and comprehensive manner in the LRR documents that are available for download on the GRG website in the "Transparency / Scientific Dossier / Public Literature" section[6]. The LRR documents contain tables where the GRG's reason for exclusion, inclusion, relevance and reliability for each of the identified 12,178 articles is transparently documented and justifications are provided for every article.

- EFSA request: "*Please consider also the additional publications referenced as part of the public consultation and ensure that study summaries are also provided.*"
    - Applicant: The GRG addresses this EFSA request by submitting additional > 300 literature articles, including their summaries, during the stop-clock period.

[6] All Literature Review Reports included in the glyphosate renewal dossier are available for download on the GRG website in the public literature transparency section: https://www.glyphosate.eu/transparency/scientific-dossier/public-literature/
1) LRR part one covering the search period Jan 2010 – Dec 2019;
2) LRR part two covering the search period Jan 2020 – Jun 2020;
3) LRR dedicated to the literature review for the endocrine disrupting properties (ED) of glyphosate
In addition, for all articles evaluated and excluded after title/abstract relevance assessment, the GRG provided comprehensive overview tables with bibliographic details and justification why articles have not been further considered. These tables are available on the AGG and GRG websites in the form of two stand-alone pdf documents.

- EFSA request: "*Applicant to provide more details about the search terms and their combination as used for the literature search in order to cover the data requirement related to human health.*"
    - Applicant: The search strategy, i.e. the combination of search terms, is described in detail, including the search terms used, in the LRR documents, following the requirements of the applicable EFSA guidance document.

- EFSA request: "*The reasons why some studies quoted during the commenting phase were not captured or further considered in the assessment.*"
    - Applicant: The GRG provided justification in their comments submitted as response to the comments in the Reporting Table to the AGG and EFSA on 10 December 2021. Due to the short procedural timeline of two weeks, that is specified in Regulation (EC) No 1107/2009, it was not possible to provide in-depth evaluation of all public stakeholder comments. However, after the AGG's and EFSA's evaluation of the public consultation comments, the GRG is addressing all the points raised by EFSA in its request for additional information as comprehensively as possible within the given timeframe and is submitting additional summaries and evaluations of the public literature articles indicated by public stakeholders.

- EFSA request: "*The applicant is requested to clarify why some of the publications retrieved by the literature searches did not enter into one of the four technical sections (residues, environmental fate, toxicology and ecotoxicology) applying search filters and whether these publications were assessed for relevance.*"
    - Applicant: The search terms for the GRG's public literature search covered glyphosate and its metabolites, including synonyms, in different languages and with all relevant identification (e.g. CAS numbers, IUPAC names) to maximise capturing all references related to glyphosate. Search filters relating to the four dossier-relevant technical sections (toxicology, residues, environmental fate, and ecotoxicology) were then applied in a focused search strategy. After removal of duplicates, 12,178 articles in total were identified. All 12,178 articles were subsequently assessed by technical expert teams for their relevance of informing on the dossier data requirements by evaluating the information provided in the article title and abstract. A total of 10,558 of the 12,178 articles were identified as "non-relevant" in this selection step. The fact that 12,178 literature articles were identified by the GRG shows the extremely broad scope of the initial search for the public literature evaluation, with the goal of minimizing the risk for missing potentially relevant articles. Consequently, the broad search strategy resulted in an increased number of ultimately non-relevant articles. The relevance assessment process is designed to ensure that literature articles that investigate any of the four dossier-relevant areas (toxicology, residues, environmental fate, and ecotoxicology) are reliably identified. The sorting into technical sections (residues, environmental fate, toxicology and ecotoxicology) was done by expert team judgement, not by applying automatic search filters. Expert team judgement for the initial article selection was based on title and abstract evaluations; all subsequent steps of the public literature selection and evaluation was done by teams of experts, thus assuring continued and proper scientific judgement at all levels of the process.

Specific concerns mentioned in public stakeholder documents:

R.I.S.K. Consultancy (18 November 2021), document "1 (109)_EFSA 8.5Guidance_glyphos dRAR'21 report_PCSF-188571_OE070"[7]

- Page 3: "*as measured against the most easily-found published papers, i.e. those we find in PubMed, on average, under 20% of toxicity findings in PubMed are found*"
    - Applicant: A concern is raised that the GRG's public literature search is not set-up in a way to identify all relevant articles. This is comprehensively addressed by the description of search strategy and selection process in the LRR documents. The fact that an exceedingly large number of literature articles has been retrieved from the search as "hit list" (> 12,000) and was evaluated by expert teams, providing justification for the relevance or non-relevance for every single article, shows the thorough and comprehensive nature of the literature search as required by EFSA guidance and as executed and submitted by the applicant. The relevance assessment process is designed to ensure that literature articles that investigate any of the four dossier-relevant areas (toxicology, residues, environmental fate, and ecotoxicology) are reliably identified. The sorting into technical sections (residues, environmental fate, toxicology and ecotoxicology) was done by expert team judgement, not by applying automatic search filters. Expert team judgement for the initial article selection was based on title and abstract evaluations; all subsequent steps of the public literature selection and evaluation was done by teams of experts based on full-text article evaluation, thus assuring continued and proper scientific judgement at all levels of the process.

- Page 3: "*we found … a lot more than the list that industry told the RMS were the "relevant" ones including many studies of formulations*"
    - Applicant: This is comprehensively addressed by the description of the search strategy and selection process in the LRR documents. Expert teams analysed each article in the "hit list" and decided on relevance following the transparently described criteria in the LRR documents. Justifications are given for each article why the article was categorized as relevant or non-relevant. All documentation on this process is available in the LRR documents and on the AGG and GRG websites. Regarding formulations: Following the applicable regulations and guidelines, only a representative formulation is relevant to the active substance renewal, since the renewal evaluation focuses on the safety of the active substance applied in one formulation authorized in at least one Member State. The representative formulation is used as a "vehicle" in the dossier to allow representative risk assessments at a broader level. Considering additional formulations is out-of-scope of the active substance renewal and subject to the dedicated product authorization at a country level, including toxicological testing of the formulated products.

- Page 4: Concern that selection criteria are too strict and too many papers are excluded.
    - Applicant: The GRG's public literature review, as documented in the literature review Reports, is a first proposal to the authorities about the relevance and reliability of the

[7] The cited report was submitted to EFSA during the public consultation on the glyphosate dRAR in 2021. The report is available on the OpenEFSA website: https://open.efsa.europa.eu/consultation/a0c1v00000HePrzAAF

evaluated public literature. All information is transparently documented. The AGG and EFSA assessed the applicant's LRR and requested additional articles in cases where they disagreed with the applicant's opinion. In addition, other public stakeholders pointed to the lack of additional articles during the public consultation, and these articles have been requested by EFSA from the applicant during the stop-clock period. This stepwise evaluation process assures that all opinions about relevant articles are considered and the justifications for exclusion are transparently recorded.

- Page 5: "*Only industry uses the OECD test methods...therefore almost every published finding is dismissed before even being evaluated. We must conclude that this is a deliberate move by EFSA–to open an escape chute by which almost all toxicity findings by academics, especially low-dose ones, are dismissed without having to evaluate them.*"
    - Applicant: "Findings by academics" as reported in scientific peer-reviewed open literature are transparently evaluated regarding their relevance and reliability, irrespective of test methods used. The guiding question is in how far the findings are contributing to the overall data relevant for the risk assessment of the active substance for humans and the environment. Some of the articles considered to be "findings by academics" are indeed part of the overall weight of evidence of scientific information for dossier evaluation, as well as are industry-sponsored GLP studies following OECD test guidelines. In the end what counts are well described and reproducible results that show a dose response for any effect relevant to the risk assessment.

- Page 6: "*immediately–at the title/abstract "rapid screening" stage–most were wrongly thrown away as irrelevant*"
    - Applicant: The table and pie chart in the chapter "Public literature identification and selection statistics" of this position paper clearly document that all identified articles were thoroughly analysed and attributed to technical categories and relevance criteria. Nothing was ignored or discarded *a-priori*. Subsequent evaluation by the AGG and EFSA, including comments from other public stakeholders, ensure that no article that is considered relevant was ignored, but rather analysed and a conscious decision was made and with justifications that were documented regarding relevance and reliability.

- Page 7: "*dismissal of … studies … called relevant yet magically "supplementary–illogically excluded from full text reliability evaluation*"
    - Applicant: As described in detail in the LRR documents, the categorization "supplementary" is the result of a thorough full text evaluation of a given article by teams of experts in the field. In this case this analysis resulted in the conclusion that the provided information does not contain sufficient details to directly contribute to the risk assessment. However, to ensure that anything is considered that could potentially add useful information to the evaluation, the article is transparently included into the dossier, for the authorities' further evaluation.

- Page 7: "*confusion of reliability criteria to dismiss findings en mass for being irrelevant.*"
    - Applicant: Applied reliability criteria are transparently described in the LRR documents, and for each article the considerations about relevance and reliability are

transparently documented in LRR tables and in the summary contained in the summary dossier.

- Page 7: "*Table 1: EVALUATION of 'RELEVANCE' of PUBLISHED TOXICITY FINDINGS*"
    - Applicant: The tables in this position paper, in the chapter "Public literature identification and selection statistics", provide in a fully transparent way the complete evaluation statistics of the consolidated GRG literature search submitted in the glyphosate AIR5 renewal dossier for the period January 2010 – June 2020 and for the additional Endocrine Disruptor (ED)-specific literature search. The footnotes provide further details. The table shows which articles the GRG submitted to the authorities in the initial dossier. During the evaluation process, AGG and EFSA requested additional articles, reflecting input from other public stakeholders during public consultation.

- Page 8: "*… [studies] deemed fully relevant … will have a study summary in the RAR, so as to evaluate their reliability*"
    - Applicant: The GRG prepared detailed summaries of all the category A studies and included them in the dossier, for the AGG and EFSA to evaluate. The AGG added their conclusion to each summary as documented in the RAR, containing transparent information of the applicant's opinion and the AGG's evaluation. This approach is in full compliance with the applicable EFSA guidance and the recommendation of the AGG as discussed during the public literature search pre-submission meeting on 11 December 2019 (minutes and presentations are publicly available on the AGG and GRG websites). According to the EFSA guidance studies of category A, that provide data for establishing or refining risk assessment parameters, need to be summarised in detail, while for studies of category B, that provide only supplementary information, and of category C, where relevance cannot be determined, the full text literature article and a justification for such a decision is provided as part of the dossier and LRR, for the authorities' further consideration.

- Page 9: "*Table 2: FATE of PUBLISHED TOXICITY FINDINGS EVALUATED for RELIABILITY*"
    - Applicant: The category A public literature articles have been summarized according to established guidance and contain transparent information of the applicant's opinion and the AGG's evaluation on the relevance and reliability of the studies. Category B and C public literature articles have been provided in full text as part of the dossier, and a justification for such a decision is provided as part of the dossier and LRR, following the EFSA guidance. EFSA will make the final decision on their relevance and reliability, also considering other public stakeholder input received during public consultation. Should an expert discussion be deemed necessary, EFSA will organize so-called peer review expert meetings later during the evaluation process that will involve experts from Member State regulatory authorities. Minutes of these peer review expert meetings will be transparently published afterwards.

Generations Futures report "Glyphosate Evaluation: A Severely Skewed Report" 16 November 2021[8]

- Page 3: "*Just by reading the title and the abstract, many relevant studies are excluded from the outset (studies judged on their reliability and not their relevance, studies described at conferences which are nevertheless internationally recognized, mechanistic studies relating the effects of glyphosate at molecular and cellular levels, studies carried out outside the EU under conditions which are considered without any explanation not transferable to Europe).*"
    - Applicant: This is comprehensively addressed by the description of search strategy and selection process in the GRG's LRR documents. Expert teams analyzed each paper in the literature search "hit list" and decided on relevance following the transparently displayed criteria in the LRR. Justifications are given for each article why the article was categorized as relevant or non-relevant. All documentation on this process is available in the LRR documents and on the AGG and GRG websites. The applicant's LRR is a first proposal to the authorities about the relevance and reliability of public literature. All information is transparently documented. The AGG and EFSA evaluated the applicant's LRR and decided on requesting additional articles in case they disagreed with the applicant's opinion. In addition, other public stakeholders pointed to additional articles during the public consultation; these articles have been requested by EFSA from the applicant during stop-clock. By this stepwise evaluation process it is assured that all opinions about relevant articles are considered.

- Page 3 "*The consequences of this selection method are that 92% of public studies are deemed irrelevant! In the end, out of the 7000 or so studies found, only 30 studies, equivalent to 0.4% of the studies found, are deemed relevant and reliable without restriction!*"
    - Applicant: The table and pie chart in the chapter "Public literature identification and selection statistics" of this position paper clearly document that all identified articles were thoroughly analysed and attributed to technical categories and relevance criteria. Nothing was ignored or discarded *a-priori*. Subsequent evaluation by the AGG and EFSA, including comments from other public stakeholders, ensure that no article that is considered relevant was ignored, but rather analysed and a conscious decision was made and with justifications that were documented regarding relevance and reliability.

[8] The cited Generations Futures report is referenced in the report R.I.S.K. Consultancy (18 November 2021), document "1 (109)_EFSA 8.5Guidance_glyphos dRAR'21 report_PCSF-188571_OE070" that was submitted to EFSA during the public consultation on the glyphosate dRAR in 2021. The Generations Futures report is available online: Evaluation du glyphosate : un rapport gravement biaisé ! - Générations Futures (generations-futures.fr)

- Page 7 "*Would the research work of academics therefore be irrelevant and unreliable 99.6% of the time? Is academic science so far removed from regulatory science?*"
    - Applicant: Regulatory science OECD guideline studies are specifically designed to address the data points required by the dossier and risk assessment, following established Regulations and guidelines[9]. Especially the long-term tox studies provide comprehensive insights into potential adverse effects under longer term exposure and under lower concentrations than in acute studies. All findings are considered in a weight of evidence approach, with the results of the long term (higher tier) studies being of specific importance and weight. Research work of academics is of upmost importance, provided it is assessed as relevant and reliable. Peer reviewed literature which reports full details of experimental work is given particular weight and is used to alert for potential effects which have not been identified in guideline studies. This warrants further investigation and may result in additional requests to the notifiers. Due to the nature of the scientific knowledge generated outside of robust approved protocols (e.g. OECD) and outside the principles of GLP, reliability of academic research work is even more increased if results are confirmed by independent scientific teams adding further knowledge and corroboration to the first publication. It is crucial for academic science in order to be considered relevant and reliable for regulatory risk assessment to sufficiently prove findings by use of controls / sufficient numbers, and to provide quantitative information.

- Page 12 "*Flaws in the reliability analysis … lack of transparency in the RAR - What criteria were used? What is the weight of each of the criteria in judging the quality of a study? What are the criteria that must absolutely be met to judge a study as reliable without restriction? Are there criteria which, if not met, automatically lead to the study being deemed unreliable or just supportive?*"
    - Applicant: It is crucial for academic science in order to be considered relevant and reliable for regulatory risk assessment to provide sufficiently detailed information. Given the often quite limited number of pages of scientific literature articles, the provided information cannot be as detailed as is the case for study reports that were particularly prepared to address a certain regulatory data requirement and that include a lot of supplementary data and information to assure that everything was in order during the conduct of an experiment. A lack of detail hinders a final conclusion on the reliability, as well as certain quality aspects in design, conduct and reporting.

[9] The study methods are listed in EU communications, to complement the data requirements. Each references the detailed methodologies which have to be followed by the laboratory which carries out the studies on behalf of the notifying company: Commission Communication in the framework of the implementation of Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52013XC0403(02)&from=EN; Commission communication in the framework of the implementation of Commission Regulation (EU) No 284/2013 of 1 March 2013 setting out the data requirements for plant protection products, in accordance with Regulation (EC) No 1107/2009: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52013XC0403(03)&from=EN
The guideline methods are typically identical or very similar to those established by the OECD. Methods are usually developed by an expert group and thoroughly tested in different laboratories (government, academic, commercial) to ensure that the outcome of the study is reliable, that the resulting data are robust and that they can be consistently interpreted and that the study is 'repeatable', allowing others to carry out the same study: http://www.oecd.org/chemicalsafety/testing/oecdguidelinesforthetestingofchemicals.htm

- Page 12 "*Worse, it appears that literature studies have been evaluated for their reliability much more severely than industry studies*"
    - Applicant: In the RAR the AGG provided detailed justification for their conclusion on all the submitted "industry studies" for being valid, supplemental or invalid. This followed similar principles like the ones applied in the evaluation of reliability of public literature articles. In both cases the justifications are fully and transparently documented in the RAR.

Appendix

Criteria for relevance assessment

Literature articles identified as "non-relevant" based on title/abstract or full article detailed assessment belong to one of the following categories. These articles were excluded from further evaluation and a justification for their non-relevance was provided.

The points below are taken from the GRG's LRR documents, under point 2.4 "Relevance assessment".

- Publications related to efficacy (resistance related articles, new uses of control of pest/crops) or to agricultural / biological research (crop science, breeding, fertilization, tillage, fundamental plant physiology / micro / molecular biology).
- Publications dealing with analytical methods / development.
- Publications describing new methods of synthesis (discovery / developments) or other aspects of basic (organic / inorganic) chemistry.
- Patents.
- Wastewater treatment.
- Abstracts referring to a conference contribution that does not contain sufficient data / information for risk assessment.
- Publications focusing on genetically modified organisms / transgenic crops; no data directly relevant to glyphosate evaluation (e.g. crop compositional analysis, gene flow, protein characterization).
- Publications where glyphosate or a relevant metabolite were not the focus of the article.
- Secondary information including scientific and regulatory reviews.
- Articles dealing with political / socio / economic analysis.
- Observations caused by mixture of compounds / potentially causal factors and thus not attributable to a substance of concern (e.g. mixture toxicity).
- Study design, test system, species tested, exposure routes etc. are not relevant for the European regulatory purposes.
- Findings not related to the areas of ecotoxicology, toxicology, metabolism, environmental fate.
- Publications not dealing with EU representative uses / conditions (e.g. field locations, soil properties, non-EU monitoring etc.).
- Publications dealing with a Roundup formulation / other glyphosate formulations that is not the representative formulation for the AIR5 dossier and thus not relevant to the EU glyphosate renewal.
- Publications dealing with general pesticide exposures (not glyphosate specific).
- Publications generating endpoints that are not relatable to the EU level regulatory risk assessment (e.g. findings based on enzyme, cellular and molecular level etc.).
- Opinion articles where no new data is provided that can be used for the EU regulatory risk assessment.

Many articles that have been considered relevant for the risk assessment of glyphosate and have been assessed for reliability on full text basis, contain experimental data on formulations different from the dossier representative formulation MON 52276 and contain different co-formulants as well

as on glyphosate. In such cases, only the toxicology data pertinent to glyphosate and to the reference formulation (if that can be clearly stated by the author of the article) are summarized and discussed. In the case of articles on exposure monitoring and epidemiology, exposure to glyphosate formulations are considered.

Criteria for reliability assessment

For literature articles, which were identified in the full article detailed assessment as relevant articles of Category A, a reliability assessment was performed. The reliability criteria for each technical section are summarized in the tables below. For relevant articles of Category A that were classified either as reliable or reliable with restrictions, summaries were compiled and included into the dossier. Articles of Category A which were classified as non-reliable were listed in Category B and a justification for such a decision was provided.

The tables below are taken from the GRG's LRR documents, under point 2.5 "Reliability assessment".

Table: Reliability criteria for ecotoxicology, environmental fate and residues

Applied for	Reliability criteria
Ecotoxicology, Environmental Fate, Residues	For guideline-compliant studies (GLP studies): OECD, OPPTS, ISO, and others. The validity/quality criteria listed in the corresponding guidelines are met.
Ecotoxicology, Environmental Fate, Residues	(No) previous exposure to other chemicals is documented (where relevant).
Ecotoxicology	For aquatic studies, the test substance is dissolved in water or where a carrier is required, it is appropriate (non-toxic) and a carrier control / positive control is considered in the test design.
Environmental Fate, Residues	The test substance is dissolved in water or non-toxic solvent.
Ecotoxicology, Environmental Fate, Residues	Test item is sufficiently documented, and reported (i.e. purity, source, content, storage conditions).
Ecotoxicology	For tests including vertebrates, compliance of the batches used in toxicity studies compared to the technical specification.
Ecotoxicology	Species used in the experiment are clearly reported, including source, experimental conditions (where relevant): strain, adequate age/life stage, body weight, acclimatization, temperature, pH, oxygen (dissolved oxygen for aquatic tests) content, housing, light conditions, humidity (terrestrial species) incubation conditions, feeding.
Ecotoxicology	The validity criteria from relevant test guidelines can be extrapolated across different species but not necessarily across different test designs. If different, then the nature of the difference and impact should ideally be discussed.
Ecotoxicology, Environmental Fate, Residues	Only glyphosate or its metabolites is the test substance (excluding mixture), and information on application of the test substance is described.
Ecotoxicology, Environmental Fate, Residues	The endpoint measured can be considered a consequence of glyphosate (or a glyphosate metabolite).
Ecotoxicology, Environmental Fate, Residues	Study design / test system is well described, including when relevant: concentration in exposure media (dose rates, volume applied, etc.), dilution/mixture of test item (solvent, vehicle) where relevant.

Applied for	Reliability criteria
Ecotoxicology, Environmental Fate, Residues	Analytical verifications performed in test media (concentration) / collected samples, stability of the test substance in test medium should be documented.
Ecotoxicology	The test has been performed in several dose levels (at least 3) including a positive / negative control where relevant.
Ecotoxicology	Suitable exposure throughout the whole exposure period was demonstrated and reported.
Ecotoxicology	A clear concentration response relationship is reported – in studies where the dose response test design is employed.
Ecotoxicology	A sufficient number of animals per group to facilitate statistical analysis reported: mortality in control groups reported, observations/findings in positive/negative control clearly reported (where relevant).
Ecotoxicology, Environmental Fate, Residues	Assessment of the statistical power of the assay is possible with reported data.
Ecotoxicology, Environmental Fate, Residues	Statistical methodology is reported (e.g., checking the plots and confidence intervals).
Ecotoxicology	Description of the observations (including time-points), examinations, and analyses performed, with (where relevant) dissections being well documented.
Ecotoxicology	For terrestrial ecotoxicological studies in the laboratory or the field, the substrates used should be adequately described e.g. nature of substrate i.e. species of leaf or soil type.
Ecotoxicology, Environmental Fate, Residues	Field locations relevant / comparable to European conditions.
Ecotoxicology, Environmental Fate, Residues	Characterization of soil: texture (sandy loam, silty loam, loam, loamy sand), pH (5.5-8.0), cation exchange capacity, organic carbon (0.5-2-5%), bulk density, water retention, microbial biomass (~1% of organic carbon).
Ecotoxicology, Environmental Fate	Other soils where information on characterization by the parameters: pH, texture, CEC, organic carbon, bulk density, water holding capacity, microbial biomass.
Ecotoxicology, Environmental Fate, Residues	For tests including agricultural soils, they should not have been treated with test substance or similar substances for a minimum of 1 year.
Ecotoxicology, Environmental Fate	For soil samples, sampling from A-horizon, top 20 cm layers; soils freshly from field preferred (storage max 3 months at 4 +/- 2°C).
Ecotoxicology, Environmental Fate, Residues	Data on precipitation is recorded.
Environmental Fate	The temperature was in the range between 20-25°C and the moisture was reported.
Environmental Fate	The presence of glyphosate identified in samples were collected from European groundwater, soil, surface waters, sediments or air.
Ecotoxicology	For lab terrestrial studies, the temperature was appropriate to the species being tested and generally should fall within the range between 20-25°C and soil moisture / relative humidity was reported.
Ecotoxicology	For bee studies, temperature of the study should be appropriate to species.
Ecotoxicology	For lab aquatic studies:
	The source and / or composition of the media used should be described.
	The temperature of the water should be appropriate to the species being tested and generally fall within the 15-25ºC.

Applied for	Reliability criteria
Ecotoxicology, Residues	The residue data can be linked to a clearly described GAP table, appropriate in the context of the renewal of approval of glyphosate (crop, application method, doses, intervals, PHI).
Ecotoxicology, Environmental Fate, Residues	Analytical results present residues measurements which can be correlated with the existing residues definition of glyphosate, and where relevant its metabolites.
Ecotoxicology, Environmental Fate, Residues	Analytical methods are clearly described; and adequate statement of specificity and sensitivity of the analytical methods is included.
Ecotoxicology	Assessment of the ECX for the width of the confidence interval around the median value; and the certainty on the level of protection offered by the median ECX is reported.
Environmental Fate	Radiolabel characterization: purity, specific activity, location of label is reported.
Environmental Fate	If degradation kinetics are included: data tables / model description / statistical parameters for kinetic fit to be provided.
Environmental Fate, Residues	Monitoring data: description of matrix analysed, and analytical methods to be fully described.
Environmental Fate	Clear description of application rate and relevance to approved uses.
Overall assessment: Reliable / Reliable with restrictions / Not reliable	

Table: Reliability criteria for toxicology – <u>epidemiology and exposure studies</u>

Reliability criteria – toxicology	
Epidemiology studies	**Exposure studies**
Guideline-specific	**Guideline-specific**
Study in accordance to valid internationally accepted testing guidelines/practices	Study in accordance to valid internationally accepted testing guidelines/practices
Study completely described and conducted following scientifically acceptable standards	Study performed according to GLP
	Study completely described and conducted following scientifically acceptable standards
Test substance	**Test substance**
Exposure to formulations with only glyphosate as a.i.	Exposure to formulations with only glyphosate as a.i.
Exposure to formulations with glyphosate combined with other a.i.	Exposure to formulations with glyphosate combined with other a.i.
Exposure to various formulations of pesticides	Exposure to various formulations of pesticides
Study	**Study**
Study design – epidemiological method followed	Study design clearly described
Description of population investigated	Population investigated sufficiently described
Description of exposure circumstances	Exposure circumstances sufficiently described
Description of results	Sampling scheme sufficiently documented
Have confounding factors been considered	Analytical method described in detail
Statistical analysis	Validation of analytical method reported
	Monitoring results reported
Overall assessment: Reliable / Reliable with restrictions / Not reliable	

Table: Reliability criteria for toxicology – *in vitro* and *in vivo* studies

Reliability criteria – toxicology and metabolism	
***In vitro* studies**	***In vivo* studies**
Guideline-specific	**Guideline-specific**
Study in accordance to valid internationally accepted testing guidelines	Study in accordance to valid internationally accepted testing guidelines.
Study performed according to GLP	Study performed according to GLP
Study completely described and conducted following scientifically acceptable standards	Study completely described and conducted following scientifically acceptable standards
Test substance	**Test substance**
Test material (Glyphosate) is sufficiently documented and reported (i.e. purity, source, content, storage conditions)	Test material (Glyphosate) is sufficiently documented and reported (i.e. purity, source, content, storage conditions)
Only glyphosate acid or one of its salts is the tested substance	Only glyphosate acid or one of its salts is the tested substance
AMPA is the tested substance	AMPA is the tested substance
Study	**Study**
Test system clearly and completely described	Test species clearly and completely described
Test conditions clearly and completely described	Test conditions clearly and completely described
Metabolic activation system clearly and completely described	Route and mode of administration described
Test concentrations in physiologically acceptable range (< 1 mM)	Dose levels reported
Cytotoxicity tests reported	Number of animals used per dose level reported
Positive and negative controls	Method of analysis described for analysis test media
Complete reporting of effects observed	Validation of the analytical method
Statistical methods described	Analytical verifications of test media
Historical negative and positive control data reported	Complete reporting of effects observed
Dose-effect relationship reported	Statistical methods described
	Historical control data of the laboratory reported
	Dose-effect relationship reported
Overall assessment: Reliable / Reliable with restrictions / Not reliable	