

ECPA Technical Guidance Paper

No: 2012/4

Technical guidance on the application of the EFSA Guidance Document „Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009“

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1. Rationale for ECPA Guidance

This ECPA Guidance is based on the EFSA Guidance Document ¹ (EFSA GD) published on 28 February 2011 and incorporates extensive industry experience in the area of literature searches. This industry guidance aims at providing both a transparent and practical process for collecting, selecting and evaluating scientific peer-reviewed open literature, which should result in a manageable workload for both evaluators and applicants **without jeopardizing the intention to ensure high level of protection for human and animal health and the environment.**

Most importantly, ECPA's guidance provides a simple yet robust definition of 'relevance', applicable to all publications, which identifies early in the process those papers that need to be taken into account in the evaluation by initially screening titles and abstracts. The EFSA guidance includes relevance criteria to be applied to each publication, depending on 'study type', which requires a detailed assessment of each publication at this stage. ECPA's guidance, however, will take forward for the reliability assessment a subset of publications compliant with the aim of the EFSA guidance.

Furthermore, ECPA's guidance provides a template for the literature review report. It contains a simple, user-friendly, tabular format to report the results of the selection process (assessment of relevance and reliability).

This ECPA guidance also serves to support any future revision of the EFSA GD (*"the Guidance may be revised when experience is gained in its application and in view of any amendments to Regulation (EC) No 1107/2009"* ¹).

For the sake of comparative purposes this ECPA guidance follows the sections and headings in the EFSA GD. Use of EFSA wording is highlighted in *italics* and marked with footnotes.

2. Intended users of the ECPA Guidance

This ECPA Guidance was written not only for applicants submitting dossiers for the approval of active substances under Regulation (EC) No 1107/2009 but also for competent authorities of the European Union.

3. Introduction

For the introduction of the subject refer to the EFSA GD, section 3, page 5.

The assessment process as described in detail in the EFSA GD can be divided into four key stages:

- Identification of scientific peer reviewed open literature (referred to subsequently as 'publications') from relevant information sources using appropriate search methods
- Selection of publications to be considered for further review using defined relevance criteria
- Evaluation of the publications and assessment of the potential impact on endpoints and risk assessment (including assessment of reliability)
- Provision of a transparent review of the entire process, including necessary details from each of the preceding steps

These are described in more detail in sections 5 and 6 in this document.

¹ Guidance of EFSA, Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) 1107/2009; EFSA Journal 2011; 9(2):2092

4. Terminology employed in Article 8(5) of Regulation (EC) No. 1107/2009

This ECPA guidance acknowledges the definitions provided in the ESFA GD; for clarity, the definition of 'relevant metabolite' as provided in Regulation (EC) No. 1107/2009 Article 3 (32) is used in this document.

5. Identification and selection of scientific peer-reviewed open literature to be incorporated into EU dossiers of active substances of plant protection products

5.1. Criteria for relevance

Publications meeting the relevance criteria are those showing new/unknown effects or information potentially contradictory to the regulatory data package for the active substance, its relevant metabolites and/or the plant protection products on human health, animal health and/or the environment, which could impact the endpoints or the risk assessment parameters.

Typically, publications providing information that do not challenge the existing regulatory data package will be treated as not meeting the relevance criteria.

The relevance criteria should be reported within the Literature Review Report(s) (LRR) as referred to in the EFSA GD (section 6, page 29).

An example of the LRR is provided in Appendix A.

5.2. Searching for scientific peer-reviewed open literature

5.2.1. Identifying sources of scientific peer-reviewed open literature

Hosted databases include, but are not limited to:

ANABSTR
BIOSIS
CA - Chemical Abstracts
CABA - CAB Abstracts
CAS REGISTRY
Embase
HSDB - Hazardous Substances Data Bank
Medline
REAXYS
RTECS
ToxCenter

5.2.2. Search strategies

Principle scientific areas to be covered are typically those having a potential impact on hazard classification/ risk assessments relating to human and animal health and the environment:

- Toxicological and toxicokinetic studies
- Residues in or on treated products, food and feed, including metabolism
- Fate and behaviour in the environment
- Ecotoxicological studies

Note:

For details please refer to EFSA GD (section 5.1, page 14 (box 2)).

*In line with Article 8(5) of Regulation (EC) No 1107/2009 applicants should consider the most recent scientific peer-reviewed open literature published during the last ten years prior to the dossier submission date... Without prejudice to Article 8(5) of Regulation (EC) No 1107/2009, the search may be updated within 6 months before the date of submission of the dossier and the search dates should be reported.*²

5.2.3. Reporting the searches and their results

The searches and their results should be reported within the Literature Review Report(s) (LRR).

An example how to report the necessary details regarding searches and their results is provided in the example for the LRR (Appendix A).

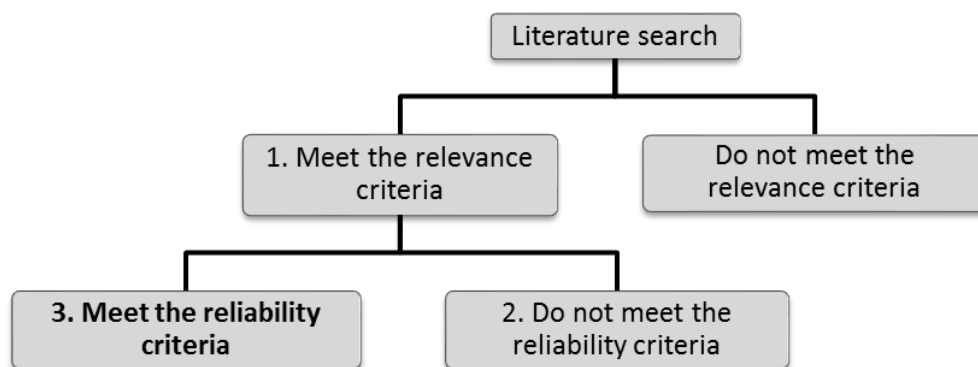
This example report reflects extensive industry experience in running and reporting such searches and describes the search in a transparent way.

5.3. Selecting the relevant studies and reporting the selection process

Generally, assessment of relevance is based on the criteria defined in section 5.1 in this ECPA guidance following the selection process as outlined in the EFSA GD (section 5.3, page 23).

An example on how to report the selection process is provided in the example for the LRR (Appendix A).

The selection process will result in three publication categories as illustrated in the figure below:



5.4. Reliability assessment

Publications that are considered to meet the relevance criteria will be further assessed for their reliability.

Based on industry experience across all chemical sectors, reliability assessments are typically carried out according to but not limited to the guidance provided in the following publications;

- Klimisch (1997)³

² Guidance of EFSA, Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) 1107/2009, EFSA Journal 2011; 9(2):2092

³ Klimisch H.-J., Andreae M and Tillmann U (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. Regulatory Toxicology and Pharmacology 25, 1-5

- Bradford-Hill (1965)⁴

Applicants should note that according to the EFSA Guidance “*the fact that a study may not be conducted in accordance with Good Laboratory Practice (GLP) does not imply that the study is irrelevant.*”⁵

6. How to present in a dossier the identification, selection and assessment of scientific peer-reviewed open literature

The identification, selection and assessment process can be provided in one or several Literature Review Report(s) (see EFSA GD, section 6, page 29).

An example of a LRR is given in Appendix A.

Typically,

- For publications meeting the relevance criteria and assessed to be reliable the full-text documents will be provided with the dossier (document K).
- Furthermore, publications meeting the relevance criteria and assessed to be reliable will be addressed at the appropriate data points in Document M of the dossier. The level of detail included should be a matter of expert judgment.
- Publications meeting the relevance criteria and assessed to be non-reliable will be fully referenced and a justification for non-reliability will be given in the reporting of the selection process (see 5.3 and example for the LRR (Appendix A)).
- Publications not meeting the relevance criteria will be fully referenced in the reporting of the selection process (see 5.3 and example for the LRR (Appendix A)).

7. Copyright

The following disclaimer is recommended for publications provided as part of the submission:

“The scientific peer-reviewed open literature is protected by copyright law. The applicant holds the right to use, reproduce and share the copies of scientific peer-reviewed open literature which are included in the dossier for evaluation purposes. This right does not include further use, reproduce and share of these copies by a Rapporteur Member State or EFSA. Own licenses are compulsory for the included copyright publications.”

⁴ Bradford-Hill A (1965). The Environment and Disease: Association or Causation. Proceedings of the Royal Society of Medicine, 58, 295-300

⁵ Guidance of EFSA, Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) 1107/2009; EFSA Journal 2011; 9(2):2092

Appendix A: Example for a Literature Review Report

Note:

- Text in blue provides general information/support.
- Text in black italic is example text that could be inserted by the author. The text/tables are not fixed and should be adapted/deleted as appropriate

1. Literature Review Report on xxx (to be completed as appropriate)

2. Author of the Literature Review Report

Insert author name

3. Summary: a brief summary indicating the purpose of the report, the methodology employed and the results obtained

This report summarizes the search and selection process for xxx.

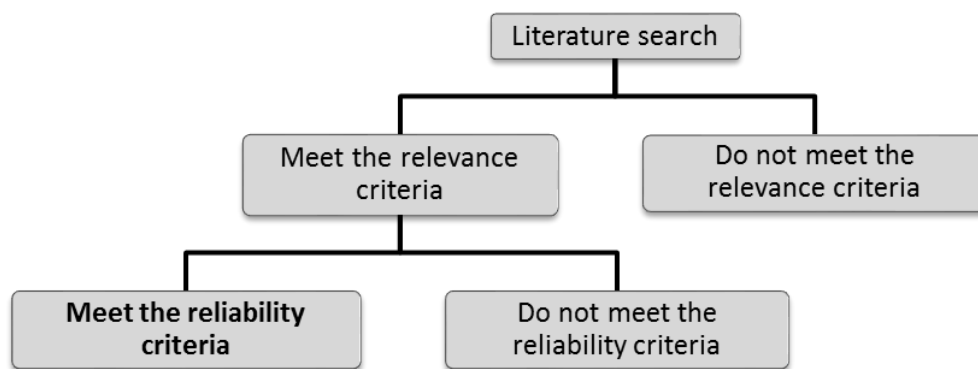
The search strategy was based on a single / multi-concept search. For details regarding the search strategy and the results obtained, please refer to section 5 of this Literature Review Report.

An overview of the results of the selection process is reported in an overview table (cf. section 5 of this Literature Review Report).

The selection process resulted in three categories of publication:

- *Publications which meet the relevance criteria and are assessed to be reliable which are addressed at the appropriate data points in Document M of the dossier.*
- *Publications which meet the relevance criteria but are assessed to be non-reliable are referenced and a justification for not meeting the reliability criteria provided in Section 6 of this Literature Review Report.*
- *Publications not meeting the relevance criteria are referenced in Section 6 of this Literature Review Report.*

The relevance criteria applied are reported in section 4 of this Literature Review Report. The reliability assessment for relevant studies was done according to Klimisch et al. (cf.) and/or (state other assessment schemes as appropriate)



4. Protocol containing the objective of the review and the criteria of relevance

4.1 Objective of the review

The review was made in order to identify scientific peer-reviewed open literature on the active substance xxx, relevant metabolites xxx and/or the plant protection products xxx which may affect the assessment on human health, animal health and/or the environment.

4.2 Criteria of relevance applied

Publications meeting the relevance criteria are those showing new/unknown effects or information potentially contradictory to the regulatory data package for the active substance, its relevant metabolites and/or the plant protection products on human health, animal health and/or the environment, which could impact the endpoints or the risk assessment parameters.

Publications providing information that do not challenge the existing regulatory data package will be treated as not meeting the relevance criteria. (Applicant to amend as appropriate).

5. Search methods and results

Search methods and the results are presented in Appendix 1. (state location of the document as appropriate; here: Appendix 1)

6. Results of the study selection process

Results of the study selection process are presented in Appendix 2. (state location of the document as appropriate; here: Appendix 2)

Appendix 1: Search methods and results (Template)

This part (Appendix 1) of the LRR could alternatively be prepared and submitted as a separate word-file.

1. Overview about databases searched

1.1 Databases searched

In this section an overview of all bibliographic databases searched and their service provider should be summarized.

STN-Databases:

ANABSTR - Analytical Abstracts
BIOSIS
CABA - CAB Abstracts
CAPLUS - Chemical Abstracts Plus
CAS REGISTRY
RTECS,
HSDB
REAXYS
Medline
Embase
ToxCenter
....

1.2 Justification for choosing the database

Address all databases as appropriate

Provider	Database	Justification
STN International*	ANABSTR - Analytical Abstracts	<p>The Analytical Abstracts database covers worldwide literature on analytical chemistry. Amongst others subject coverage includes Agriculture, Environment, and Food.</p> <p>Sources include journals, books, conference proceedings, reports, and standards.</p> <p>Bibliographic information, indexing terms, abstracts, chemical names, and CAS Registry Numbers are all searchable.</p>
STN International*	BIOSIS	<p>BIOSIS Previews® is the largest and most comprehensive life science database in the world. Amongst others subject coverage includes Agriculture, Biochemistry, Biophysics, Botany, Environmental Biology, Physiology, Toxicology.</p> <p>Sources include periodicals, journals, conference proceedings, reviews, reports, patents, and short communications. Nearly 6,000 life source journals, 1,500 international meetings as well as review articles, books, and monographs are reviewed for inclusion.</p> <p>Bibliographic information, indexing terms, abstracts, and CAS Registry</p>

		<i>Numbers are all searchable.</i>
<i>STN International*</i>	CAB Abstracts	<p><i>The CAB Abstracts database covers worldwide literature from all areas of agriculture and related sciences including Agriculture, Agricultural chemicals, Animal sciences and production, Crop protection, Crop sciences and production, Environment, Soils and fertilizers.</i></p> <p><i>Sources for CABA include journals, books, reports, published theses, conference proceedings, and patents.</i></p> <p><i>Bibliographic information, indexing terms, abstracts, and CAS Registry Numbers are searchable.</i></p>
<i>STN International*</i>	CAPLUS Chemical Abstracts Plus	<p><i>The Chemical Abstracts (CA) database covers all areas of Biochemistry, Chemistry and Chemical engineering, and related sciences.</i></p> <p><i>Sources include over 8,000 journals, patents from 38 national patent offices and two international patent organizations, technical reports, books, conference proceedings, and dissertations. Electronic only journals and Web preprints are also covered.</i></p> <p><i>Bibliographic terms, indexing terms, roles, CAS Registry Numbers, International Patent Classification, and abstracts are searchable.</i></p>

** For STN databases reference is made to STN database summary sheets*

2. Overview about substances searched

In this section a overview of all unique descriptors used (e.g. CAS No, CAS name and/or IUPAC name) should be provided.

Substance-Search in CAS Registry File:

[Insert information](#)

Resulting CAS Registry numbers for search:

[Active substance](#) including salts, isotopes:

(xxxxx-xx-x or)

[Active substance](#) metabolites:

(xxxxxx-xx-x or.....)

[Active substance](#) mixtures:

(xxxxx-xx-x or.....)

Search of common and trade names

Common trade name 1 or.....

The number and structure of the following chapters depends on the search concept and on the authors' decision how to reflect this in LRRs (one or several LRRs) as explained in the EFSA GD in Section 5.2.2. In this example a multi-concept search is given in one LRR.

3. Search for “Toxicological and metabolism studies”

In this section information about the search strategy for “Toxicological and metabolism studies” and an overview of the search results should be summarized.

Databases:

List all relevant databases which have been used for this group of data requirements.

Medline

ToxCenter

....

Search Limitation:

Indicate search limitations, if appropriate (e.g. no patents)

Search strategy for substances:

Insert information about the search strategy for substances applied for the relevant databases as appropriate

in Medline: all CAS Registry numbers, common/trade names (cf. section 2)

in ToxCenter: all CAS Registry numbers (cf. section 2)

Search strategy for data:

Insert description of the search strategy/strategies

Substances AND

mouse or rat or dog....

Table 3.1 Reporting/Overview of the search process for Toxicological and Metabolism studies

Database:	Total	Medline	ToxCenter		
Date of the search:		dd/mm/yyyy	dd/mm/yyyy		
Date span of the search:		State appropriate information (e.g.2001-2011)	State appropriate information (e.g.2001-2011)		
Date of the latest database update includes in the search:		State appropriate information	State appropriate information		
Total number of summary records retrieved:	xxx	xxx	xxx		
Total number of summary records retrieved after removing duplicates:	xxx	xxx	xxx		

4. Search for “Metabolism and Residue data”

In this section information about the search strategy for “Metabolism and Residue data” and an overview of the search results should be summarized.

With regard to content, please refer to section 3 of this LRR.

5. Search for “Fate and behaviour in the environment”

In this section information about the search strategy for “Fate and behaviour in the environment” and an overview of the search results should be summarized.

With regard to content, please refer to section 3 of this LRR.

6. Search for “Ecotoxicological studies”

In this section information about the search strategy for “Ecotoxicological studies” and an overview of the search results should be summarized.

With regard to content, please refer to section 3 of this LRR.

Appendix 2: Results of the study selection process (Template)

This part of the LRR is intended to be prepared and submitted as a separate excel-file containing different table sheets as appropriate (e.g. differentiated by data requirements searched for). An example for a table sheet (toxicological and metabolism studies) is provided here.

Number	Author	Year	Title	Reference	Meet relevance criteria	Meet reliability criteria		Assessed in Doc M Annex Point
					Y or N	Y,N or N/A	Result of reliability assessment/ Justification if not reliable	
1	Smith, A, Jones, B	2006	Acute tox of Active x to rats	Journal of abc, Vol 6 pp 123-124	N	N/A	N/A	N/A
2	White, A, Black, B and Grey, B	2008	New toxic effects of active x to mice	Journal of abc, Vol 8 pp 123-124	Y	N	Klimisch score 3: plus a short explanation	N/A
3	Schumacher, M	2003	Acute toxicity of active x to mice	Journal of abc, Vol 3 pp 123-124	Y	Y	Klimisch score 2	IIA 5.5.1
4	Miller, D	2009	Impact of cumulative doses of active x over the lifetime of horses	Journal of abc, Vol 9 pp 123-124	Y	Y	Klimisch score 2	IIA 5.5.1