GUIDANCE OF EFSA

Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009[1, 2]

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ABSTRACT

This Guidance of EFSA provides instructions on how to identify and select "*scientific peer-reviewed open literature"* and how to report it in a dossier, as required by Article 8(5) of Regulation (EC) No 1107/2009 on the placing of plant protection products on the market. The EFSA Guidance is intended for: (1) applicants submitting dossiers on active substances of plant protection products under Regulation (EC) No 1107/2009; (2) EU Member States' competent authorities evaluating the dossiers and preparing the draft assessment reports; and (3) the European Food Safety Authority (EFSA), responsible for drawing conclusions on the dossiers. This EFSA Guidance provides a definition of scientific peer-reviewed open literature and instructions on how to minimise bias in the identification, selection and inclusion of peer-reviewed open literature in dossiers, according to the principles of systematic review (i.e. methodological rigour, transparency, reproducibility). The EFSA Guidance is compatible with existing OECD Guidance documents for the preparation of active substances dossiers.

KEY WORDS

Literature search, metabolite, OECD dossier, plant protection product, relevance assessment, reliability assessment, study selection.

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[1] Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, p. 1.

[2] On request from EFSA, Question No EFSA-Q-2009-00827, issued on 24 February 2011.

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[4] Acknowledgement: EFSA wishes to thank the members of the Working Group on EFSA Guidance on Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 for the work on this scientific output Geoff Frampton (Rapporteur) and Julie Glanville and EFSA staff Elisa Aiassa, José Oriol Magrans and Laura Ciccolallo. EFSA wishes to thank EFSA staff Manuela Tiramani and Danièle Court Marques for the support in finalising the Guidance and former EFSA staff Karin M. Nienstedt for the input provided at the beginning of the process.

Suggested citation: European Food Safety Authority; Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (OJ L 309, 24.11.2009, p. 1-50). EFSA Journal 2011;9(2):2092. [49 pp.]. doi:10.2903/j.efsa.2011.2092. Available online: www.efsa.europa.eu

SUMMARY

Article 8(5) of Regulation (EC) No 1107/2009 requires that applicants submitting dossiers for the approval of active substances of plant protection products under Regulation (EC) No 1107/2009 shall provide "*Scientific peer-reviewed open literature*, […], *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 submission of the dossier…"* as determined by the European Food Safety Authority.

This EFSA Guidance provides a definition of scientific peer-reviewed open literature. The EFSA Guidance also provides instructions on how to identify, select and include scientific peer-reviewed open literature as required by Article 8(5) of Regulation (EC) No 1107/2009, and how to report the literature search and selection process in a dossier.

The intended users of this EFSA Guidance are: (1) applicants submitting dossiers for the approval of active substances of plant protection products under Regulation (EC) No 1107/2009; (2) competent authorities of the European Union Member States in charge of evaluating the submitted dossiers; and (3) EFSA, responsible for drawing conclusions on the dossiers.

This EFSA Guidance is based on recognised best practices for evidence synthesis and is consistent with the fundamental principles of systematic review, to ensure methodological rigour and transparency, and to minimise bias in the identification and selection of scientific information in dossiers. The method for identifying and selecting scientific peer-reviewed open literature for active substances, their metabolites or plant protection products in this EFSA Guidance is based on three initial steps of the systematic review process, namely: (1) clarification of the objective of the review of the scientific literature and setting of the criteria for study relevance to the dossier; (2) searching for scientific literature; and (3) selection of relevant scientific literature for inclusion in the dossier. The method is also consistent with a later step of the systematic review process, namely the clear and systematic reporting of the searching and study selection processes.

This EFSA Guidance was developed by a working group that considered in detail how to pragmatically integrate best practices in evidence synthesis with the structure of existing Guidance documents to avoid unnecessarily increasing the effort needed to prepare and appraise dossiers. This EFSA Guidance is consistent with the existing EU and OECD Guidance documents that are widely used to assist the preparation of dossiers (SANCO, 2005; OECD, 2005, 2006).

The EFSA Guidance does not currently include safeners and synergists, since data requirements for these compounds are not yet available. In principle, this EFSA Guidance could also apply (with adaptation if necessary) to these compounds.

This EFSA Guidance may be revised when experience is gained in its application and in view of any amendments to Regulation (EC) No 1107/2009.

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BACKGROUND AS PROVIDED BY EFSA

Directive 91/414/EEC[5] concerning the placing of plant protection products on the market will be replaced by a Regulation of the same name that is expected to be adopted by Council and Parliament in October 2009[6]. The new Regulation shall enter into force on the 20th day following that of its publication. However, it shall only apply 18 months after the date of entry into force. The basic principle of the new Regulation is comparable to that of Directive 91/414/EEC: the active substance is assessed and approved at EU level, the plant protection products are assessed and authorised at Member State level. Member States can only authorise plant protection products containing approved active substances, synergists and safeners. Chapter II of the Regulation lays down the procedure for the approval of active substances. The producer applying for the approval of a substance has to submit an application to a Member State, together with a summary and a complete dossier. The Member State will then prepare a draft assessment report and submit it to EFSA. EFSA shall adopt a conclusion on the substance.

Article 8 of the new Regulation lays down what should be included in the summary dossier and the complete dossier the applicant has to submit to the rapporteur Member State. Article 8 refers to the data requirements to be laid down in separate Regulations (and corresponding to the current Annexes II and III of Directive 91/414/EEC). However, Article 8(5) adds a further 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".

EFSA is requesting the Assessment Methodology Unit (AMU), through a self-tasking mandate, to develop a guideline for the applicants on how to implement Article 8(5).

TERMS OF REFERENCE AS PROVIDED BY EFSA

In view of the above, EFSA shall produce a Guidance document for the implementation of Article 8(5) of the new Regulation[6] concerning the placing of plant protection products on the market. For the development of the Guidance a working group of internal EFSA staff and external scientific experts shall be constituted. Particularly, the Guidance shall be produced by the Assessment Methodology Unit, which is responsible for developing and implementing decision support approaches in all fields within EFSA's remit, such as methods for extensive and standardised information retrieval, objective selection of relevant studies, data extraction, appraisal and synthesis. The core concepts of the project on the application of systematic review methodology to food and feed safety assessments in support of decision making , for which AMU[7] Unit is currently responsible, should be integrated in the Guidance. Close coordination and cooperation with the PRAPeR[8] Unit are recommended in order to address all specific content issues related to plant protection products, active substances, synergists and safeners. The external experts shall have relevant scientific knowledge (toxicology, ecotoxicology, environmental chemistry, pesticides) and expertise in systematic information retrieval, assessment and synthesis. The Guidance is for use by the applicants for the approval of active substances and should therefore be practical. It shall include a definition of "scientific peer-reviewed open literature" and indicate the basic principles and standard methods required for a comprehensive collection of peer-reviewed open literature in a way that is systematic, transparent and reproducible. Instructions shall also be provided on standard methods for objectively selecting the literature (documenting the reasons for excluding potentially relevant studies), and appraising and synthesising data from the studies that are included in the dossiers.

[5] Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market. OJ L 230, 19.8.1991, p. 1-32.
[6] Regulation (EC) No 1107/2009 (OJ L 309, 24.11.2009, p. 1-50), adopted by the European Parliament and the Council on 21 October 2009 and not yet adopted at the time of the preparation of the EFSA mandate.
[7] Assessment Methodology Unit.
[8] Pesticide Risk Assessment Peer Review Unit.

EVALUATION

1. Approach to the mandate

For the development of this EFSA Guidance, the Assessment Methodology Unit (AMU) of the European Food Safety Authority (EFSA) established a working group which comprised EFSA external members and EFSA staff. After three working group meetings a first draft of the EFSA Guidance was completed by the working group on the 20th of April 2010.

The first draft of the EFSA Guidance document was submitted to the EFSA Panel on Plant Protection Products and their Residues and the Pesticide Steering Committee. The feedback from both groups of experts was considered by the working group during a meeting and was used to produce a second draft of the EFSA Guidance, which was made available on the EFSA website, for public consultation.

The public consultation lasted from 23 July to 15 October 2010. The draft EFSA Guidance was commented on by sixteen interested parties including individuals, non-governmental organisations, industry organisations and national assessment bodies. All comments received that related to the remit of EFSA were assessed and the EFSA Guidance was revised taking relevant comments into consideration. The comments received and a Report on the outcome of the public consultation were published on the EFSA website.

2. Intended users of the EFSA Guidance

This EFSA Guidance was written for the use of applicants submitting dossiers for the approval of active substances of plant protection products under Regulation (EC) No 1107/2009. Intended users of this EFSA Guidance are also the competent authorities of the European Union Member States in charge of evaluating the submitted dossiers and preparing the draft assessment reports, and EFSA, as the authority responsible for peer-reviewing and drawing conclusions on the dossiers.

3. Introduction

This EFSA Guidance provides instructions with respect to Article 8(5) of Regulation (EC) No 1107/2009: "*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 submission of the dossier shall be added by the applicant to the dossier*".

Regulation (EC) No 1107/2009 lays down the rules for the approval of active substances, safeners and synergists. At the time of preparing this EFSA Guidance, data requirements are clearly defined only for active substances. The principles outlined in this EFSA Guidance on how to identify and select the scientific peer-reviewed open literature are likely to be applicable also for safeners and synergists. However, adaptations may be needed when data requirements for these compounds become available.

This EFSA Guidance was written in light of the general principles of systematic reviews as described in the EFSA Guidance "Application of systematic review methodology to food and feed safety assessments to support decision making" (EFSA, 2010) and is consistent with the EU and OECD Guidance documents for the preparation of dossiers (SANCO, 2005; OECD, 2005, 2006).

As this EFSA Guidance applies to data requirements as indicated in Regulation (EC) No 1107/2009, it is recommended that applicants consider it at an early stage of the process when compiling a dossier on an active substance.

This EFSA Guidance may be revised when experience is gained in its application and in view of any amendments to Regulation (EC) No 1107/2009. The applicants should consult the EFSA Journal[9] to make sure they have the latest version of the EFSA Guidance.

[9] <http://www.efsa.europa.eu/en/efsajournal.htm>.

4. Terminology and glossary

This section provides an explanation of the terminology used in this EFSA Guidance.

4.1. Application of terminology employed in Article 8(5) of Regulation (EC) No 1107/2009

Article 8(5) of Regulation (EC) No 1107/2009 states that "*"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 submission of the dossier shall be added by the applicant to the dossier".*

Scientific peer-reviewed open literature is literature that has been through a peer-review process. In this EFSA Guidance, peer review is defined as the critical assessment of manuscripts (e.g. draft journal articles, reports, or scientific conference abstracts) prior to publication[10], performed by independent and competent experts (adapted from ICMJE, 2006; Hames, 2007; RIN, 2010). The peer reviewers examine and assess matters such as the research design and methodology; and the validity, accuracy, originality and significance of the findings, making a recommendation as to accept, reject or ask the author(s) to amend and resubmit the manuscripts.

For the purposes of this EFSA Guidance, an "*active substance*" is defined as in Regulation (EC) No 1107/2009: "*substances including micro-organisms having general or specific action against harmful organisms or on plants, parts of plants or plant products*". To assess the "*side effects*" of the active substance, the applicants should consider also the plant protection products containing the relevant active substance.

"*Relevant metabolites*" of a particular active substance as defined by Regulation (EC) No 1107/2009 can only be definitively identified at the end of the risk assessment process. Therefore, for the purposes of this EFSA Guidance the scientific literature search should focus on metabolites, degradation products, or transformation products of an active substance formed either in organisms or in the environment, for which further assessment is required according to the data requirements and the Guidance documents applicable at the time of submitting the dossier[11].

In this EFSA Guidance, "*side effects on health, environment, and non-target species*" refers either: (1) to any *unintended effects* that may occur in humans, animals, or non-target organisms, caused by exposure to the active substance, its relevant metabolites or plant protection products as a result of intended usage; or (2) exceeding regulatory limits for environmental contamination (e.g. of groundwater), by the active substance, its relevant metabolites or plant protection products as a result of intended usage.

In line with Article 8(5) of Regulation (EC) No 1107/2009 the applicants should include in the dossier the most recent scientific peer-reviewed open literature *published during the ten years prior to the dossier submission date.* Scientific peer-reviewed open literature may also be included from more than

[10] Post-publication peer review is not included in this definition.

[11] Relevant Guidance documents to decide for which metabolites a *scientific literature* search should be performed are, for example:

- Guidelines for the generation of data concerning residues as provided in Annex II part A, section 6 and Annex II, part A, section 8 of Directive 91/414/EEC concerning the placing of plant protection products on the market (Directorate-General for Agriculture, 1999).
- Guidance document on the assessment of the relevance of metabolites in groundwater of substances regulated under council Directive 91/414/EEC. SANCO/221/2000 rev.10 final. 25 February 2003 (SANCO, 2003).
- Guidance document to determine the toxicological relevance of metabolites of PPP active substances (Evaluation of the toxicological relevance of metabolites and degradates of pesticide active substances for dietary risk assessment) (EFSA, in progress).

These are only examples and other Guidance documents may need to be considered at the time of preparing the dossier to decide for which metabolites a *scientific literature* search is needed.

ten years prior to dossier submission, provided that the literature is identified and selected in compliance with this EFSA Guidance and that clear justification is provided.

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 (section 5.2).

The applicants are responsible for providing dossiers with full relevant information as specified in this EFSA Guidance. Ensuring that copyright, licensing, and data protection issues relevant to the information included in the dossiers have been fully satisfied remains the responsibility of the applicants. The applicants should consult their national copyright licensing authority for guidance on purchasing copyright licenses to reproduce any copyright publications submitted to Rapporteur Member States and EFSA. It should be noted that applicants remain the sole legal or natural persons responsible and liable for obtaining all necessary authorisations and rights to use, reproduce and share the publications submitted in their applications. Under no circumstances may EFSA be held liable for any breach of the relevant legal framework.

4.2. Other relevant definitions

Bibliographic database	A searchable database which contains summary records (often with abstracts and sometimes linking to full-text documents) of scientific literature and, in some cases, providing indexing terms (e.g. subject headings) to assist searching
Bibliographic reference	The information used to identify a full-text document. Typically this includes the author name(s), publication date, the title of the document, and publication details of the document (e.g. the name, volume and page numbers of a scientific journal, or the URL and publisher of a website)
Boolean operator	Boolean operators are words used to combine terms or concepts when conducting electronic bibliographic searches. Examples include "AND" (used to narrow a search), "OR" (used to broaden a search) and "NOT" (used to exclude terms from a search).
Co-formulant	A substance or preparation which is used or intended to be used in a plant protection product or adjuvant, but is not an active substance, safener or synergist (Regulation (EC) No 1107/2009).
Document K	A document in the dossier containing individual test and study reports in accordance with the legislative requirements of the country to which the dossier application is made.
Document M	A comprehensive summary and assessment of tests and studies included in the dossier, in accordance with relevant evaluative and decision making criteria.
Dossier	Documentation providing the evidence submitted by applicants for the approval of active substances of plant protection products, under Regulation (EC) No 1107/2009.
Full-text document	A document (e.g. journal article, dissertation) in which details of one or more studies are reported; provides more information than a summary record.
Plant protection product(s)	A product, in the form in which it is supplied to the user, consisting of or containing active substances, safeners or synergists, and intended for one of the following uses (Regulation (EC) No 1107/2009): a. protecting plants or plant products against all harmful organisms or preventing the action of such organisms, unless the main purpose of these products is considered to be for reasons of hygiene rather than for the protection of plants or plant products; b. influencing the life processes of plants, such as substances influencing their growth, other than as a nutrient; c. preserving plant products, in so far as such substances or products are not subject to special Community provisions on preservatives; d. destroying undesired plants or parts of plants, except algae unless the products are applied on soil or water to protect plants;

	e. checking or preventing undesired growth of plants, except algae unless the products are applied on soil or water to protect plants.
Primary research study	The original study in which data were produced. The term is sometimes used to distinguish such studies from secondary research studies (e.g. reviews) that re-examine previously collected data.
Publication bias	The preferential reporting of certain types of primary research results (e.g. positive results may be more likely to be reported than negative ones). When primary research is synthesised in a secondary research study, publication bias can lead to findings which deviate from the truth.
Safener	A substance or preparation which is added to a plant protection product to eliminate or reduce phytotoxic effects of the plant protection product on certain plants (Regulation (EC) No 1107/2009).
Secondary research study	A study (e.g. a review) that re-examines existing data from one or more primary research studies (see primary research study).
Selection bias	The selection of primary research results that are not representative (e.g. if researchers preferentially choose full-text documents of studies that are well known to them). Selection bias can lead to findings which deviate from the truth.
Sources of scientific literature other than bibliographic databases	Any repository of information other than a bibliographic database that contains scientific literature in the form of bibliographic references, abstracts and/or full-text documents. Examples include internet search engines which access information in a variety of formats, internet pages, online journals and their tables of contents, and reference lists within full-text documents.
Study	A scientific analysis which aims to establish facts. A study can be either a primary research study or a secondary research study. A study might be reported in one or more full-text documents.
Summary record	Summary information about a full-text document or conference presentation, typically included in a bibliographic database, which may include a bibliographic reference and one or more of the following: an abstract or summary of the scientific content, additional categorisations or indexing terms.
Synergist	A substance or preparation used in a plant protection product which, while showing no or only weak activity, can give enhanced activity to the active substance(s) in the plant protection product (Regulation (EC) No 1107/2009).

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

The process of identifying and selecting scientific peer-reviewed open literature for active substances, their metabolites, or plant protection products (sections 5.1 – 5.4) is based on the fundamental principles of systematic review, which are: methodological rigour; transparency; and reproducibility.

A systematic review is an overview of existing evidence pertinent to a clearly formulated question, which uses pre-specified and standardised methods to identify and critically appraise relevant research, and to extract, report and analyse data from the studies that are included in the review (EFSA, 2010)[12].

It is important to clarify two fundamental but distinct aspects of scientific studies when preparing a dossier in the context of Article 8(5) of Regulation (EC) No 1107/2009. These are the concepts of relevance and reliability.

In this EFSA Guidance, studies relevant to the dossier are those that inform the data requirement(s) set out in Regulation (EC) No 1107/2009 (referring to Directive 91/414/EEC - and subsequent updates), including hazard identification, hazard characterisation and exposure assessment, for the active substance under assessment, its relevant metabolites, or plant protection products. Based on the initial steps of a systematic review (summarised in Box 1[13]), this EFSA Guidance provides general principles and suggestions on how to define studies relevant to the dossier and on how to search for and select them for inclusion in the dossier and risk assessment (sections 5.1-5.3). The method is described taking into consideration issues unique to the process of dossier approval.

Study reliability concerns methodological quality and refers to the extent to which a study is free from bias and its findings reflect true facts. Some issues around reliability are highlighted later (section 5.4).

Box 1: Initial steps of the systematic review process (from EFSA, 2010)

1. *A priori* clarification of the review question and scope, and *a priori* definition of the eligibility criteria for the inclusion of studies into the review. This information is stated, together with the methods to be used in the review, in a protocol (project plan), which helps to reduce biases in the review, as the process is clearly specified in advance and the reviewers are committed to follow it.

2. Extensive searches for relevant research studies. This involves the development of a search strategy (combinations of search terms) and identification of information sources that must be searched in order to retrieve as many relevant studies as possible. Biases in the selection of research studies are minimised by an extensive and reproducible search strategy and a transparent reporting of how studies are selected and included in the review. The search method (the search strategies and information sources used) is thoroughly reported in order to allow readers to judge how much of the relevant literature is likely to have been found.

3. Detailed assessment of studies against the pre-defined eligibility criteria, to determine whether they are eligible for inclusion in the review. The process by which decisions on study selection are made is clearly reported.

[12] Systematic reviews typically do not include primary collection of new data.
[13] For details see "Application of systematic review methodology to food and feed safety assessments to support decision making" (EFSA, 2010).

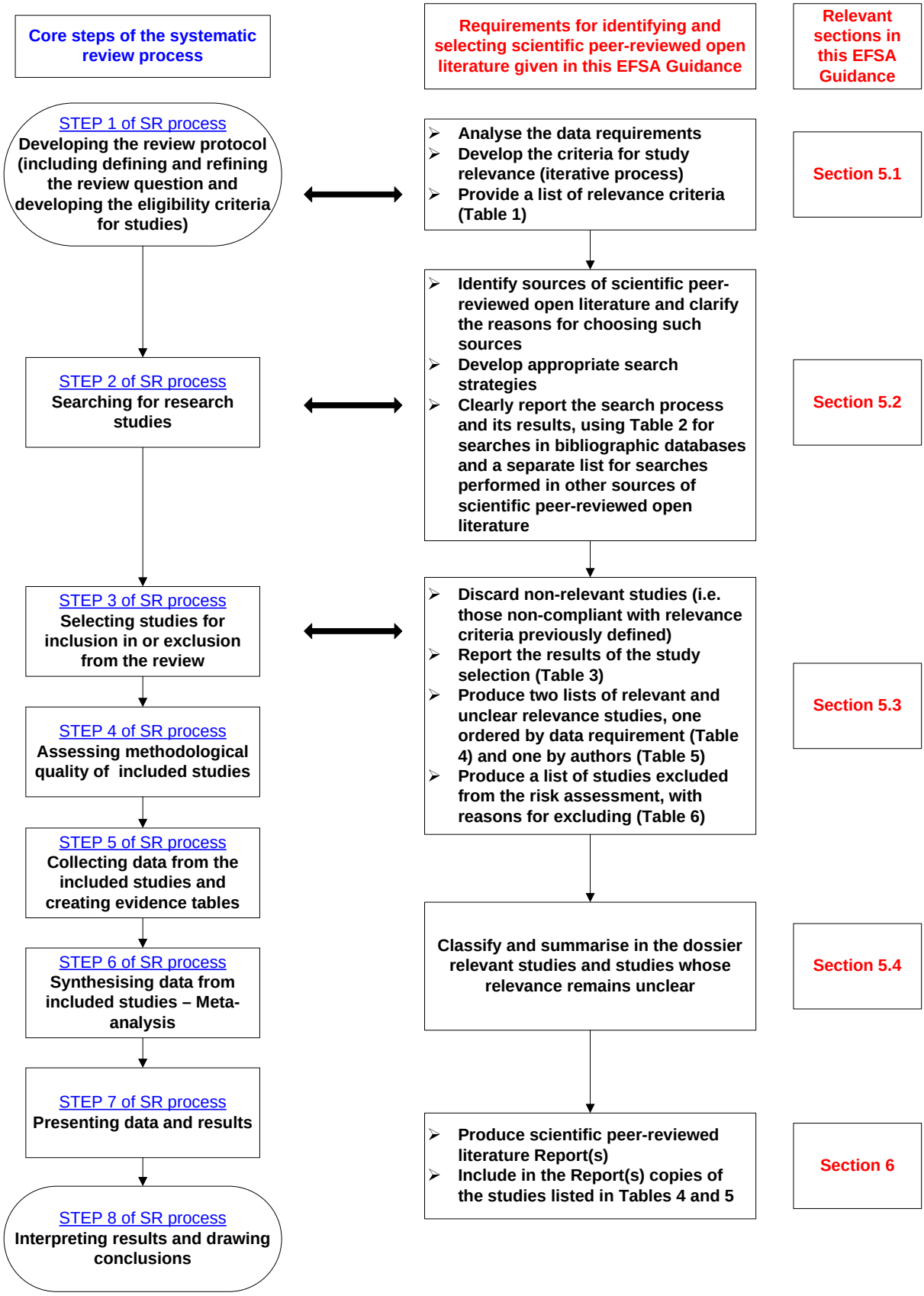

Figure 1: Core steps for performing a systematic review (SR) (EFSA, 2010) and requirements for identifying and selecting *peer-reviewed open scientific literature* set out in this EFSA Guidance

5.1. Developing criteria for study relevance in relation to the data requirements

A systematic review starts with a thorough consideration of the question which the review seeks to answer and a definition of the criteria for inclusion of studies in the review. In the case of dossiers, the review questions are represented by the data requirements illustrated in Box 2 (set out in Regulation (EC) No 1107/2009, referring to Directive 91/414/EEC and subsequent updates).

Studies relevant to the dossier are those that inform one or more data requirement(s), including hazard identification, hazard characterisation and exposure assessment, for the active substance under assessment, its relevant metabolites, or plant protection products.

Relevance criteria generally applicable to all data requirements cannot be defined here as they will depend on the availability and structure of information in the peer-reviewed open scientific literature. This EFSA Guidance provides a framework of general principles to help develop relevance criteria for including studies in a dossier.

To avoid missing relevant studies, the relevance criteria should not be too restrictive. Only clearly irrelevant studies should be excluded from a dossier. The assessment of study relevance does not involve considerations of study reliability (which may be addressed in a later step - section 5.4).

Developing relevance criteria is likely to be an iterative process that starts with a clear analysis of the different components that characterise the data requirements, to set the characteristics of the relevant studies. A preliminary search of the literature may be useful to test and refine the relevance criteria on a subset of summary records or full-text documents, to assess their applicability. Some examples of how the components of the data requirements may be analysed to develop relevance criteria are illustrated in Box 3.

For the purposes of this 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.

Once the relevance criteria used for each data requirement have been determined, they should be clearly reported, using Table 1. This table should be included in the corresponding protocol of the scientific peer-reviewed Literature Review Report(s) of the dossier, described in section 6.

Box 2: The main categories of data requirements given in Regulation (EC) No 1107/2009 (referring to Directive 91/414/EEC), for which scientific peer-reviewed open literature should be searched. Note that any changes to the data requirements arising from updates of Regulation (EC) No 1107/2009 should be considered by the applicants when compiling a dossier[14]

1. Data requirements on chemical active substances (Annex II, part A, Directive 91/414/EEC):
   a. Toxicological and toxicokinetic studies (OECD code: IIA 5)
   b. Residues in or on treated products, food and feed (metabolism and residues data) (OECD code: IIA 6)
   c. Fate and behaviour in the environment (OECD code: IIA 7)
   d. Ecotoxicological studies (OECD code: IIA 8)
   e. Other data requirements for which information may have a direct or indirect effect on overall risk assessment (OECD code: IIA 1- IIA2 -IIA 3 - IIA 4) (only data requirements under these points having a direct impact on the risk assessment need to be considered)

2. Data requirements on microbial active substances (including viruses) (Annex II, part B, Directive 91/414/EEC):
   a. Effects on human health (Toxicological and exposure data)(OECD code: IIM 5)
   b. Residues in or on treated products, food and feed (metabolism and residues studies)(OECD code: IIM 6)
   c. Fate and behaviour in the environment (OECD code: IIM 7)
   d. Effects on non-target organisms (Ecotoxicological studies, environmental impact) (OECD code: IIM 8, IIM 9)
   f. Other data requirements for which information may have a direct or indirect effect on the overall risk assessment (OECD code: IIM 1 – IIM2 - IIM 3 - IIM 4) (only data requirements under these points having a direct impact on the risk assessment need to be considered)

3. Data requirements on plant protection products based on chemical preparations (Annex III, part A, Directive 91/414/EEC):
   a. Toxicological studies (and exposure data) (OECD code: IIIA 7)
   b. Residues in or on treated products, food and feed (metabolism and residues studies) (OECD code: IIIA 8)
   c. Fate and behaviour in the environment (OECD code: IIIA 9)
   d. Ecotoxicological studies (OECD code: IIIA 10)
   g. Other data requirements for which information may have a direct or indirect effect on the overall risk assessment (OECD code: IIIA 1 - IIIA 2 - IIIA 3 - IIIA 4 - IIIA 5) (only data requirements under these points having a direct impact on the risk assessment need to be considered)

4. Data requirements on plant protection products based on preparations of micro-organisms including viruses (Annex III, part B, Directive 91/414/EEC):
   a. Effects on human health (toxicological studies and exposure data) (OECD code: IIIM 7)
   b. Residues in or on treated products, food and feed (metabolism and residue data) (OECD code: IIIM 8)
   c. Fate and behaviour in the environment (OECD code: IIIM 9)
   d. Effects on non-target organisms (ecotoxicological studies) (OECD code: IIIM 10)
   h. Other data requirements for which information may have a direct or indirect effect the overall risk assessment (OECD code: IIIM 1 - IIIM 2 - IIIM 3 - IIIM 4 - IIIM 5) (only data requirements under these points having a direct impact on the risk assessment need to be considered)

[14] The OECD codes are taken from OECD, 2005; 2006.

Box 3: Examples of how to consider the different components that characterise the data requirement(s) to develop relevance criteria for studies

Example 1 (Persistence in soil). When addressing persistence in soil (data requirement "fate and behaviour in soil", "rate of degradation" (data requirement 7.1.1.2 in Directive 91/414/EEC, Annex II, part A; OECD IIA 7.2.1 and IIA 7.3), two types of studies may be sought: laboratory controlled degradation studies (data requirement 7.1.1.2.1; OECD IIA 7.2.1) or field dissipation studies (data requirement 7.1.1.2.2; OECD IIA 7.3). In the laboratory studies, appropriate components for defining relevance would be the substrate used in the degradation experiments (soil) and its experimental conditions (temperature, soil moisture), the application rates (exposure), and the measurements of the amount of substance remaining over time and the calculated degradation kinetic parameters (endpoints). Relevance criteria in this case could be based on the substrate used (agricultural soils, non-agricultural soils and artificial substrates), on the exposure (application rates within the range expected for the representative uses) or the reporting of the actual measured concentration (endpoint). In the particular case of studies that aim to determine the effect of photolysis on the degradation of an active substance in soil (data requirement 7.1.1.1.2; OECD 7.1.3), another component to consider would be the presence of a dark control (comparator) and therefore the reporting of dark control results in the *peer-reviewed open scientific literature* would be another appropriate relevance criterion. For field dissipation studies (data requirement 7.1.1.2.2; OECD IIA 7.3), appropriate components would be the geoclimatic conditions (setting), the application rates (exposure) and the data to derive dissipation half lives (endpoints). Relevance criteria based on the geoclimatic conditions could, for example, be used to exclude studies performed in tropical or other areas not representative of European geoclimatic conditions.

Example 2 (Residues). If residue trials are sought (data requirement 6.3 in Directive 91/414/EEC, Annex II, part A; OECD IIA 6.3), appropriate components would be the crops and the cultivation conditions (population and setting), the application rates (exposure) and the residues analysed (endpoint). In this example relevance criteria may be established by considering the agricultural cropping scenarios for the representative use, the application rates within the range of good agricultural practices proposed, and the measurement of all the components of the residue in the residue definition.

Example 3 (Toxicological and metabolism studies). For the data requirements "toxicological and metabolism studies" (data requirements 5.1 to 5.7 and 5.8.2 in Directive 91/414/EEC, Annex II, part A; OECD IIA 5.1 to 5.7* and OECD IIA 7.1 and 7.2), fundamental components are, among others, the test species, the test material and the use of different doses and the specific endpoints of interest. Thus studies relevant to these data requirements are studies that appropriately address these components, i.e. studies that present a well-identified test material (including its purity and impurity profile); a test relevant to the mammalian toxicological assessment (preferred species will be rodents - rats and mice, the dog is the preferred non-rodent species); a number of animals per group sufficient to establish a statistical significance; several dose levels tested (at least 3), preferably including a negative control, to establish a dose-response; relevant route of administration in terms of risk assessment (oral, dermal or by inhalation); and a description of the observations, examinations, analysis performed, or necropsy.

* OECD data points 5.1 and 5.4 present more specific protocols (toxicokinetics and genotoxicity studies, respectively) for which different relevance criteria would be applicable.

Table 1: How to report the list of criteria for relevance for each data requirement[15]

Data requirement(s) (indicated by the correspondent OECD data point number(s))	Criteria for relevance
Example: **Toxicological and metabolism studies (OECD IIA 5.1 to 5.7* and OECD IIA 7.1 and 7.2)**	*Example:* 1. Well defined test material (including its purity and impurity profile) 2. Relevant test species (to the mammalian toxicological assessment - preferred species are rodents - rats and mice, the dog is the preferred non-rodent species) 3. Number of animals per group sufficient to establish a statistical significance 4. Several dose levels tested (at least 3), preferably including a negative control, to establish a dose-response 5. Relevant route of administration in terms of risk assessment (oral, dermal or by inhalation) 6. Description of the observations, examinations, analysis performed, or necropsy 7. In addition: studies which may be helpful for the interpretation of other studies present in the dossier, but do not fit under a specific toxicological endpoint

* This example excludes OECD data points 5.1 and 5.4 which present more specific protocols (toxicokinetic and genotoxicity studies, respectively); in practice, these two data points and their relevance criteria would be specified separately in the table

[15] For a specific example see Appendix C.

5.2. Searching for scientific peer-reviewed open literature

In order to retrieve as much relevant scientific peer-reviewed open literature as possible (thereby reducing selection biases and publication biases), the applicants should perform an extensive[16] literature search and report it in detail in the scientific peer-reviewed open literature review Report(s) (section 6). The principles of extensive and sensitive literature searches are illustrated below.

5.2.1. Identifying sources of scientific peer-reviewed open literature

There may be a number of different sources which will yield relevant scientific peer-reviewed open literature. The applicants should make reasonable efforts to locate all sources of relevant scientific peer-reviewed open literature and provide their reasons for choosing such sources. If the Rapporteur Member States or EFSA identify relevant sources not included in the dossier, they may require the applicants to include such sources.

Examples of sources of scientific peer-reviewed open literature are represented by:

- Bibliographic databases which record documents such as journals, reports, conference proceedings and books;
- Sources other than bibliographic databases, such as reference lists of full-text journal articles (e.g. reviews); journals' tables of contents; or websites of conferences or organisations.

Searching various sources of scientific peer-reviewed open literature is likely to result in duplication of summary records. In addition, different reports of the same study may be identified and care should be taken to avoid double counting of data.

Advice on identifying suitable sources of scientific peer-reviewed open literature can be sought from information specialists, web-based resource lists and library guides. Support may also be asked from Rapporteur Member States and EFSA.

5.2.2. Developing appropriate search strategies

Appropriate search strategies (i.e. search terms and their combinations) should be developed in such a way as to capture concepts related to the active substance, its metabolites, plant protection products containing the active substance and components of the data requirements (e.g. the population under assessment, the exposure scenarios or endpoints).

Different approaches can be used for developing searches:

- Using a single concept search strategy that captures all data requirements of interest in one search, for example by searching using search terms for the active substance and its synonyms only (or a metabolite, or plant protection product and their synonyms only);
- Using separate focused search strategies for individual or grouped data requirements by searching for the active substance and its synonyms (or metabolites, or plant protection products and their synonyms) combined with one or more other concepts relating to the data requirement(s) in question. In this case the additional concepts will capture one or more components of the data requirements.

An advantage of the first (single concept) approach is that the search is likely to be highly sensitive, and less time consuming than a series of more focused searches, and to produce fewer duplicate

[16] Comprehensive literature searches are rather difficult to perform because of the number of databases in different languages available to be searched. Therefore, this Guidance aims to give advice on how to perform literature searches in such a way that they are as extensive as possible.

summary records. As summary records identified by searching are assessed for relevance they will need to be classified according to the data requirements they may inform. A disadvantage of a single concept search strategy is that potentially a large number of search results may be returned which would need to be assessed for relevance to each of the data requirements.

If the number of summary records returned by a single concept search is extremely large, focused searches for individual or grouped data requirements could be developed. Such searches could combine synonyms for the active substance (one concept) with terms and synonyms for characteristics of the data requirement (second concept). The concepts would usually be combined using the AND Boolean operator to produce summary records which contain both concepts. For example, for a data requirement about mutagenicity, the active substance combined together with the concept of mutagenicity (or other concepts such as the test species, or the type of test design) could form the search strategy. If conducting a focussed search, care should be taken not to include too many concepts, as relevant studies may be missed by such an approach.

EFSA does not recommend any specific approach for the search strategy and the applicants may choose the most practical on a case by case basis. However, all data requirements listed in Box 2 should be addressed.

Search strategies should ideally be designed to be sensitive so that they retrieve as much potentially relevant scientific peer-reviewed open literature as possible. This usually involves using as many synonyms and related terms as possible for an individual concept to compensate for the fact that the information available to be searched (i.e. summary records) may be quite brief and the way authors describe their research can vary. The combination of search terms (using the OR Boolean operator) is crucial for sensitive searching and applicants should not rely on single search terms alone. For example, to capture the concept of mutagenicity, the range of terms which may signal the theme of mutagenicity would need to be included in the strategy (e.g. including terms for genotoxicity)[17].The search strategy must be capable of capturing scientific peer-reviewed literature published during the *ten years* prior to the dossier submission date (as required by Article 8(5) of Regulation (EC) No 1107/2009). Scientific peer-reviewed literature may also be included from more than ten years prior to dossier submission, although it is not mandatory, provided that the literature is identified and selected in compliance with this EFSA Guidance and appropriate justification is provided.

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.

Search strategies should be in English and will need to be adapted to run successfully in different information sources. Considerations when adapting strategies include differences in search syntax, for example truncation symbols and subject indexing schemes may vary among information sources.

In some cases, the search may be made more sensitive by including trade product names. Any limits applied to the search strategy (for example to exclude non-peer-reviewed publication types such as commentaries or editorials) should be explicitly reported in the dossier.

The Rapporteur Member States and EFSA may request an updated search if the submitted search is inadequately sensitive.

Examples of searches for scientific peer-reviewed open literature for some specific active substances are illustrated in Appendices A and B of this EFSA Guidance. Advice on preparing search strategies can be found in Appendix B of the EFSA Guidance "Application of Systematic Review Methodology

[17] A search of the literature can help to identify synonyms and different ways that a concept may be described; thus, the process of developing a search strategy may be iterative, with the literature identified in searches providing information that can assist further refinement of search strategies.

to Food and Feed Safety Assessments to Support Decision Making" (EFSA, 2010) and is also available in other guides to systematic reviews (CRD, 2009; Higgins JPT, Green S (editors), 2009).

Recently, guidance on assessing search strategies has been published (Sampson et al., 2009). This may assist in developing and checking search strategies.

5.2.3. Reporting clearly the searches and their results

To promote transparency and to allow an assessment of the quality of the searches for scientific peer-reviewed open literature, the search process and its results should be clearly documented and reported.

For searches in bibliographic databases, the following information should be provided for each database:

1. the bibliographic database name and the service provider used;
2. the justification for choosing the database;
3. the date on which the search was conducted;
4. the date of the most recent update of the bibliographic database;
5. the date span of the search;
6. the complete search strategy or strategies used, including all the search terms, text-words (words in titles or abstracts), subject index headings (thesaurus terms or descriptors), and the relationship between the search terms (how they have been combined using Boolean operators). The search strategies ideally should be copied and pasted in Table 2 (see below) exactly as they were run in the databases and included in full, in such a way that they can be rerun;
7. any limits applied to the search (e.g. publication types);
8. the total number of summary records retrieved from the database after removing duplicates.

The details above should be reported in a table (Table 2) that can be expanded by columns and/or rows to include as many bibliographic databases and/or search strategies as necessary. If only a single-concept search is applied (i.e. a wide search on the active substance alone), there will be only one table. If separate search strategies are run for individual data requirements, or groups of similar data requirements, there will be a separate table for each of the data requirements or groups of data requirements searched. The table(s) should contain the most current searches at the date of submission of the dossier.

If peer-reviewed literature is found in sources other than bibliographic databases, the following information should be reported:

1. a justification for choosing the source;
2. for a website (e.g. a conference or organisation website containing peer-reviewed scientific literature):
    a. the website name and the service publisher used (e.g. Author/Editor/Organisation's name and Title of the page);
    b. the URL (internet address);
    c. the date on which the search was conducted;
    d. the date of the most recent website update at the time it was searched;
    e. the date span of the search;
    f. the search terms used;
    g. any limits applied to the search (e.g. publication types);
    h. the number of relevant summary records or full-text documents retrieved.

3. for journal tables of contents:
    a. the journal name;
    b. the journal URL (internet address) or publisher;
    c. the dates, volumes and issues searched;
    d. the method of searching, e.g. scanning tables of contents for each issue, or using a search engine;
    e. the search terms used (if any);
    f. the number of relevant summary records or full-text documents retrieved.
4. for reference lists:
    a. the bibliographic details of the documents whose reference lists were scanned;
    b. the number of relevant bibliographic references retrieved.

Searches for peer-reviewed literature performed in sources other than bibliographic databases should be reported systematically, in the format indicated above, as one or more text list(s) immediately following Table 2.

Table 2 and the text list(s) describing the searches performed in sources other than bibliographic databases should be included in the scientific peer-reviewed open literature review Report(s) (details of the structure of this Report(s) are given in section 6 of this EFSA Guidance).

Examples of how to report the search process are shown in Appendix A.4.

Table 2[18]: Reporting of the search process for scientific peer-reviewed open literature in bibliographic databases

Data requirement(s) captured in the search	**Details of the searches** *Insert additional columns for additional databases; insert additional rows for additional search strategies* *Use a separate Table for every individual data requirement, or group of data requirements searched*			
Insert here the data requirement(s) being addressed by each reported search strategy (i.e. whether specific data requirements, groups of requirements, or all data requirements together)	**Database 1**	**Database 2**	**Database n**	
	Justification for choosing the source:	**Justification for choosing the source:**	**Justification for choosing the source:**	
	Date of the search:	**Date of the search:**	**Date of the search:**	
	Date span of the search:	**Date span of the search:**	**Date span of the search:**	
	Date of the latest database update included in the search:	**Date of the latest database update included in the search:**	**Date of the latest database update included in the search:**	
	Search strategies[19] used for this data requirement	**Search strategies[19] used for this data requirement**	**Search strategies[19] used for this data requirement**	
	Paste here search strategy 1	*Paste here search strategy 1*	*Paste here search strategy 1*	
	Paste here search strategy 2	*Paste here search strategy 2*	*Paste here search strategy 2*	
	Paste here search strategy n	*Paste here search strategy n*	*Paste here search strategy n*	
	Total number of summary records retrieved:	**Total number of summary records retrieved:**	**Total number of summary records retrieved:**	
	Total number of summary records retrieved after removing duplicates			**n=**

[18] This Microsoft Word Table (or several Tables if appropriate) should contain the most current searches before the date of submission of the dossier.
[19] An example is given in Appendix A.4.

5.3. Selecting the relevant studies and reporting the selection process

Following the initial removal of any duplicate summary records retrieved, the remaining summary records should be assessed for relevance by *applying the relevance criteria that have been previously defined* (section 5.1).

The process of selection of relevant scientific peer-reviewed open literature is normally undertaken in two steps. Each of these steps may be iterative. If the first iteration results in a large number of studies that are of unclear relevance, refinement of the selection criteria may be considered.

1. *Rapid assessment* for relevance based on summary records (e.g. titles and abstracts), to exclude summary records which are obviously irrelevant. Summary records which appear to be relevant and those of unclear relevance go to the next step. If there is insufficient information in the summary record to determine relevance, then assessment of full-text documents (step 2 below) will be required. During this assessment, a summary record may be excluded on the basis of the title alone (e.g. if an abstract is not available), provided that the title provides sufficient information to clearly indicate non-relevance.

2. *Detailed assessment* of full-text documents. Full-text documents should be obtained for those summary records not excluded in step 1 and assessed in detail for their relevance. During this step, individual primary or secondary research studies should be identified, bearing in mind that some full-text documents may report more than one study, whilst some studies may be reported in more than one full-text document. All information relating to the same study should be grouped together as a single unit for assessing relevance. Studies not excluded by the detailed assessment in this step should be classified (either as relevant or of unclear relevance) and summarised in the dossier (section 5.4).

Once assessed as relevant, full-text documents should preferably be provided in English; however, official EU languages would be accepted. Relevant full-text documents in non-EU languages should be translated to English.

Peer-reviewed secondary research studies (i.e. reviews) may include bibliographic references to, or summaries of, potentially relevant primary research studies that address the data requirements under assessment. Potentially relevant primary research studies identified in reviews should be assessed individually for relevance as outlined above. If reviews are identified as a source of relevant bibliographic records, this should be reported in the search results for reference lists (section 5.2.3).

The process for selecting scientific peer-reviewed open literature is illustrated in Figure 2. A specific example of the first step of the study selection process (i.e. rapid assessment of summary records) is illustrated in Appendix C.

The following information concerning the selection of *studies* should be clearly reported in the scientific peer-reviewed literature review Reports(s) (section 6):

1. The results of the selection process for each data requirement or group of data requirements searched, recorded using Table 3.

2. A list of the bibliographic references, in a format exportable to reference management software[20], for all relevant studies and for studies whose relevance remains unclear (i.e. the studies which were not excluded after the detailed assessment of the full-text documents), *ordered by data requirement*, recorded using Table 4.

[20] Applicants may need to consult the competent authorities to agree on the most suitable format.

3. A list of the bibliographic references, in a format exportable to reference management software, for all relevant studies and for studies whose relevance remains unclear (i.e. the studies which were not excluded after the detailed assessment of the full-text documents), *ordered by first author*, recorded using Table 5.

4. A list of the bibliographic references, in a format exportable to reference management software, for all studies excluded from the dossier after detailed assessment of full-text documents for relevance, with justification for their exclusion, recorded using Table 6.

Table 3: Results of the study selection process, for each data requirement or group of data requirements searched

Data requirement(s) captured in the search (as indicated in Table 2):	**n**
Total number of *summary records* retrieved after *all** searches of peer-reviewed literature (excluding duplicates)	
Number of *summary records* excluded from the search results after rapid assessment for relevance	
Total number of *full-text documents* assessed in detail*	
Number of *studies* excluded from further consideration after detailed assessment for relevance	
Number of *studies* not excluded for relevance after detailed assessment (i.e. relevant studies and studies of unclear relevance)	

*both from bibliographic databases and other sources of peer-reviewed literature

Table 4: Report of all relevant studies and studies of unclear relevance that are included in a dossier after detailed assessment of full-text documents for relevance: ordered by data requirement(s)

List of bibliographic references for all relevant and unclear *studies*, classified by data requirements (in a format exportable to reference management software)

Data requirement (indicated by the corresponding OECD data point number)	**Author(s)**	**Year**	**Title**	**Source**

Where for a particular author there is more than one bibliographic reference, they should be listed in chronological order (most recent last). In cases where for a particular author, more than one bibliographic reference is listed for the same year, the references should be distinguished by inserting letters after the year i.e. 2009a, 2009b, 2009c, etc. If a study is represented by more than one full-text document (e.g. where different full-text documents report different data from the same study), this should be indicated by coding all full-text documents that refer to a study using the same letter in square brackets i.e. [A], [B], [C], etc. The list should be compiled using a Microsoft Word compatible table, with a separate row for each bibliographic reference.

Table 5: Report of all relevant studies and studies of unclear relevance that are included in a dossier after detailed assessment of full-text documents for relevance: ordered by author(s)

List of bibliographic references for all relevant and unclear *studies*, classified by authors (in a format exportable to reference management software)				
Author(s)	**Data requirement (indicated by the corresponding OECD data point number)**	**Year**	**Title**	**Source**

The bibliographic references to studies should be listed alphabetically by author, and for individual authors, in chronological order, following the same principles as in Table 4. The list should be compiled using a Microsoft Word compatible table, with a separate row for each bibliographic reference.

Table 6: Report of the studies excluded from the risk assessment after detailed assessment of full-text documents

List of bibliographic references for all *studies* excluded from the risk assessment, classified by authors (in a format exportable to reference management software)				
Author(s)	**Year**	**Title**	**Source**	**Reason(s) for not including this study in the dossier**
				Examples of how to fill in this table: • The study does not fulfil any of the relevance criteria listed in Table 1 • The study does not provide information on criteria 2 and 4 listed in Table 1

The bibliographic references to studies should be listed alphabetically by author, and for individual authors, in chronological order, following the same principles as in Table 4. The list should be compiled using a Microsoft Word compatible table, with a separate row for each bibliographic reference.

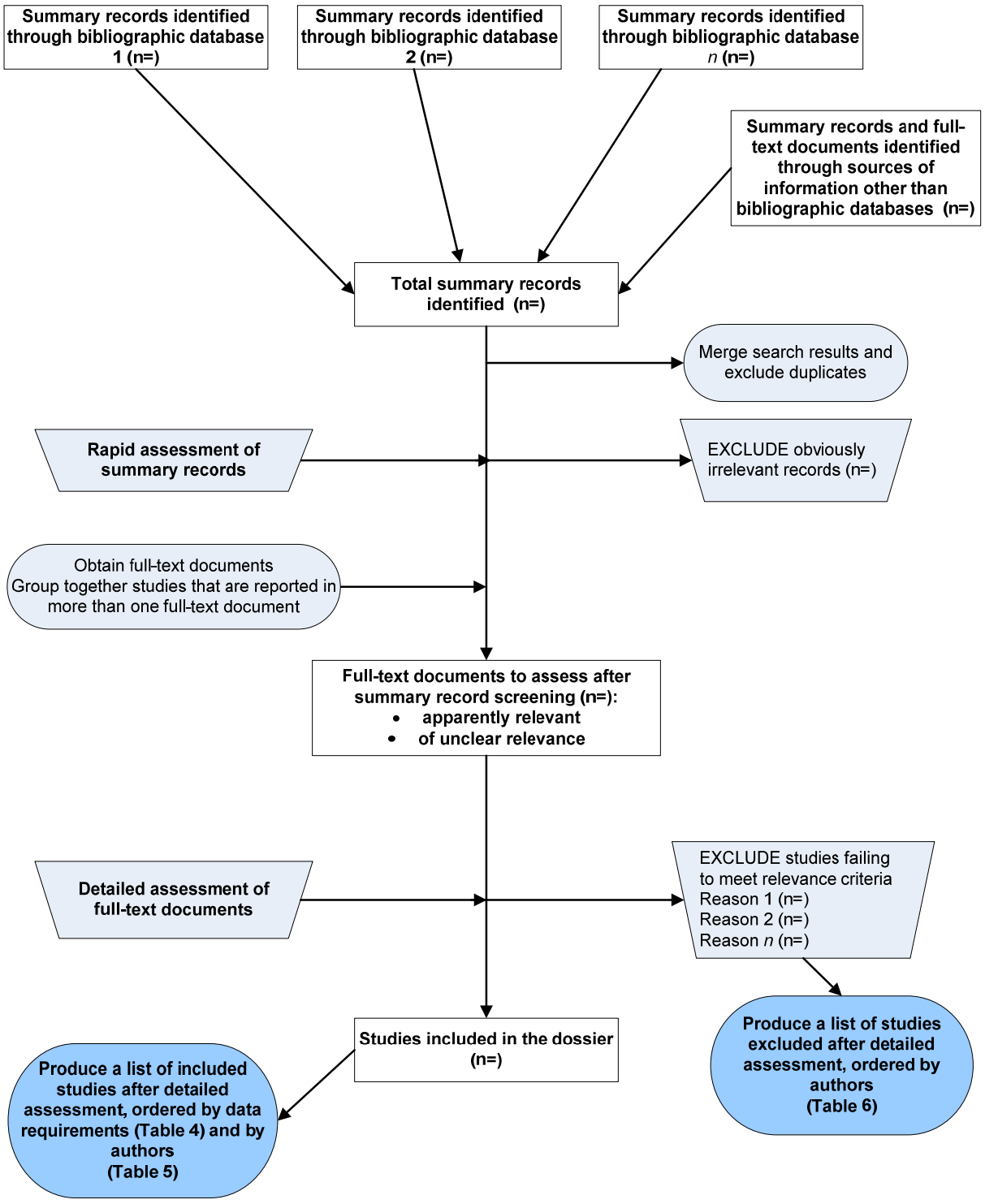

Figure 2: The process for selecting studies to be included in a dossier

5.4. Including in a dossier the studies classified as relevant or of unclear relevance

Once studies have been identified and selected for inclusion in a dossier, they should be classified and summarised (section 5.4.1). Studies that are clearly relevant to the risk assessment may then be considered for reliability assessment (section 5.4.2).

5.4.1. Classification of the studies in a dossier

The studies in a dossier should be classified and summarised as follows for each data requirement:

(a) Studies that provide data for establishing or refining risk assessment parameters. These studies should be summarised in detail following the subsequent steps of the OECD Guidance documents (OECD, 2005; 2006) and should be considered for reliability (see 5.4.2).

(b) Studies that are relevant to the data requirement, but in the opinion of the applicant provide only supplementary information that does not alter existing risk assessment parameters. A justification for such a decision should be provided.

(c) Studies for which relevance cannot be clearly determined. For each of these studies the applicants should provide an explanation of why the relevance of such studies could not be definitively determined.

5.4.2. Reliability assessment

Reliability refers to the extent to which a study is free from bias and its findings reflect true facts. For peer-reviewed studies available in the open literature the reliability of studies is likely to vary. In addition, the level of reliability of a study depends on the nature of the risk assessment the study is going to inform. For example, a study may be considered not reliable enough to provide information to establish a deterministic endpoint to assess human toxicity but reliable enough for an ecotoxological probabilistic risk assessment.

There are some general principles that may be considered when assessing the reliability of the studies described under point a) in section 5.4.1 (e.g. statistical power; verification of measurement methods and data; control of experimental variables that could affect measurements; universality of the effects in validated test systems using relevant animal strains and appropriate routes of exposure; biological plausibility of results; and uniformity among substances with similar attributes and effects) (adapted from Becker et al., 2009).

For many data requirements, guidance already developed to support the risk assessment of plant protection products in the regulatory framework of directive 91/414/EEC provide minimum quality criteria for studies considered in the risk assessment. These guidance documents should be considered when assessing the reliability of scientific peer-reviewed literature for a particular risk assessment as appropriate. Links to the guidance documents normally used in the European assessment of plant protection active substances are:

- European Commission:

  http://ec.europa.eu/food/plant/protection/resources/publications_en.htm#council

- FOCUS: http://focus.jrc.ec.europa.eu/

- EFSA: http://www.efsa.europa.eu/en/ppr/pprscdocs.htm

- OECD: http://www.oecd.org/document/7/0,3343,en_2649_34377_37051368_1_1_1_1,00.html)

- WHO: http://www.inchem.org/

The methodological quality of studies may alternatively be assessed by applying other criteria to classify the studies according to their likely reliability for use in risk assessments. Some possible classification schemes are illustrated by Klimisch et al. (1997), Durda and Preziosi (2000), Hobbs et al. (2005), Schneider et al. (2009), Küster et al. (2009) and Küster et al. (2010). However, attention should be paid to the advantages, disadvantages, applicability, and compatibility of such schemes as they may not provide similar results (Ågerstrand et al., 2010). It must be emphasised that compliance with good laboratory practice (GLP) standards should not be considered as a guarantee of reliability. Study reliability must be judged solely on the basis of the accuracy and reproducibility of the facts reported. The main difference between GLP and non-GLP peer-reviewed studies is in the background information reported and the potential access to raw data that may be lacking in the latter type of studies. Therefore, reliability appraisal for non-GLP studies may be more difficult.

When reliability assessment is performed, the applicants should provide both a detailed documentation of the process used and a summary of it in *document M* of the dossier. After the reliability assessment, the results of each study should be incorporated in the risk assessment following Regulation (EC) No 1107/2009.

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

The applicants should produce one or more Literature Review Reports.

The number of Literature Review Reports provided is at the discretion of the applicant, to optimise clarity of presentation (e.g. to prevent tables which report multiple search strategies or multiple data requirements becoming very large). For single-concept searches covering all data requirements a single Literature Review Report would normally be provided, whereas multiple-concept searches focusing on specific data requirements may be more clearly reported in separate Literature Review Reports (e.g. one for each data requirement, or group of related data requirements, searched).

Each Literature Review Report should contain the following sections:

1. Title.

2. Authors of the review.

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

4. Protocol, which should contain:

   - A statement of the objective of the review (i.e. to provide information on side effects of (a) determined active substance(s), metabolite(s), plant protection product(s));

   - The criteria for relevance with which decisions to select studies in the dossier were made (Table 1).

5. Search methods and results, including a descriptive summary, together with:

   - Table 2, which reports the search process for scientific peer-reviewed open literature in bibliographic databases;

   - A structured text list documenting any searches and related results performed in sources of peer-reviewed literature other than bibliographic databases (section 5.2.3).

6. Results of the study selection process (section 5.3), including a descriptive summary, together with:

   - Table 3, reporting the results of the study selection process, for each data requirement or group of data requirements searched;

   - Table 4, reporting the bibliographic references to all relevant studies and studies whose relevance remains unclear after detailed assessment for relevance of full-text documents (i.e. the second step of the selection process), ordered by data requirement(s);

   - Table 5, reporting the bibliographic references to all relevant studies and studies whose relevance remains unclear after detailed assessment for relevance of full-text documents (i.e. the second step of the selection process), ordered by author(s);

   → Copies of the full-text documents listed in Table 4 and Table 5 should be provided with the dossier (document K). These copies should be placed within the subfolders that contain studies relevant to the data requirements for which the full-text document has been found relevant. If studies are relevant to more than one data requirement, only one copy of the corresponding full-text document should be provided, but cross references would need to be inserted in the other folders for which the full text document is considered relevant. Relevant

full-text documents should preferably be provided in English; however, official EU languages would be accepted. Relevant full-text documents in non-EU languages should be translated to English.

- Table 6, reporting the bibliographic references to studies considered non-relevant after detailed assessment of full-text documents (i.e. second step of the selection process).

Copies of the full-text documents considered irrelevant after either rapid or detailed assessment do not need to be submitted with the dossier. However, the applicants should be prepared to provide them later if requested by the competent authorities evaluating the dossiers.

All Literature Review Reports should be incorporated in document K of the dossier, in a folder IIA 0.

The applicants are responsible for providing dossiers with full relevant information. Ensuring that copyright, licensing and data protection issues concerning the information included in the dossiers have been fully satisfied remains the responsibility of the applicants. The applicants should consult their national copyright licensing authority for guidance on purchasing copyright licenses to reproduce copyright publications which must be submitted to Rapporteur Member States and EFSA. It should be noted that applicants remain the sole legal or natural persons responsible and liable for obtaining all necessary authorisations and rights to use, reproduce and share the publications submitted in their applications. Under no circumstances may EFSA be held liable for any breach of the relevant legal framework.

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OECD (Organisation for Economic Co-operation and Development), 2006. OECD Guidance for Industry Data Submissions for Microbial Pest Control Products and their Microbial Pest Control Agents. August 2006. OECD Environment Directorate. Available from <http://www.oecd.org/document/48/0,2340,en_2649_34383_2085104_1_1_1_1,00.html>

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APPENDIX A - EXAMPLE OF A FOCUSSED SEARCH FOR PEER-REVIEWED OPEN SCIENTIFIC LITERATURE (ACTIVE SUBSTANCE COMBINED WITH A SPECIFIC DATA REQUIREMENT)

A.1. Introduction

Topic: side effects of Chlorpyrifos active substance in human health.

This example suggests possible search approaches for identifying the active substance and its side effects in humans.

Chlorpyrifos is an organophosphate insecticide that inhibits acetylcholinesterase and is used to control insect pests.

IUPAC name: Diethoxy-sulfanylidene-(3,5,6-trichloropyridin-2-yl)oxy-λ5-phosphane.

Trade names include Brodan, Detmol UA, Dowco 179, Dursban, Dursban F, Empire, Eradex, Lorsban, Paqeant, Piridane, Scout, and Stipend.

Other names given to the substance include: chlorpyrifos-ethyl, ENT 27311, ethion, NA 2783, OMS-0971, o,o-diaethyl-o-3,5,6-trichlor-2-pyridylmonothiophosphat, o,o-diethyl o-3,5,6-trichloro-2-pyridyl phosphorothioate, phosphorothioic acid, o,o-diethyl o-(3,5,6-trichloro-2-pyridyl)ester, pyrinex, Phosphorothioicacid, O,O-diethyl O-(3,5,6-trichloro-2-pyridyl) ester (7CI,8CI), Bonidel, Chlora, Chloroban, Chloropyrifos-ethyl, Chloropyriphos, Chlorpyrifos, Chlorpyrifos E, Chlorpyrifos-ethyl, Chlorpyriphos, Clorpiran, Clorpirifos, Coroban, Cyfos, Danusban, Dhanusban, Dowco 179, Durmet, Dursban 10CR, Dursban 4E, Dursban Pro, Dursban R, Dursban TC, Dursband, Dursband 48, EF 1315, Emperor, Equity, Ethyl chlorpyriphos, FE, Geodinfos, Gigant, Grofo, Killmaster, Lentrek, Lock-On, Lorsban 50SL, Nufos 4E, O,O-Diethyl O-(3,5,6-trichloro-2-pyridinyl)phosphorothioate, O,O-Diethyl O-(3,5,6-trichloro-2-pyridyl) phosphorothioate, O,O-DiethylO-(3,5,6-trichloro-2-pyridyl) thiophosphate, O,O-Diethyl-O-3,5,6-trichloro-2-pyridylphosphorothionate, Pyrifos, Pyrinex, Radar, Sabre, Saurus, Spannit, Stipend, Tafaban, Terial, Terial 40L, XRM 429, XRM 5160, Xinnongba, suSCon, suSCon Blue, suSCon Plus, suScon Green.

It is the active substance in over 800 pesticide products.

In this example, only a few of these alternative names for the active substance are included in the search strategy. For some information sources it may be sufficient to use the CAS number/s or the SMILES structure array.

A.2. Identifying the search concepts

Search concepts are likely to be either:

- The active substance alone: chlorpyrifos (section A.3.1)
- The active substance (chlorpyrifos) AND its side effects (section A.3.2)

A.3. Building the search term lists for each concept

A.3.1. The active substance

Identify the Registry Number of the substance (i.e. 2921-88-2).

The search on the trade names shows that some, for example “Empire”, are used in multiple contexts, not all specific to chlorpyrifos. So the search on those terms needs to be linked to the area of interest, i.e. pesticides. This is shown in line 5 of the search strategy in Figure 3.

Many products contain the active substance chlorpyrifos. There may be some significant products which represent those in widest use or use in Europe which could be introduced into the search.

One possible bibliographic database strategy to retrieve summary records about chlorpyrifos is shown in Figure 3. A combination of search terms in the title, indexing and registry number fields are required to ensure that recent summary records which have not yet been indexed with Subject Headings are also captured.

Search strategy	Number of summary records retrieved
1. Chlorpyrifos/	1473
2. 2921-88-2.rn.	1473
3. chlorpyrifos.ti,ab.	2075
4. (Brodan or Detmol or (Dowco adj "179") or Dursban or eradex or Lorsban or Paqeant or Piridane).ti,ab.	132
5. ((scout or stipend or empire) and (pesticide$ or insect$)).ti,ab.	9
6. or/1-5	2341

Legend:
- /: Indicates a Subject Heading assigned to a summary record by an indexer
- .rn.: Indicates that the search is restricted to registry numbers
- .ti,ab.: Indicates that the search is restricted to words in the title and abstract
- adj: Indicates that the words must appear next to each other
- $: Indicates that all words beginning with the stem before the $ will be retrieved, e.g. insect$ retrieves insect, insects, insecticide, insecticides
- and: Boolean operator to focus search by ensuring both concepts are present in a summary record
- or/1-5: Boolean operator combining sets 1 to 5, to widen search by ensuring all summary records with any of the terms are captured

Figure 3: Bibliographic database strategy to identify summary records about chlorpyrifos conducted May 21 2010 using the Ovid search interface

A.3.2. Possible side effects

In this EFSA Guidance, "*side effects on health, environment, and non-target species*" refers either: (1) to any *unintended effects* that may occur in humans, animals, or non-target organisms, caused by exposure to the active substance, its relevant metabolites or plant protection products as a result of intended usage; or (2) exceeding regulatory limits for environmental contamination (e.g. of groundwater), by the active substance, its relevant metabolites or plant protection products as a result of intended usage. This example focuses on side effects in humans and in particular on the data requirement "toxicological and toxicokinetic studies". This approach can be adapted to capture other data requirements if required (illustrated in Box 2 of this EFSA Guidance) by adding in terms referring to concepts linked to those data requirements.

In humans chlorpyrifos may cause a range of specific side effects, which can be captured in the search strategy using the following concepts:

- neurological effects (neurotoxic/neurotoxin);
- reproductive and developmental disorders (mental and motor development delays, attention deficit hyperactivity disorder, low birthweight);
- autoimmune disorders;

- endocrine disruption;
- asthma.

Capturing all the potentially relevant terms which could signal a side effect (e.g. toxicity) is challenging. The terms identified above have emerged from searching on the pesticide name and looking at a sample of summary records and full-text documents to explore the terminology and indexing they use. This selection is not exhaustive and illustrates why, for some substances, it may be more efficient to search on the substance name alone and not limit the results further to side effects. There is a risk of missing relevant studies if all relevant side effects have not been identified. The side effects strategy in Figure 4 is combined with the chlorpyrifos strategy (as illustrated in Figure 5) to provide a focused search and to reduce the number of summary records that need to be assessed for relevance.

The strategy in Figure 4 makes use of a range of features provided by a bibliographic database:

- Subject Headings such as Toxicity tests/ or Consumer product safety/.
- Floating subheadings. The bibliographic database indexers assign subheadings to the Subject Headings to signal the focus of a summary record. Subheadings of relevance to these searches include toxicity (to), drug effects (de), chemically induced (ci) and adverse effects (ae).
- Some journals focus on safety issues, and the search interface may allow searches using single journal words, such as interactions.jw., to retrieve highly relevant journals.
- A further approach might be to search the author address field to capture research conducted in toxicology departments. This has not been demonstrated in Figure 4 but could be achieved by adding a search term such as "toxicology.in.", where "in" is the field limit for "institution".

In human health research, searches for adverse events are not consistently described and advice on searching for adverse events in the medical literature suggests adopting a variety of approaches including searching for the generic issue (adverse events) as well as specific known issues (e.g. developmental delay, autism). This is demonstrated in Figure 4, but is only an example.

Search strategy	Number of summary records retrieved
9. to.fs. or toxico$.ti,ab. or neurotoxic$.ti,ab. or deleterious$.ti,ab. or toxic effect$.ti,ab.	346569
10. (Residue$ or breakdown$ or degrade$ or degrading or disrupt$ or deficit$ or inhibit$ or impair$ or expression or expressing or harmful or biodegrad$).ti,ab.	2789180
11. (hazard$ or risk assess$ or exposure assess$).ti,ab.	107094
12. (Adverse event$ or adverse effect$ or side effect$).ti,ab.	247544
13. (Health risk$ or Drug effects).ti,ab. or de.fs.	2060100
14. Toxicity tests/ or Consumer product safety/ or Risk assessment/	128960
15. Maximum allowable concentration/ or Pesticide residues/ or Drug-induced liver injury/ or Maternal exposure/	37598
16. (Androgen biosynthesis or Endocrine disrupt$ or Memory deficit$ or neurobehavioral deficit$ or neurobehavioural deficit$ or autism).ti,ab.	20178

17. (mental delay$ or developmental or behavio$ or brain development).ti,ab.	681889
18. (metabolism or safety or interactions).jw.	98465
19. or/9-18	4992333

Legend:
- /: Indicates a Subject Heading assigned to a summary record by an indexer
- .rn.: Indicates that the search term is restricted to registry numbers
- .ti,ab.: Indicates that the search is restricted to words in the title and abstract
- adj: Indicates that the words must appear next to each other
- .fs.: Indicates that the subheading is searched as a floating subheading (unattached to a specific subject heading)
- .jw.: Indicates that the search term is searched within journal titles
- $: indicates searches for words beginning with a word stem, for example the search term "degrade$" would retrieve summary records containing the words "degrade", "degraded" or "degrades"
- de: is the subheading for drug effects
- to: is the subheading for toxicity
- and: Boolean operator to focus search by ensuring both concepts are present in a summary record
- or/9-18: Boolean operator combines sets 9 to 18, to widen search by ensuring all summary records with any of the terms are captured

Figure 4: Example bibliographic database search strategy to identify side effects for toxicity (data requirement: "toxicological and toxicokinetic studies"), conducted May 21 2010

A.3.3. Limiting the search results

There are several ways to limit the results retrieved by searches. One option is to limit by date of publication. Figure 5 shows how to limit search results to scientific literature published in the last ten years (Figure 5, line 21). Another option to limit results is to exclude summary records of document types which may not be relevant such as letters, editorials and comments, which are not peer-reviewed. This latter exclusion is demonstrated in the full strategy shown in Figure 5 (as lines 7 and 8).

A.3.4. The full strategy

The full strategy (Figure 5) combines the search terms for chlorpyrifos and for side effects and removes unwanted document types. Scientific peer-reviewed literature is limited to that published in the ten year period 2000 to 2010 (line 21), as requested by Article 8(5) of Regulation (EC) No 1107/2009. Searching for chlorpyrifos alone generates 2519 summary records. In this example for human toxicity, focusing the search by adding the side effects concept reduces the summary record yield a little, to 2002 summary records. The decision facing the searcher is whether the reduction in the number of summary records identified repays the effort of developing the side effects search and also whether relevant scientific peer-reviewed literature is missed.

Search strategy	Number of summary records retrieved
1. Chlorpyrifos/	1580
2. 2921-88-2.rn.	1580
3. chlorpyrifos.ti,ab.	2246
4. (Brodan or Detmol or (Dowco adj "179") or Dursban or eradex or Lorsban or Paqeant or Piridane).ti,ab.	132
5. ((scout or stipend or empire) and (pesticide$ or	10

insect$)).ti,ab.	
6. or/1-5	2519
7. (letter or editorial or comment).pt.	1072596
8. 6 not 7	2487
9. to.fs. or toxico$.ti,ab. or neurotoxic$.ti,ab. or deleterious$.ti,ab. or toxic effect$.ti,ab.	361830
10. (Residue$ or breakdown$ or degrade$ or degrading or disrupt$ or deficit$ or inhibit$ or impair$ or expression or expressing or harmful or biodegrad$).ti,ab.	3281843
11. (hazard$ or risk assess$ or exposure assess$).ti,ab.	114017
12. (Adverse event$ or adverse effect$ or side effect$).ti,ab.	257948
13. (Health risk$ or Drug effects).ti,ab. or de.fs.	2131467
14. Toxicity tests/ or Consumer product safety/ or Risk assessment/	137226
15. Maximum allowable concentration/ or Pesticide residues/ or Drug-induced liver injury/ or Maternal exposure/	38781
16. (Androgen biosynthesis or Endocrine disrupt$ or Memory deficit$ or neurobehavioral deficit$ or neurobehavioural deficit$ or autism).ti,ab.	21989
17. (mental delay$ or developmental or behavio$ or brain development).ti,ab.	723616
18. (metabolism or safety or interactions).jw.	101670
19. or/9-18	5481145
20. 8 and 19	2002
21. limit 20 to yr="2000 - Current"	1499

Legend:
- /: Indicates a Subject Heading assigned to a summary record by an indexer
- .rn.: Indicates that the search term is restricted to registry numbers
- .ti,ab.: Indicates that the search is restricted to words in the title and abstract
- adj: Indicates that the words must appear next to each other
- .fs.: Indicates that the subheading is searched as a floating subheading (unattached to a specific subject heading)
- .jw.: Indicates that the search term is searched within journal titles
- $: indicates searches for words beginning with a word stem, for example the search term “degrade$” would retrieve summary records containing the words “degrade”, “degraded” or “degrades”
- de: is the subheading for drug effects
- to: is the subheading for toxicity
- .pt.: Indicates that the search terms are Publication Types
- and: Boolean operator to focus search by ensuring both concepts are present in a summary record
- or: Boolean operator to widen search by ensuring all summary records with any of the terms are captured
- not: Boolean operator to limit search by excluding terms or concepts

Figure 5: Example strategy (conducted Oct 10, 2010) to identify adverse events of chlorpyrifos in a bibliographic database, after removing specific publication types

A.4.Reporting the search process

This section illustrates how to report the searches performed in bibliographic databases for the topic "side effects of the active substance chlorpyrifos in human health", described above. Table 7 shows how the search strategy illustrated in Figure 3 and an adaptation of the same search strategy performed in another bibliographic database would be reported using the template provided in Table 2.

Table 7: Example search process for the active substance chlorpyrifos, as recorded in the template (Table 2) of section 5.2.3

Data requirement(s) captured in the search	**Details of the searches** *Insert additional columns for additional databases; insert additional rows for additional search strategies* *Use a separate Table for every individual data requirement, or group of requirements, searched*		
Active substance only (chlorpyrifos) (covers all data requirements)	**Database 1**	**Database 2**	
	Justification for choosing the source: this database has over 19 million biomedical summary records and related full-text documents and has excellent coverage of human toxicology studies	**Justification for choosing the source:** this database is a major cross disciplinary database covering scientific publications in agricultural, biological, and environmental sciences, engineering, technology, applied science, medical and life sciences, and physical and chemical sciences	
	Date of the search: 10 Oct 2010	**Date of search:** 11 Oct 2010	
	Date span of the search: 1950 to Oct Week 1 2010[21]	**Date span of the search:** 1900 to 10 Oct 2010[21]	
	Date of the latest database update included in the search: Oct week 1 2010	**Date of the latest database update included in the search:** 10 Oct 2010	
	Search strategies used for this data requirement (including any limits)	**Search strategies used for this data requirement (including any limits)**	
	1. Chlorpyrifos/ 2. 2921-88-2.rn. 3. chlorpyrifos.ti,ab. 4. (Brodan or Detmol or (Dowco adj "179") or Dursban or eradex or Lorsban or Paqeant or Piridane).ti,ab. 5. ((scout or stipend or empire) and (pesticide$ or insect$)).ti,ab. 6. or/1-5	1. ts=Chlorpyrifos 2. ts=(Brodan or Detmol or Dowco 179 or Dursban or eradex or Lorsban or Paqeant or Piridane) 3. ts=((scout or stipend or empire) and (pesticide* or insect*)) 4. #3 OR #2 OR #1	
	Total number of summary records retrieved: 2555	**Total number of summary records retrieved: 4642**	
	Total number of summary records retrieved after removing duplicates		**n= 5306**

[21] The date span illustrated is the default for this bibliographic database, used for convenience. The applicants should include in the dossier all scientific peer-reviewed open literature published within the ten years prior to the dossier submission date.

Table 8 shows how the search strategy illustrated in Figure 5 and an adaptation of the same search strategy performed in another bibliographic database would be reported using the template provided in Table 2.

Table 8: Example search process for side effects of the active substance chlorpyrifos according to data requirement "toxicological effects", as recorded in the template (Table 2) of section 5.2.3

Data requirement(s) captured in the search	**Details of the searches** *Insert additional columns for additional databases; insert additional rows for additional search strategies* *Use a separate Table for every individual data requirement, or group of requirements, searched*	
Active substance (chlorpyrifos) and side effect "toxicity" (included in the data requirement: "toxicological effects") (OECD code: AII 5)	**Database 1**	**Database 2**
	Justification for choosing the source: this database has over 19 million biomedical summary records and related full-text documents and has excellent coverage of human toxicology studies	**Justification for choosing the source:** this database is a major cross disciplinary database covering scientific publications in agricultural, biological, and environmental sciences, engineering, technology, applied science, medical and life sciences, and physical and chemical sciences.
	Date of the search: 11 Oct 2010	**Date of the search:** 11 Oct 2010
	Date span of the search: Scientific literature published 2000 to 2010	**Date span of the search:** 2000 to 2010
	Date of the latest database update included in the search: Oct week 1 2010	**Date of the latest database update included in the search:** 10 Oct 2010
	Search strategies used for this data requirement (including any limits)	**Search strategies used for this data requirement (including any limits)**
	1. Chlorpyrifos/ 2. 2921-88-2.rn. 3. chlorpyrifos.ti,ab. 4. (Brodan or Detmol or (Dowco adj "179") or Dursban or eradex or Lorsban or Paqeant or Piridane).ti,ab. 5. ((scout or stipend or empire) and (pesticide$ or insect$)).ti,ab. 6. or/1-5 7. (letter or editorial or comment).pt. 8. 6 not 7 9. to.fs. or toxico$.ti,ab. or neurotoxic$.ti,ab. or deleterious$.ti,ab. or toxic effect$.ti,ab. 10. (Residue$ or breakdown$ or degrade$ or degrading or disrupt$ or deficit$ or inhibit$ or impair$ or expression or expressing or harmful or biodegrad$).ti,ab.	1. Ts=(chlorpyrifos SAME (toxico*.ti,ab. or neurotoxic* or deleterious* or toxic effect*)) 2. Ts=(chlorpyrifos SAME (Residue* or breakdown* or degrade* or degrading or disrupt* or deficit* or inhibit* or impair* or expression or expressing or harmful or biodegrad*)) 3. Ts=(chlorpyrifos SAME (hazard* or risk assess* or exposure assess*)) 4. Ts=(chlorpyrifos SAME (Adverse event* or adverse effect* or side effect*)) 5. Ts=(chlorpyrifos SAME (Health risk* or Drug effects)) 6. Ts=(chlorpyrifos SAME (concentration or liver injury or Maternal exposure)) 7. Ts=(chlorpyrifos SAME (Androgen biosynthesis or Endocrine disrupt* or Memory deficit* or neurobehavioral deficit* or neurobehavioural deficit* or autism))

	11. (hazard$ or risk assess$ or exposure assess$).ti,ab. 12. (Adverse event$ or adverse effect$ or side effect$).ti,ab. 13. (Health risk$ or Drug effects).ti,ab. or de.fs. 14. Toxicity tests/ or Consumer product safety/ or Risk assessment/ 15. Maximum allowable concentration/ or Pesticide residues/ or Drug-induced liver injury/ or Maternal exposure/ 16. (Androgen biosynthesis or Endocrine disrupt$ or Memory deficit$ or neurobehavioral deficit$ or neurobehavioural deficit$ or autism).ti,ab. 17. (mental delay$ or developmental or behavio$ or brain development).ti,ab. 18. (metabolism or safety or interactions).jw. 19. or/9-18 20. 8 and 19 21. limit 22 to yr="2000 - 2010"	8. Ts=(chlorpyrifos SAME (mental delay* or developmental or behavio* or brain development)) 9. Ts=((Brodan or Detmol or Dowco 179 or Dursban or eradex or Lorsban or Paqeant or Piridane) SAME (toxico*.ti,ab. or neurotoxic*.ti,ab. or deleterious*.ti,ab. or toxic effect*)) 10. Ts=((Brodan or Detmol or Dowco 179 or Dursban or eradex or Lorsban or Paqeant or Piridane) SAME (Residue* or breakdown* or degrade* or degrading or disrupt* or deficit* or inhibit* or impair* or expression or expressing or harmful or biodegrad*)) 11. Ts=((Brodan or Detmol or Dowco 179 or Dursban or eradex or Lorsban or Paqeant or Piridane) SAME (hazard* or risk assess* or exposure assess*)) 12. Ts=((Brodan or Detmol or Dowco 179 or Dursban or eradex or Lorsban or Paqeant or Piridane) SAME (Adverse event* or adverse effect* or side effect*)) 13. Ts=((Brodan or Detmol or Dowco 179 or Dursban or eradex or Lorsban or Paqeant or Piridane) SAME (Health risk* or Drug effects)) 14. Ts=((Brodan or Detmol or Dowco 179 or Dursban or eradex or Lorsban or Paqeant or Piridane) SAME (concentration or liver injury or Maternal exposure)) 15. Ts=((Brodan or Detmol or Dowco 179 or Dursban or eradex or Lorsban or Paqeant or Piridane) SAME (Androgen biosynthesis or Endocrine disrupt* or Memory deficit* or neurobehavioral deficit* or neurobehavioural deficit* or autism)) 16. Ts=((Brodan or Detmol or Dowco 179 or Dursban or eradex or Lorsban or Paqeant or Piridane) SAME (mental delay* or developmental or behavio* or brain development)) 17. Ts= ((scout or stipend or empire) SAME (toxico* or neurotoxic* or deleterious*or toxic effect*)) 18. Ts= ((scout or stipend or empire) SAME (Residue* or breakdown* or degrade* or degrading or disrupt* or deficit* or inhibit* or impair* or expression or expressing or harmful or biodegrad*)) 19. Ts= ((scout or stipend or empire) SAME (hazard* or risk assess* or exposure assess*)) 20. Ts= ((scout or stipend or empire) SAME (Adverse event* or adverse effect* or side effect*))	

		21. Ts= ((scout or stipend or empire) SAME (Health risk* or Drug effects)) 22. Ts= ((scout or stipend or empire) SAME (concentration or liver injury or Maternal exposure)) 23. Ts= ((scout or stipend or empire) SAME (Androgen biosynthesis or Endocrine disrupt* or Memory deficit* or neurobehavioral deficit* or neurobehavioural deficit* or autism)) 24. Ts= ((scout or stipend or empire) SAME (mental delay* or developmental or behavio* or brain development)) 25. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 26. #25 AND py=2001-2010 27. #25 AND py=2000 28. #26 OR #27	
	Total number of summary records retrieved: 1499	**Total number of summary records retrieved: 1026**	
		Total number of summary records retrieved after removing duplicates	**n=1791**

APPENDIX B – EXAMPLES OF SINGLE CONCEPT SEARCHES FOR PEER-REVIEWED OPEN SCIENTIFIC LITERATURE (ACTIVE SUBSTANCE ONLY)

This section provides some examples of single concept searches (i.e. using the active substance names and its synonyms) for three active substances. The results of such searches show that a small amount of open scientific literature is available for these particular substances.

For the three active substances the publication type "patent" was excluded. Three bibliographic databases were searched.

1. The first active substance searched was substance Isopyrazam, a new broad spectrum foliar fungicide:

    - CAS Name: 3-(difluoromethyl)-1-methyl-N-[1,2,3,4-tetrahydro-9-(1-methylethyl)-1,4-methanonaphthalen-5-yl]-1H-pyrazole-4-carboxamide.
    - CAS registry nr. 881685-58-1.
    - Other names: BONTIMA.

The results of this search are illustrated in Table 9.

2. The second active substance searched was Ipconazole, a new fungicide for certain seed fungal diseases:

    - Other names: Vortex FL, Rancona, Acceleron.
    - CAS Name: 2-[(4-chlorophenyl)methyl]-5-(1-methylethyl)-1-(1H-1,2,4-triazol-1-ylmethyl)cyclopentanol.
    - CAS registry nr. 125225-28-7.

The results of this search are illustrated in Table 10.

3. The third active substance searched was Valiphenal, a new systemic fungicide:

    - CAS Name: β-Alanine, N-[(1-methylethoxy)carbonyl]-L-valyl-3-(4-chlorophenyl)-, methyl ester (9Cl).
    - Other names: IR 5885, Valifenalate.
    - CAS Registry Nr: 1018966-01-2; 283159-91-1; 283159-90-0 (stereoisomer 283159-94-4 only 3 references in CAS).

The results of this search are illustrated in Table 11.

Table 9: Example search process for the active substance Isopyrazam, as recorded in the template (Table 2) of section 5.2.3

Data requirement(s) captured in the search	Details of the searches *Insert additional columns for additional databases; insert additional rows for additional search strategies* *Use a separate Table for every individual data requirement, or group of requirements, searched*			
Active substance only (Isopyrazam) (covers all data requirements)	**Database 1**	**Database 2**	**Database 3**	
	Justification for choosing the source: this database has over 19 million biomedical summary records and related full-text documents and has excellent coverage of human toxicology studies	**Justification for choosing the source:** this database is a major cross disciplinary database covering scientific publications in agricultural, biological, and environmental sciences, engineering, technology, applied science, medical and life sciences, and physical and chemical sciences	**Justification for choosing the source:** one of the most comprehensive databases on chemical substances	
	Date of the search: 21 Nov 2010	**Date of search:** 21 Nov 2010	**Date of search:** 8 Dec 2010	
	Date span of the search: 1950 to Oct Week 1 2010[22]	**Date span of the search:** 1900 to 10 Oct 2010[22]	**Date span of the search:** 1900 to 8 Dec 2010[22]	
	Date of the latest database update included in the search: Oct week 1 2010	**Date of the latest database update included in the search:** 10 Oct 2010	**Date of the latest database update included in the search**: 8 Dec 2010	
	Search strategies used for this data requirement (including any limits)	**Search strategies used for this data requirement (including any limits)**	**Search strategies used for this data requirement (including any limits)**	
	1. Isopyrazam OR 881685-58-1 [rn] OR bontima	1. ts=(isopyrazam OR 881685-58-1 OR bontima)	Isopyrazam	
	Total number of summary records retrieved: 1	**Total number of summary records retrieved:** 0	**Total number of summary records retrieved:** 2	
			Total number of summary records retrieved after removing duplicates	**n= 2**

[22] The date span illustrated is the default for this bibliographic database, used for convenience. The applicants should include in the dossier all scientific peer-reviewed open literature published within the ten years prior to the dossier submission date.

Table 10: Example search process for the active substance Ipconazole, as recorded in the template (Table 2) of section 5.2.3

Data requirement(s) captured in the search	**Details of the searches** *Insert additional columns for additional databases; insert additional rows for additional search strategies* *Use a separate Table for every individual data requirement, or group of requirements, searched*			
Active substance only (Ipconazole) (covers all data requirements)	**Database 1**	**Database 2**	**Database 3**	
	Justification for choosing the source: this database has over 19 million biomedical summary records and related full-text documents and has excellent coverage of human toxicology studies	**Justification for choosing the source:** this database is a major cross disciplinary database covering scientific publications in agricultural, biological, and environmental sciences, engineering, technology, applied science, medical and life sciences, and physical and chemical sciences	**Justification for choosing the source:** one of the most comprehensive databases on chemical substances	
	Date of the search: 21 Nov 2010	**Date of search:** 21 Nov 2010	**Date of search**: 8 Dec 2010	
	Date span of the search: 1950 to Oct Week 1 2010[23]	**Date span of the search:** 1900 to 10 Oct 2010[23]	**Date span of the search**: 1900 to 8 Dec 2010[23]	
	Date of the latest database update included in the search: Oct week 1 2010	**Date of the latest database update included in the search:** 10 Oct 2010	**Date of the latest database update included in the search**: 8 Dec 2010	
	Search strategies used for this data requirement (including any limits)	**Search strategies used for this data requirement (including any limits)**	**Search strategies used for this data requirement (including any limits)**	
	1. ipconazole OR 125225-28-7 [rn] 2. (ancona OR acceleron OR vortex) AND fungicide*	1. TS=(ipconazole OR 125225-28-7) 2. TS=((rancona OR acceleron OR vortex) AND fungicide*) 3. #1 OR #2	**Ipconazole**	
	Total number of summary records retrieved: 3	**Total number of summary records retrieved:** 14	**Total number of summary records retrieved:** 25	
			Total number of summary records retrieved after removing duplicates	**n= 36**

[23] The date span illustrated is the default for this bibliographic database, used for convenience. The applicants should include in the dossier all scientific peer-reviewed open literature published within the ten years prior to the dossier submission date.

Table 11: Example search process for the active substance Valiphenal, as recorded in the template (Table 2) of section 5.2.3

Data requirement(s) captured in the search	**Details of the searches** *Insert additional columns for additional databases; insert additional rows for additional search strategies* *Use a separate Table for every individual data requirement, or group of requirements, searched*			
Active substance only (Valiphenal) (covers all data requirements)	**Database 1**	**Database 2**	**Database 3**	
	Justification for choosing the source: this database has over 19 million biomedical summary records and related full-text documents and has excellent coverage of human toxicology studies	**Justification for choosing the source:** this database is a major cross disciplinary database covering scientific publications in agricultural, biological, and environmental sciences, engineering, technology, applied science, medical and life sciences, and physical and chemical sciences	**Justification for choosing the source:** one of the most comprehensive databases on chemical substances	
	Date of the search: 21 Nov 2010	**Date of search:** 21 Nov 2010	**Date of search**: 8 Dec 2010	
	Date span of the search: 1950 to Oct Week 1 2010[24]	**Date span of the search:** 1900 to 10 Oct 2010[24]	**Date span of the search**: 1900 to 8 Dec 2010[24]	
	Date of the latest database update included in the search: Oct week 1 2010	**Date of the latest database update included in the search:** 10 Oct 2010	**Date of the latest database update included in the search**: 8 Dec 2010	
	Search strategies used for this data requirement (including any limits)	**Search strategies used for this data requirement (including any limits)**	**Search strategies used for this data requirement (including any limits)**	
	1. Valiphenal OR IR 5885 OR IR5885 OR Valifenalate OR 1018966-01-2[rn]	1. TS=(Valiphenal OR (IR SAME 5885) OR IR5885 OR Valifenalate)	**Valiphenal**	
	Total number of summary records retrieved: 0	**Total number of summary records retrieved:** 0	**Total number of summary records retrieved:** 1	
			Total number of summary records retrieved after removing duplicates	**n= 1**

[24] The date span illustrated is the default for this bibliographic database, used for convenience. The applicants should include in the dossier all scientific peer-reviewed open literature published within the ten years prior to the dossier submission date.

APPENDIX C – EXAMPLE OF THE FIRST STEP OF THE STUDY SELECTION PROCESS: RAPID ASSESSMENT OF SUMMARY RECORDS

This Appendix provides an example of the first step of the study selection process (i.e. rapid assessment of summary records) for the topic "side effects of the active substance chlorpyrifos in human health" (Table 9 in section A.4). The example covers the data requirements "toxicological and toxicokinetic studies" as set out in Annex II of Directive 91/414/EEC (data points: Annex II 5 and Annex IIIA 7; equivalent to OECD dossier data points IIA 5 and IIIA 7). The rapid assessment consists of the screening for relevance of the summary records, without examination of the full-text documents. Hereafter, this example refers only to the OECD dossier data point codes.

C.1. Setting of relevance criteria

The criteria for relevance were developed in an iterative process that involved discussion and agreement among the reviewers. The experts agreed that relevant studies were those that would inform, or partly inform, the data requirements set out in Regulation (EC) No 1107/2009 (referring to Directive 91/414/EEC - and subsequent updates), by presenting the following characteristics:

1. For data requirements OECD IIA 5.1 to 5.7[25] and OECD IIA 7.1 and 7.2 relevant studies would:
    - present a well identified test material, including its purity and impurity profile; include test species that are likely to be relevant to the mammalian toxicological assessment (preferred species are rodents - rats and mice, the dog is the preferred non-rodent species);
    - include a sufficient number of animals per group to establish statistical significance;
    - test several dose levels (at least 3);
    - preferably include a negative control, to establish a dose-response relationship; and include a relevant route of administration in terms of risk assessment (oral, dermal or by inhalation);
    - describe the observations, examinations, analyses performed, or necropsy.

2. For data requirements OECD IIA 5.9 and OECD IIIA7.3 to 7.5, and 7.7 to 7.11 all summary records regarding epidemiological studies, medical reports and actual exposure measurements were considered relevant at this stage without limitation by the above mentioned considerations, except the identification of the test material.

3. For data requirement OECD IIIA 7.6 relevant studies would:
    - present a well identified test material, including its purity and impurity profile, as well as the presence of co-formulants in the tested formulation;
    - include test species (preferred species are rats);
    - test relevant dose levels;
    - describe the analysis and calculations performed.

4. For data requirements under OECD IIA 5.8 IIIA. Studies which may be helpful for the interpretation of other studies present in the dossier, but do not fit under a specific toxicological endpoint (broadly included in the OECD code referred as "other toxicological studies") would be relevant. Their use for regulatory purposes is generally limited to help addressing species sensitivity and safety factors. Examples of these studies would be:

[25] For OECD data points 5.1 and 5.4 the mentioned criteria apply only partially, due to the specificity of these protocols (toxicokinetic and genotoxicity studies, respectively).

- Studies indicating the effects of combined exposures.
- Studies on hormonal effects.
- Studies indicating hyper-susceptibility of specific subpopulation groups.
- Studies indicating effects of sensitisation other than skin sensitisation.
- Studies indicating gender and age variation in susceptibility.
- Studies clarifying the mode of action of the active substance.

Unusual routes of exposure would be included in this section as they may introduce important information on other possible toxicological effects.

C.2. Rapid assessment of study relevance based on summary records

The information to assess relevance according to the criteria listed in section C.1 were not always reported in the summary records (abstracts and/or titles) examined for this example of the first step of the study selection process for chlorpyrifos.

Typically an abstract illustrated the test material (without giving details of purity and impurities), the species and dose(s) tested, the route of administration, and in some cases a reference to observations or examinations was given.

Due to the lack of relevance information in the summary records, the following revised criteria were used to classify a summary record as potentially relevant to the toxicological risk assessment:

- Test material identified in the summary record (regardless the purity/impurity profile).
- Test species relevant to the mammalian toxicological assessment.
- Sufficient number of doses tested (except for OECD code 5.1 and 5.4).
- Relevant route(s) of administration.
- Epidemiological studies, medical reports and actual exposure measurements were always considered relevant at this stage.
- Studies which may be helpful for the interpretation of other studies present in the dossier, but do not fit under a specific toxicological endpoint (broadly included in the OECD code referred as “other toxicological studies”).

In total, 1791 summary records were retrieved from bibliographic databases (Table 9 in section A.4) and were screened by expert reviewers and grouped into two categories according to their likely relevance after rapid assessment of titles and, when available, abstracts:

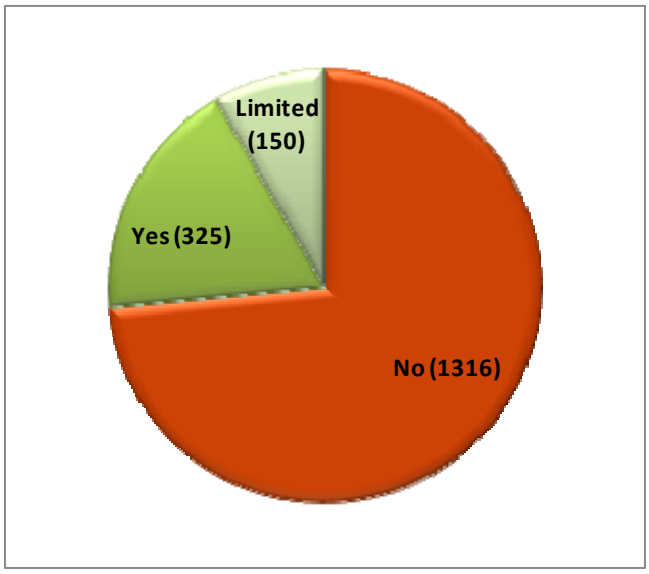
1. Obviously not relevant: 1316 summary records.

   These summary records were either lacking of the information on the animal species or their object was not relevant to the toxicological assessment (and maybe relevant to another data requirement, e.g. to method of analysis, eco-toxicity, or efficacy).

2. Not excluded after rapid assessment: 475 summary records were classified as potentially relevant and thus to be assessed in detail (i.e. step 2 of the study selection process, detailed assessment of the full-text documents).
   Within this category, the reviewers were able to identify summary records (150) that were likely to have a limited relevance on the risk assessment (i.e. likely to provide only supplementary information that does not alter existing risk assessment parameters – point b) in section 5.4.1. These were mostly experimental, molecular and biochemical investigations (which might be helpful for the comprehension of the whole toxicological picture, but whose use at regulatory level is expected to be rather limited) and studies that would be useful for developing guidance

documents or models (as QSAR Quantitative structure-activity relationship investigations, or exposure models).

The rapid selection of the 1791 summary records was undertaken in a total of 45 working hours. The results of the rapid assessment process are illustrated in Figure 6.



No: obviously irrelevant summary records, after assessment
Yes: summary records not excluded after rapid assessment
Limited: within the "yes" category, summary records that are likely to have a limited relevance to the final risk assessment

Figure 6. Results of the rapid assessment of summary records for the topic "side effects of chlorpyrifos active substance in human health"

ABBREVIATIONS

AMU	Assessment Methodology Unit
CAS	Chemical Abstracts Service
EFSA	European Food Safety Authority
EU	European Union
GLP	Good Laboratory Practice
IUPAC	International Union of Pure and Applied Chemistry
PRAPeR	Pesticide Risk Assessment Peer Review Unit
SMILES	Simplified molecular input line entry specification
SR	Systematic review
URL	Uniform Resource Locator