GUIDANCE OF EFSA - DRAFT

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 provides instructions on how to identify and select "*scientific peer-reviewed open literature"* as required by Article 8(5) of Regulation (EC) No 1107/2009 on the placing of plant protection products on the market and how to report it in a dossier. The 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 Guidance is based upon the principles of systematic review, to ensure methodological rigour and transparency, and to minimise bias in the identification and selection of scientific information in dossiers. It is compatible with existing OECD Guidance documents for the preparation of active substances dossiers. This Guidance acknowledges that peer-review does not guarantee rigour, validity or transparency of scientific literature and that potentially admissible (i.e. methodologically sound and unbiased) scientific evidence may originate from non-peer-reviewed sources. Accordingly, the "*scientific peer-reviewed open literature"* referred to in Article 8(5) of Regulation (EC) No 1107/2009 is given a wider definition, to enable inclusion of non-peer-reviewed scientific literature, where justified. Research recommendations include clarification of the types of literature and information sources most appropriate/useful for dossiers; assessment of publication bias in pesticide research, which would help to define the level of detail of the searching requirements; and clarification of appropriate methods for appraising data reliability in dossiers.

KEY WORDS

Active substance, metabolite, plant protection product, dossier, peer-reviewed open literature, literature search.

[1] OJ L309, 21.10.2009, p. 1.

2 On request of EFSA, Question No EFSA-Q-2009-00827.

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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 Guidance provides instructions on how to identify and select "*scientific peer-reviewed open literature"* as required by Article 8(5) of Regulation (EC) No 1107/2009 and how to report the results of the search and the selection of "*scientific peer-reviewed open literature"* in a dossier.

The intended users of this 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 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 literature* for active substances, their metabolites or plant protection products in this Guidance is equivalent to three initial steps of the systematic review process, namely: (1) clarification *a priori* 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 documentation and report of the searching and study selection processes.

This Guidance was developed by a working group that considered in detail how to 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 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 working group noted that peer-review may not guarantee rigour, validity or transparency of scientific literature and that potentially admissible (i.e. methodologically sound and unbiased) scientific evidence may or may not originate from sources which are peer-reviewed. For the purposes of this Guidance the interpretation of "*scientific peer-reviewed open literature"* in Article 8(5) of Regulation (EC) No 1107/2009 has been widened to include some types of non-peer-reviewed literature.

This Guidance on how to identify and select scientific peer-reviewed open literature for the regulatory approval of active substances does not currently include safeners, synergists and adjuvants, since data requirements for these compounds are not yet available. In principle, this Guidance could also apply to safeners, synergists and adjuvants (with adaptation if necessary).

Research recommendations include clarification of the types of literature and information sources most appropriate or useful for dossiers; assessment of publication bias in pesticide research, which would help to define the level of detail of the searching requirements; and clarification of appropriate methods for appraising data reliability in dossiers.

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BACKGROUND AS PROVIDED BY EFSA

Directive 91/414/EEC[3] 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[4]. 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[4] 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[5] Unit is currently responsible, should be integrated in the Guidance. Close coordination and cooperation with the PRAPeR[6] 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.

[3] OJ L230, 19.8.1991, p. 1.
[4] Regulation (EC) No 1107/2009 (OJ L309, 21.10.2009, p. 1), 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.
[5] Assessment Methodology Unit.
[6] Pesticide Risk Assessment Peer Review Unit.

EVALUATION

1. Approach to the mandate

For the development of this Guidance, the Assessment Methodology Unit (AMU) of the European Food Safety Authority (EFSA) established a working group which comprised EFSA external members and scientific officers. The Guidance was developed through three working group meetings and teleconferences and was first approved by the working group on the 20th of April 2010.

An advanced draft of the Guidance document was submitted to the EFSA Panel on Plant Protection Products and their Residues (PPR) and the Pesticide Steering Committee (PSC). The feedback from both groups of experts was considered by the working group during a final meeting and was used to finalise the Guidance.

2. Intended users of the Guidance

This Guidance was written for the use of applicants submitting dossiers for the approval of active substances of plant protection products (PPP) under Regulation (EC) No 1107/2009. Intended users of this 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, responsible for peer-reviewing and drawing conclusions on the dossiers.

3. Introduction

This 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, synergists, adjuvants, and co-formulants. At the time of preparing this Guidance document, data requirements are clearly defined only for active substances. The principles outlined in this Guidance on how to identify and select the scientific peer-reviewed open literature are likely to be applicable also for safeners, synergists, and adjuvants. However, adaptations may be needed when data requirements for these compounds become available.

The Guidance was written in the light of the general principles of systematic reviews as described in the EFSA Guidance on "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 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 active substances.

This Guidance may be revised in view of amendments of Regulation (EC) No 1107/2009. The applicants shall consult the EFSA Journal[7] to make sure they have the latest version of the Guidance.

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

4. Interpretation and application of terminology employed in Article 8(5) of Regulation (EC) No 1107/2009

Article 8(5) of Regulation (EC) No 1107/2009 refers to "*scientific peer-reviewed open literature".* However, the working group developing this Guidance noted that: (1) Different interpretations exist concerning the definition of "peer-reviewed" literature. (2) Potentially admissible (i.e. methodologically sound and unbiased) scientific evidence may or may not originate from sources which are peer-reviewed. (3) It is unclear whether the process of peer-review guarantees rigour, validity, or transparency of scientific literature. (4) Scientific reports of agencies and academic institutions may be produced to a consistently high standard without employing the same processes of external review employed by scientific journals. (5) The review processes used in the production of academic or agency reports are not always clearly documented. For the purposes of this Guidance, the interpretation of "*scientific peer-reviewed open literature"* in Article 8(5) of Regulation (EC) No 1107/2009 has been widened to include some types of non-peer-reviewed literature, where justified[8].

For the purposes of this Guidance, the following interpretation with regard to the terminology of Article 8(5) of Regulation (EC) No 1107/2009 shall be applied:

Terminology in Article 8(5) of Regulation (EC) No 1107/2009	Interpretation and application to this Guidance	Explanation and comments
• "*Scientific peer-reviewed open literature*"	For the purpose of this Guidance, it is defined as publicly available *scientific literature*, which includes primary research studies[9] or well conducted evidence syntheses (i.e. secondary research studies) produced according to systematic review (SR) principles (i.e. methodological rigour; transparency; and reproducibility – section 5). In this Guidance, the above is referred to as "*scientific literature*".	It is unlikely that most handbooks, pesticide manuals, catalogues, editorials, or commentaries would comply with this description. The fact that a study is not peer-reviewed does not imply that it is not scientifically valid (e.g. studies included in official agencies reports or academic theses). Non-peer-reviewed reports are admissible upon justification for their inclusion.
• "*Active substance*"	For the purpose of this Guidance, it shall be 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 product*,".	To assess the "*side effects*" of the active substance, the applicants shall consider also the plant protection products containing the relevant active substance.
• "*Relevant*	For the purpose of this Guidance, relevant metabolites are the metabolites,	

[8] Note that in other chemical regulatory areas stricter criteria are set (e.g. theses are not considered acceptable) (Küster et al, 2009). Research is recommended to clarify the implications for risk assessments of setting different criteria for the types of literature permissible for inclusion in dossiers. The current Guidance may be revised in light of experience.

[9] A study is a scientific analysis which aims to establish facts. A study can be either a primary research study or a secondary research study. A primary research study is original study in which data were collected. The term is sometimes used to distinguish such studies from secondary research studies (e.g. reviews) that re-examine data produced through primary research studies.

Terminology in Article 8(5) of Regulation (EC) No 1107/2009	Interpretation and application to this Guidance	Explanation and comments
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[10].	
• "*side effects on health, environment, and non-target species*"	For the purpose of this Guidance, *side effects* refer to *risks* to human health, animal health and non target organisms and the risk of groundwater contamination above the regulatory limits. Thus relevant data on side effects shall include data on hazard identification, hazard characterisation, and exposure assessment.	
• "*published within the last ten years before the date of dossier submission*"	For the purpose of this Guidance, the time of publication refers to **when the information first became publicly available** (e.g. print publication, online publication ahead of print versions, or dissemination of unpublished reports). This must include (but need not be limited to) the most recent ten years prior to the dossier submission date.	*Scientific literature* may be included from more than ten years prior to dossier submission, provided that the literature is identified and selected in compliance with this Guidance. As the search must be as current as possible at the time of dossier submission, this Guidance requires the applicants to update the search within three months before the date of the submission of the dossier.

The applicants are responsible for providing dossiers with full relevant information. 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.

[10] 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.

5. Requirements for identifying and selecting scientific literature to be incorporated into the EU dossiers of active substance of plant protection products

The requirements for identifying and selecting *scientific literature* for active substances, their metabolites, or plant protection products illustrated in this Guidance are based on the fundamental principles of systematic review (methodological rigour, transparency, and reproducibility) and are illustrated in sections 5.1 – 5.4.

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)[11].

Based on the initial steps of a systematic review (summarised in Box 1[12]), this Guidance describes the requirements for identifying and selecting *scientific literature* for inclusion in the dossier, taking into consideration issues unique to the process of dossier approval. For instance, this Guidance is not prescriptive with regard to the method for selection of *scientific literature*, which would be reported in more detail in a full systematic review. Once the relevant *scientific literature* has been incorporated into the dossier, the applicants shall follow the subsequent steps for dossier preparation according to the OECD Guidance (OECD, 2005, 2006).

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 illustrated, 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 were selected and included in the review. The search method (the search strategies and information sources used) is thoroughly documented 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 were made is clearly documented.

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

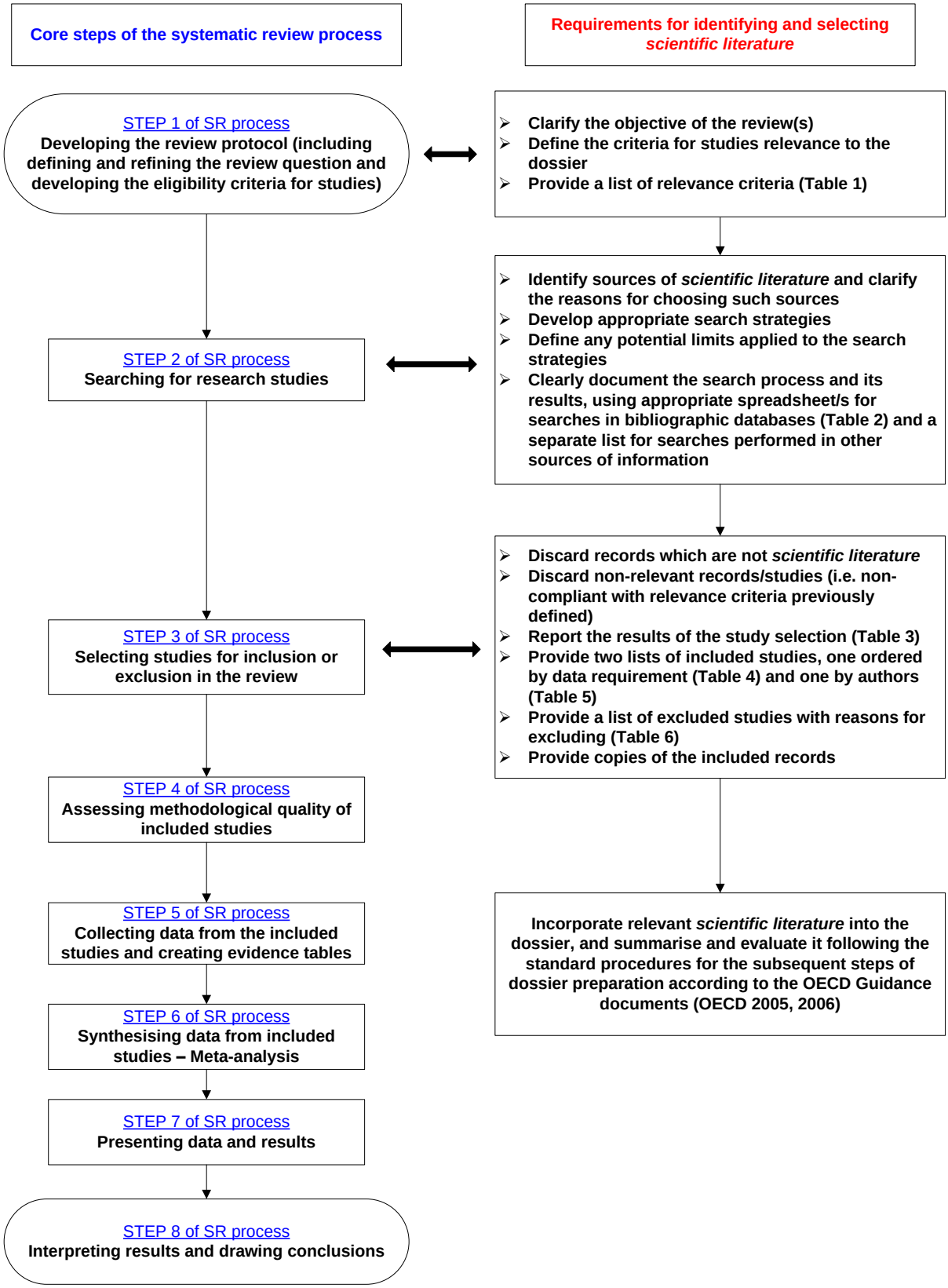

Figure 1: Core steps for performing a systematic review (EFSA, 2010) and requirements for identifying and selecting *scientific literature* set out in this Guidance

5.1. Clarify *a priori* the objective of the review of the scientific literature and set the criteria for study relevance to the dossier

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 into the review. In the case of dossiers, there are numerous questions that need to be answered in order to satisfy the data requirements (Box 2) set out in Regulation (EC) No 1107/2009 (referring to Directive 91/414/EEC and subsequent updates).

Applicants may decide to perform separate reviews of the *scientific literature* for different data requirements. The objective(s) of the review(s) (i.e. to provide information on (a) determined active substance(s), metabolite(s), plant protection product(s) and data requirement(s)) must be clarified *a priori*. This information shall be clearly documented in the protocol of the *scientific literature review report* (details on the structure of these reports are given in section 6 of this Guidance).

This *a priori* clarification is fundamental for specifying the criteria for assessing the relevance of the studies (and thus inclusion/exclusion in/from the dossier) and for developing a search strategy (i.e. combinations of search terms) appropriate for the review question (section 5.2.1).

For each review of data requirement(s) only clearly irrelevant studies shall be excluded. Relevant studies are those that provide information for a particular hazard identification, hazard characterisation, exposure assessment, or risk characterisation for an active substance, its relevant metabolites, or plant protection products, as defined by the data requirement(s) in question.

A useful means to determine relevance criteria could be to inspect each data requirement to identify its key elements. The key elements are those components of a data requirement whose characteristics are fundamental to fully answer the data requirement[13]. Key elements may be populations (e.g. taxa), settings (e.g. geographical areas), processes or procedures (e.g. specified test methods), exposure scenarios (e.g. acute, chronic, lethal, sublethal, different doses or concentrations), or outcomes (endpoints) of interest (e.g. toxicity, mortality, species composition). *Scientific literature* that does not provide all specified key elements would be classified as not relevant and would be excluded from further consideration.

Some examples of how to use the key elements of the data requirements to develop relevance criteria are illustrated in Box 3. It should be noted that such a detailed approach is likely to be applicable for reviews of individual data requirements only. The level of detail when setting relevance criteria will depend upon the focus of the search (e.g. whether the search focuses on one specific data requirement, a group of related data requirements or all data requirements).

Applicants will need to define *a priori* clear relevance criteria that can be applied systematically to all records and that shall not be too restrictive, to avoid missing relevant studies. Developing relevance criteria is likely to be an iterative process. A preliminary search of the literature may be useful, to identify how frequently potential relevance criteria are reported and how they are described. It may be helpful to test and refine the relevance criteria on a subset of *scientific literature* to assess their applicability and whether they need to be refined. A preliminary search may also be useful to assess the quantity of the evidence available and to decide the level of detail required for the relevance criteria. Careful selection of relevance criteria should ensure that relevant studies are not missed, or too many irrelevant studies captured.

The relevance criteria shall be clearly documented in the protocol of the *scientific literature review report* (section 6) for each data requirement, using Table 1.

[13] For details see "Application of systematic review methodology to food and feed safety assessments to support decision making" (EFSA, 2010).

Box 2: The main categories of data requirements given in Regulation (EC) No 1107/2009 (referring to Directive 91/414/EEC). Note that any changes to the data requirements arising from updates of Regulation (EC) No 1107/2009 shall be considered by the applicants when compiling a dossier

1. Data requirements on chemical active substances (Annex II, part A, Directive 91/414/EEC):
    a. Toxicological and metabolism studies (toxicokinetic studies) (point 5)
    b. Residues in or on treated products, food and feed (metabolism and residues data) (point 6)
    c. Fate and behaviour in the environment (point 7)
    d. Ecotoxicological studies (point 8)
    e. Other data requirements for which information may have a direct or indirect effect on overall risk assessment (points 1-4)
2. Data requirements on microbial active substances (including viruses) (Annex II, part B, Directive 91/414/EEC):
    a. Effects on human health (point 5)
    b. Residues in or on treated products, food and feed (point 6)
    c. Fate and behaviour in the environment (point 7)
    d. Effects on non-target organisms (point 8)
    e. Other data requirements for which information may have a direct or indirect effect on the overall risk assessment (points 1-4)
3. Data requirements on plant protection products based on chemical preparations (Annex III, part A, Directive 91/414/EEC):
    a. Efficacy data (point 6)
    b. Toxicological studies (point 7)
    c. Residues in or on treated products, food and feed (point 8)
    d. Fate and behaviour in the environment (point 9)
    e. Ecotoxicological studies (point 10)
    f. Other data requirements for which information may have a direct or indirect effect on the overall risk assessment (points 1-5)
4. Data requirements on plant protection products based on preparations of micro-organisms including viruses (Annex III, part B, Directive 91/414/EEC):
    a. Efficacy data (point 6)
    b. Effects on human health (point 7)
    c. Residues in or on treated products, food and feed (point 8)
    d. Fate and behaviour in the environment (point 9)
    e. Effects on non-target organisms (point 10)
    f. Other data requirements for which information may have a direct or indirect effect the overall risk assessment (points 1-5)

Box 3: Examples of how to use the key elements of the data requirements to develop relevance criteria for study inclusion in the dossier

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), two types of studies may be sought: laboratory controlled degradation studies (data requirement 7.1.1.2.1) or field dissipation studies (data requirement 7.1.1.2.2). In the laboratory studies, appropriate key elements 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 (outcomes). 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 for each data point (outcome). 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), another *key element* would be the presence of a dark control (comparator) and therefore the reporting of dark control results in the *scientific literature* would be another appropriate relevance criterion. For field dissipation studies (data requirement 7.1.1.2.2), appropriate key elements would be the geoclimatic conditions (setting), the application rates (exposure) and the data to derive dissipation half lives (outcomes). 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), appropriate key elements would be the crops and the cultivation conditions (population and setting), the application rates (exposure) and the residues analysed (outcome). In this example relevance criteria may be established 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 (Acute toxicity). For the data requirement "acute toxicity" (5.2 in Directive 91/414/EEC, Annex II, part A), appropriate key elements would be the population (e.g. mammals); the active substance, its metabolites, or PPP (exposure); and the endpoint (toxicity). In this data requirement, the *key element* "exposure" would include, among other relevance criteria, the purity of the test substance and information on the identity and content of impurities, as these are recognised requirements for acute toxicity tests.

Table 1: How to document the list of criteria for relevance for each data requirement

Data requirement(s) (indicated by the correspondent OECD data point number(s))	**Criteria for relevance**

5.2. Search for scientific literature

In order to retrieve as much relevant *scientific literature* as possible (thereby reducing selection biases[14] and publication biases[15]), the applicants shall perform an extensive[16] literature search and document it in detail in the *scientific literature review report* (section 6). The principles of extensive and sensitive literature searches are illustrated below. For the purposes of this Guidance, the documents identified from searches reporting or summarising one or more scientific *studies* are referred to as *records* (e.g. abstracts, full papers, web pages, or reports). A *study* is a scientific analysis which aims to establish facts; it can be either a *primary research study* or a *secondary research study*[17] and might be reported in more than one *record*.

5.2.1. Identify sources of scientific literature

There may be a number of different sources which will yield relevant *scientific literature* (e.g. bibliographic databases, websites, or reference lists). The applicants shall consider which sources are likely to yield relevant records and provide their reasons for choosing such sources. Examples of information sources are represented by journals and books recorded in electronic bibliographic databases; full text journals; journal tables of contents; grey literature (such as unpublished and published[18] reports and conference proceedings); reference lists; citations analysis; websites; ongoing and recently completed research; research results registers; and relevant research centres and experts.

Searching various sources of *scientific literature* is likely to result in duplication of 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 literature* can be sought from information specialists, web listings such as Intute[19] and library guides.

5.2.2. Develop appropriate search strategies

Appropriate search strategies (i.e. search terms and their combinations) shall 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 data requirements (e.g. characteristics of key elements, when the approach for developing relevance criteria is based on the key elements, or any other concepts linked to the relevance criteria, as explained in section 5.1).

Different approaches can be used for developing searches:

- Using a single 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 PPP 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 PPP and their synonyms) combined with one or more other concepts.

[14] In secondary research selection bias refers to the selection of primary research records that are not representative (e.g. if researchers preferentially choose records of studies that are well known to them). Selection bias can lead to findings which deviate from the truth.
[15] Publication bias refers to the preferential reporting of certain types of evidence in records of primary research (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. An extensive search for primary research records (as it is performed in systematic review) may help to reduce the effect of publication bias.
[16] "Comprehensive" literature searches are rather difficult to perform. Therefore, this Guidance aims to give advice on how to perform literature searches in such a way that they are as extensive as possible.
[17] See the definitions in the Glossary.
[18] With the advent of the internet anything appearing on the internet may be classes as "published", but it may not be recorded in bibliographic databases.
[19] <http://www.intute.ac.uk/>.

An advantage of the first approach is that the search is likely to be highly sensitive, to be less time consuming than a series of more focused searches, and to produce fewer duplicate records. Single concept search strategies may also be useful because records retrieved may prove relevant to more than one data requirement. As records 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 set of search results may be returned which needs to be assessed for relevance to each of the data requirements.

If the number of 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 e.g. characteristics of a *key element* of the data requirement (second concept). The concepts would usually be combined using the AND Boolean operator to produce 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.

Search strategies conducted within electronic databases and web search interfaces shall ideally be designed to be sensitive so that they retrieve as much potentially relevant *scientific literature* as possible. This usually involves using as many synonyms and related terms as possible to compensate for the fact that the data available to be searched (author abstracts typically) is 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 need to be included in the strategy (e.g. genotoxicity)[20].

The search strategy must be capable of capturing all *scientific literature* made **publicly available** (e.g. print publication, online publication ahead of print versions, or dissemination of unpublished reports) **during the most recent ten years prior to the dossier submission date** (as required by Article 8(5) of Regulation (EC) No 1107/2009). Older *scientific literature* may also be searched, provided that the methods for locating it and reporting the search results comply with the requirements set out in this Guidance. An important aspect to consider when planning the dossier is that the search must be as current as possible at the time of dossier submission. The applicants shall update the search within **three months** before the date of the submission of the dossier.

Any limits applied to the search strategy, such as e.g. publication type or other features of studies shall be explicitly justified. Language limits shall not be applied to the search strategy.

An example of a search for *scientific literature* for a specific active substance is illustrated in Appendix A of this Guidance. Advice on preparing search strategies can be found in Appendix B of the EFSA Guidance on Application of systematic review methodology 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).

[20] 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.

5.2.3. Use of reference management software to manage the records of scientific literature

The use of bibliographic reference management software (e.g. EndNote or Reference Manager) is very helpful for undertaking the following tasks:

- Creating a structured database (library) of records;
- Identifying and removing duplicate records;
- Identifying new records when updating the searches;
- Managing the selection of records and recording selection decisions.

5.2.4. Clearly document the search and its results

To promote transparency and to allow the assessment of the quality of the searches for *scientific literature*, the search process and its results shall be clearly documented.

For bibliographic databases, the search processes shall be documented in such a way as to include the following information:

1. the specific databases searched and the service provider used (for example, Medline on Ovid, Medline on DIMDI[21], Index of Scientific and Technical Proceedings on Web of Science);
2. the date on which the search was conducted;
3. the date of the latest database update included in the search;
4. the date span of the search (which must include the most recent ten years);
5. the complete search strategies used for each database, 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 into the dossier exactly as they were run in the databases and included in full, in such a way that they can be rerun;
6. any limits applied to the search (e.g. publication types);
7. the total number of records retrieved after removing duplicates.

The details above shall be reported in Excel spreadsheet(s) (Table 2) and included in the *scientific literature review reports* (details on the structure of these reports are given in section 6 of this Guidance).

The spreadsheet (Table 2) can be expanded by columns and/or rows to include as many bibliographic databases and/or search strategies as necessary. The number of spreadsheets will depend on the number of data requirement(s) searched. If only one search strategy is developed there will be one spreadsheet only. The Excel spreadsheet(s) must be completed both for the original searches and for any updated searches (to be performed within **three months** before the date of the submission of the dossier).

For other sources of *scientific literature* (section 5.2.1), information shall be provided in a separate list along with the search terms used in the searches, as follows:

[21] German Institute for Medical Documentation and Information.

- List all grey literature sources used: provide the bibliographic details, URL if available, and the date searched.

- List all individuals or organisations contacted: provide the names and positions of individuals, the names and locations of organisations, as well as the date of the communication.

- List all journals and conference proceedings specifically hand-searched for studies: provide the name of the publication and the years, volumes or issues searched.

- List all other sources searched (e.g. reference lists, the internet): describe the sources, providing any available location information (such as a URL) and the date searched.

- List all company reports: describe how they were identified and selected, including any steps taken to minimise selection biases; provide the name and location of the company, the nature and content of the information source, and the date of the search.

The details above shall be reported in the *scientific literature review reports* (section 6). The searches performed in all information shall also be updated within **three months** before the date of the submission of the dossier.

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

Table 2 (Excel spreadsheet)[22]: Documentation of the search process for *scientific literature* for bibliographic databases

Data requirement(s) captured in the search	**Details of the searches (note: language limits shall not be applied)** *Insert additional columns for additional databases; insert additional rows for additional search strategies* *Use a separate spreadsheet for every individual data requirement, or group of requirements, searched*			
Insert here the data requirement(s) being addressed by each reported search (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 used for this data requirement	**Search strategies used for this data requirement**	**Search strategies 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 records retrieved after removing duplicates			**n=**

[22] This Excel spreadsheet(s) must be completed both for the original searches and for any updated searches.

5.3. Select relevant studies for inclusion in the dossier

Following the initial removal of any duplicate records retrieved, the remaining records are assessed for relevance by applying the previously defined relevance criteria (section 5.1).

The process of selection of relevant *scientific literature* is normally undertaken in two steps:

1. Rapid assessment for relevance based on summaries such as database records (e.g. titles and abstracts), to exclude records which are not *scientific literature* and those which are obviously irrelevant. Records which appear to be relevant and those of unclear relevance go to the next step. For summaries of records with only a title (i.e. for which no abstract or summary are available), the rapid assessment will not be applicable unless the title alone is sufficient to conclude irrelevance; where the title is unclear or uninformative a full text version must be obtained.

2. Full texts are obtained where possible and are assessed in detail for relevance. During this step, individual primary or secondary research studies are identified and duplicate information reported in more than one full text is removed. For studies that are reported in more than one full text, the texts can be grouped together as one unit for assessing relevance.

The *scientific literature* selection process is illustrated in Figure 2.

The following information concerning the selection of *studies* shall be clearly reported in the *scientific literature review reports* (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 of all studies included in the dossier, ordered by data requirement, recorded using Table 4.

3. A list of the bibliographic references of all studies included in the dossier, ordered by first author, recorded using Table 5.

4. A list of studies excluded from the dossier after detailed assessment of full texts for relevance, with justification for their exclusion, recorded using Table 6.

5. Copies of the full texts corresponding to the included studies shall be provided with the dossier (section 6 of this Guidance). Copies of full texts do not need to be provided for studies found in the literature referring to the active substance, PPP or its metabolites that are considered not relevant and excluded from the dossier.

For non-English studies, translation to English shall be provided.

Table 3 (Excel spreadsheet): 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 *records* retrieved after the searches from bibliographic databases and all other information sources (excluding duplicates)	
Number of *records* excluded from the search results after rapid assessment for relevance	
Number of *studies* excluded from the dossier after detailed assessment for relevance	
Number of *studies* included in the dossier	

Table 4 (Excel spreadsheet): Documentation of the included studies, **to be ordered by data requirement(s)**

List of included *studies*, classified by data requirements

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 study, they should be listed in chronological order (most recent last). In cases where for a particular author, more than one reference is listed for the same year, the references shall 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 (e.g. where different full texts report different data from the same study, this should be indicated by coding all full texts that refer to a study using the same letter in square brackets i.e. [A], [B], [C], etc. The list shall be compiled using an Excel spreadsheet, with a separate row for each reference.

Table 5 (Excel spreadsheet): Documentation of the included studies, **to be ordered by author(s)**

List of included *studies*, classified by authors

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

The studies shall 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 an Excel spreadsheet, with a separate row for each reference.

Table 6 (Excel spreadsheet): Documentation of the excluded studies

List of excluded *studies*, classified by authors				
Author(s)	**Year**	**Title**	**Source**	**Reason(s) for not including this study in the dossier**

The studies shall 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 an Excel spreadsheet, with a separate row for each reference.

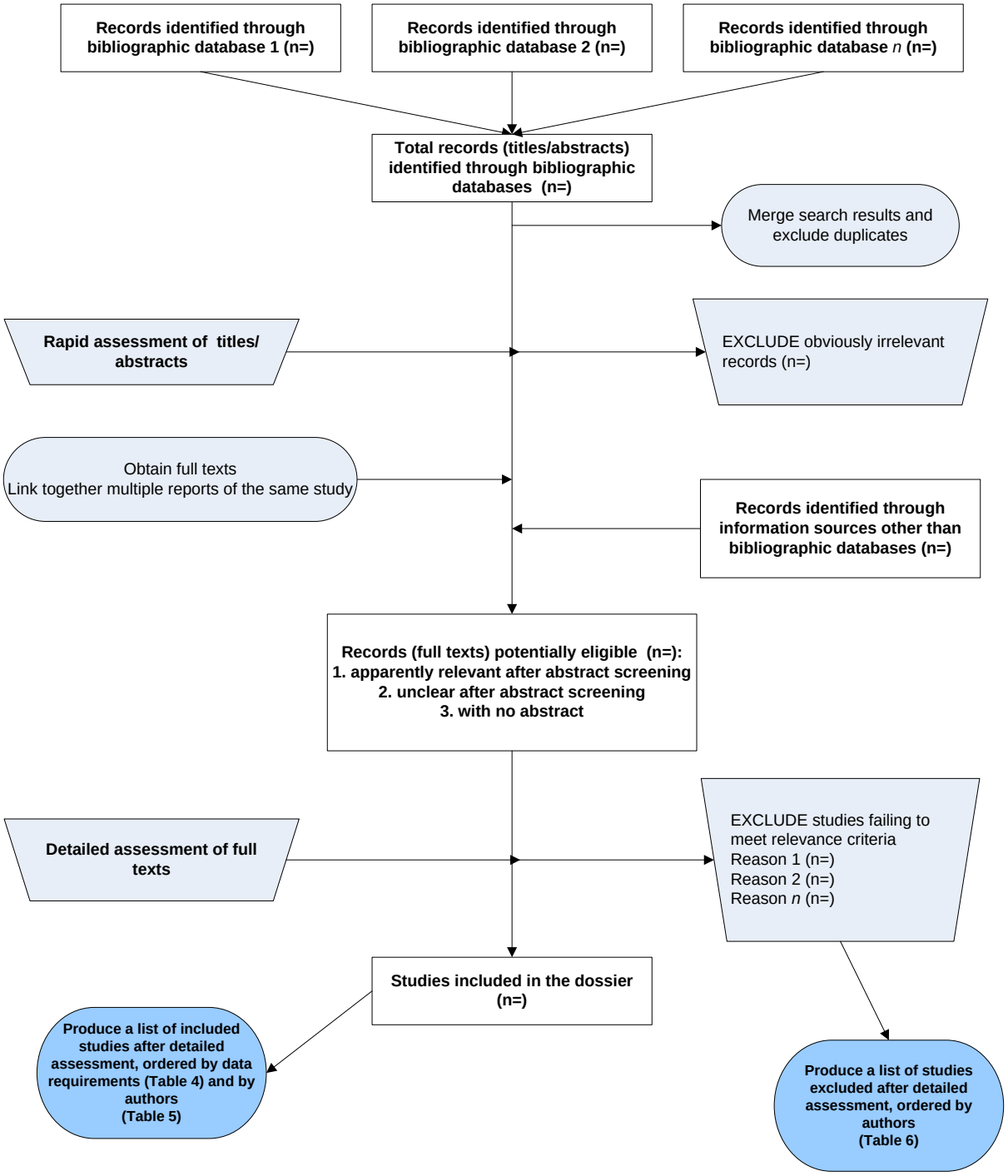

Figure 2: The process for selecting studies to be included in the dossier

5.4. Evaluation and use of the included scientific literature in the dossier

Once the relevant *scientific literature* has been identified and the corresponding records have been incorporated into the dossier (section 6 of this Guidance), each study shall be summarised and evaluated following the standard procedures for the subsequent steps of dossier preparation according to the OECD Guidance documents (OECD, 2005, 2006).

It should be noted that the OECD Guidance documents provide specific suggestions on how to summarise GLP[23] and non-GLP studies. For publicly available *scientific literature* the quality of studies is likely to vary. The quality of studies may be assessed by applying 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), and Küster et al. (2009). 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., oral communication, 2010). If reliability assessment is performed, the applicants shall document the process used and explain how any variation in data reliability influenced the risk assessment process for each data requirement. This should be reported in *document M* of the dossier. After the reliability assessment, each study should be evaluated in light of Regulation (EC) No 1107/2009 and the corresponding risk assessment Guidance documents.

[23] Good Laboratory Practice.

6. How to present in the dossier the methods and the results of the searches of the scientific literature

The applicants shall produce one or more *scientific literature review reports*, each of them containing 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 shall at least contain (section 5.1):
   - A statement of the objective of the review (i.e. to provide information on (a) determined active substance(s), metabolite(s), PPP(s) and data requirement(s));
   - The criteria for relevance with which decisions to include or exclude studies in the dossier will be made (Table 1).
5. Search methods, including a descriptive summary, together with:
   - Table 2, which lists the bibliographic databases searched;
   - A list of all other sources of *scientific literature* searched, together with the relevant information on the method and the results of the searches as described in section 5.2.4.
6. Results of the study selection process (section 5.3), including a descriptive summary, together with:
   - Table 3, which includes the results of the study selection process, for each data requirement or group of data requirements searched;
   - Table 4, which lists the included studies, ordered by data requirement;
   - Table 5, which lists the included studies, ordered by author;
   - Table 6, which lists the excluded studies and the reasons for excluding.

Each of these reports shall be incorporated in *document K* of the dossier. These reports shall be included in a folder *IIA 0*, which incorporates all the *scientific literature review reports* performed during the preparation of the active substance dossier.

Additionally, copies of the full texts corresponding to the included studies (listed in Table 4 and Table 5 of the *scientific literature review report*) shall be provided with the dossier (document K). These copies shall be placed within the subfolder(s) that contain studies relevant to the data requirements for which the record has been found relevant. In case of studies relevant to more than one data requirement a copy of the corresponding full paper shall be provided for each data requirement section. Attention shall be paid to the legibility of these papers.

Copies of the records found in the literature referring to the active substance, PPP or its metabolites that are considered not relevant and excluded from the dossier do not need to be provided.

The applicants are responsible for providing dossiers with full relevant information. 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.

RECOMMENDATIONS FOR FUTURE RESEARCH

When this Guidance is applied, it would be helpful to assess which types of publicly available scientific evidence is found to be acceptable and useful (or unacceptable and unhelpful) by the competent authorities of the Member States and by EFSA for informing risk assessments in dossiers on active substances. Such information could help to clarify the importance of peer-reviewed and non-peer-reviewed literature; enable precise definitions of the types of scientific literature admissible for dossiers; and assist with future revisions of this Guidance.

Information on which sources of scientific evidence are most useful for identifying evidence for the different data requirements would also be useful, in order to develop a list of minimum resources which should be searched for each data requirement.

Developing evidence on the scale of any publication bias in pesticide research would also assist with future revision of this Guidance. If publication bias is not an issue in pesticide research then fewer resources may need to be searched. In the event that publication bias is an issue in pesticide research then more stringent searching requirements might need to be developed.

A universally accepted system would be helpful for appraising the methodological rigour of data obtained from the scientific literature for inclusion in dossiers. Classification systems have been proposed for ecotoxicological data in general and for pharmaceutical data, but it is unclear whether all available systems are compatible and reliable.

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APPENDIX A - EXAMPLE OF A SEARCH FOR SCIENTIFIC LITERATURE FOR A SPECIFIC ACTIVE SUBSTANCE

A.1. Introduction

Topic: side effects of Chlorpyrifos and its metabolites

This example suggests possible search approaches for identifying the active substance and its side effects in humans. To keep this example focused, metabolites of the active substance or side effects elsewhere such as e.g. in the environment are not considered.

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, 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, Radar (fungicide), Sabre, Saurus, Spannit, Stipend, Tafaban, Terial, Terial 40L, XRM 429, XRM 5160, Xinnongba, suSCon, suSCon Blue, suSCon Plus, suScon Green.

It is the active ingredient in over 800 pesticide products.

To keep this example manageable, only a few of these alternative names for the active substance are included in the search strategy.

A.2. Identifying the search concepts

Search concepts are likely to be either:

- The active substance alone: chlorpyrifos
- The active substance AND its side effects: chlorpyrifos AND its side effects

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

A.3.1. The active substance

Searching MEDLINE on the single term Chlorpyrifos allows us to identify the Registry Number of the substance (i.e. 2921-88-2).

The search on the trade names allows us to see 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.

There are so many products of which chlorpyrifos is an active substance that it is not feasible to search for all of the named products – it may be that there are some significant products which represent those in widest use or use in Europe which could also be introduced into the search.

One possible MEDLINE strategy to retrieve 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 records which have not yet been indexed with Medical Subject Headings (MeSH) are also captured.

Search strategy	Number of 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 Medical Subject Heading (MeSH) assigned to a 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 record
- or/1-5: Boolean operator combining sets 1 to 5, to widen search by ensuring all concepts are gathered together into one set

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

A.3.2. Possible side effects

Side effects refer to risks to human and animal health and to non-target organisms and the risk of groundwater contamination above the regulatory limits. Thus relevant data on side effects shall include data on hazard identification, hazard characterisation, and exposure assessment. This example focuses on side effects in humans and in particular on the data requirement "toxicological studies". However, this approach can be adapted to capture other data requirements illustrated in Box 2 of this Guidance by adding in terms referring to concepts such as "risk assessment, or "exposure assessment".

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 records to explore the terminology and indexing they use. This selection is not exhaustive and illustrates why, for some products, it may be more efficient to search on the product 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. However, a large search strategy such as that illustrated in Figure 4, when combined with the strategy in Figure 1 (see Figure 5), may provide a way of reducing the number of records to be assessed for relevance.

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

- Subject headings (Medical Subject Headings or MeSH) such as Toxicity tests/ or Consumer product safety/.
- Floating subheadings. MEDLINE indexers assign subheadings to the MeSH subheadings to signal the focus of a record. Subheadings of relevance to these searches include toxicity (to), drug effects (de), chemically induced (ci) and adverse effects (ae).
- Some journals such as *Drug Metabolism & Drug Interactions* focus on safety issues, and the Ovid interface to MEDLINE allows 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 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 Medical Subject Heading (MeSH) assigned to a 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 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 record
- or/9-18: Boolean operator combines sets 9 to 18, to widen search by ensuring records with any of the terms are captured

Figure 4: Example Ovid MEDLINE search strategy to identify side effects for toxicity (data requirement: “toxicological 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. Another is to exclude publication types which may not be relevant such as letters, editorials and comments. This latter exclusion is demonstrated in the full strategy shown in Figure 5 as line 8.

A.3.4. The strategy

The final strategy (Figure 5) combines the search terms for chlorpyrifos and for side effects (data requirement: toxicological studies) (specific side effects such as behavioural delay and general side effects terms such as "side effects") and removes unwanted publication types. Searching for chlorpyrifos alone generates 2300 records. In this example for human toxicity, focusing the search by adding the side effects concept reduces the record yield a little, to 1780 records. The decision facing the searcher is whether the reduction in the number of records identified repays the effort of developing the side effects search and also whether relevant records are missed.

Search strategy	Number of 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$)).ti,ab.	9
6. or/1-5	2341
7. (letter or editorial or comment).pt.	1037410
8. 6 not 7	2310
9. to.fs. or toxico$.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
20. 8 and 19	1780

Legend:
- /: Indicates a Medical Subject Heading (MeSH) assigned to a 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 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 record
- or: Boolean operator to widen search by ensuring all records which mention the concepts in the combined sets are selected
- not: Boolean operator to limit search by excluding terms or concepts

Figure 5: Sample strategy to identify adverse events in Ovid MEDLINE for chlorpyrifos and removing specific publication types, conducted May 21 2010

A.4.Documentation of the search process

A.4.1. Search process for bibliographic databases

Table 7 shows how the search strategy illustrated in Figure 3 and another search strategy performed in another bibliographic database (Science Citation Index on Web of Science) would be reported using the template provided in Table 2.

Table 7 (Excel spreadsheet): Example search process for active substance chlorpyrifos, as would be recorded in the template (**Table 2**) of section 5.2.4[24]

Data requirement(s) captured in the search	**Details of the searches (note: language limits shall not be applied)** *Insert additional columns for additional databases; insert additional rows for additional search strategies* *Use a separate spreadsheet for every individual data requirement, or group of requirements, searched*		
Active substance only (chlorpyrifos) (covers all data requirements)	**Database 1: MEDLINE (Ovid interface)**	**Database 2: Science Citation Index on Web of Science**	
	Justification for choosing the source: MEDLINE **has over 19 million** biomedical records and has excellent coverage of human toxicology studies	**Justification for choosing the source:** SCI 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: 21 May 2010	**Date of search:** 30 May 2010	
	Date span of the search: 1950 to May Week 2 2010, including Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations up to May 20, 2010	**Date span of the search:** 1900 to 29 May 2010	
	Date of the latest database update included in the search: May week 2 2010	**Date of the latest database update included in the search: 29 May 2010**	
	Search strategies used for this data requirement	**Search strategies used for this data requirement**	
	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 records retrieved after removing duplicates	**n=**

[24] This Excel spreadsheet(s) must be completed both for the original searches and for any updated searches.

Table 8 shows how the search strategy illustrated in Figure 5 and another search strategy performed in another bibliographic database (Science Citation Index on Web of Science) would be reported using the template provided in Table 2.

Table 8 (Excel spreadsheet): Example search process for side effects of active substance chlorpyrifos according to data requirement "toxicological effects", as would be recorded in the template (**Table 2**) of section 5.2.4[25]

Data requirement(s) captured in the search	**Details of the searches (note: language limits shall not be applied)** *Insert additional columns for additional databases; insert additional rows for additional search strategies* *Use a separate spreadsheet 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: AII5)	**Database 1: MEDLINE**	**Database 2: Science Citation Index on Web of Science**
	Justification for choosing the source: MEDLINE **has over 19 million** biomedical records and has excellent coverage of human toxicology studies	**Justification for choosing the source:** SCI 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: 21 May 2010	**Date of the search: 30 May 2010**
	Date span of the search: 1950 to May Week 2 2010, including Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations up to May 20, 2010	**Date span of the search:** 1900 to 29 May 2010
	Date of the latest database update included in the search: May week 2 2010	**Date of the latest database update included in the search:** 29 May 2010
	Search strategies used for this data requirement	**Search strategies used for this data requirement**
	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	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))

[25] This Excel spreadsheet(s) must be completed both for the original searches and for any updated searches.

	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$).ti,ab. 11. (hazard$ 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	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)) 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	
		Total number of records retrieved after removing duplicates	**n=**

A.4.2. Search process for other scientific information sources

Example of a list of other sources of *scientific literature*, as specified in section 5.2.4:

We identified relevant reports from searching the following resources:

- We searched OAISTER[26] for grey literature. Searched 27/5/2010:
    - Chlorpyrifos AND (adverse OR side OR detrimental);
    - This returned 44 studies.
- We contacted Dr [name], University of [name], Italy on 20/5/10. Dr [name] provided 6 studies, 5 of which we had already retrieved and one which was new to our collection.
- We hand-searched the *Journal of Environmental Science and Health*, Part. B issues, Vol 45 issues 1-4 for 2010. This hand-search identified 2 relevant records.
- 6 studies, which we had not previously identified, were retrieved by looking at the reference lists of the papers assessed for relevance.
- We searched our in-house research databases, [name]. This is a database containing over 20,000 records relevant to our products and contains research we have commissioned and records of research conducted by others. The search strategy was the simple term "Chlorpyrifos" and produced 1,200 records which we added to the results database.

[26] <http://www.oaister.worldcat.org/>.

GLOSSARY

Active substance	Any substance, including micro-organisms, having general or specific action against harmful organisms or on plants, parts of plants or plant products (Regulation (EC) No 1107/2009).
Adjuvant	A substance or preparation which consists of *co-formulants* or preparations containing one or more co-formulants, in the form in which it is supplied to the user and placed on the market to be mixed by the user with a *plant protection product* and which enhance its effectiveness or other pesticidal properties (Regulation (EC) No 1107/2009).
Boolean operator	Boolean operators are used to combine terms when conducting electronic bibliographic searches. The operators are "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	Individual test and study reports in accordance with the legislative requirements of the country to which the dossier application is made (OECD, 2005).
Document M	A comprehensive summary and assessment of the individual tests and studies and groups of tests and studies, as appropriate, in the light of relevant evaluative and decision making criteria (OECD, 2005).
Dossier	Documentation submitted by applicants for the approval of active substances of plant protection products, under Regulation (EC) No 1107/2009.
Grey literature	Types of publication which are less systematically recorded in bibliographic tools such as catalogues and databases than journals and books.
Key elements	Identifiable components of a question or data requirement whose characteristics are fundamental to fully answer the data requirement (see EFSA (2010) for a more detailed discussion of key elements).
Metabolite	Any metabolite or a degradation product of an *active substance*, *safener* or *synergist*, formed either in organisms or in the environment (Regulation (EC) No 1107/2009).
Plant protection product(s) (PPP)	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 collected. The term is sometimes used to distinguish such studies from *secondary research studies* (e.g. reviews) that re-examine previously collected data.
Publication bias	It refers to the preferential reporting of certain types of evidence in records of primary research (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. An extensive search for primary research records (as it is performed in systematic review) may help to reduce the effect of publication bias.
Record	A document reporting or summarising one or more scientific studies (e.g. abstracts, full papers, web pages, or reports).
Relevant metabolites	The 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 the data requirements and the Guidance documents applicable at the time of submitting the dossier.
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 data produced through primary research studies (see *primary research study*).
Selection bias	In secondary research it refers to the selection of primary research records that are not representative (e.g. if researchers preferentially choose records of studies that are well known to them). Selection bias can lead to findings which deviate from the truth.
Sources of *scientific literature*	Any sources of information containing or providing access to *scientific literature* (e.g. bibliographic databases, websites, individuals, organisations or reference lists)
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 more than one *record*.
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).
Systematic review (SR)	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). The fundamental principles of SR are methodological rigour, transparency, and reproducibility.

ABBREVIATIONS

AMU	Assessment Methodology Unit
EFSA	European Food Safety Authority
EU	European Union
GLP	Good Laboratory Practice
IUPAC	International Union of Pure and Applied Chemistry
PPP	Plant protection product
PPR	Plant Protection Products and their Residues
PRAPeR	Pesticide Risk Assessment Peer Review Unit
PSC	Pesticide Steering Committee
SR	Systematic review