



Guidance to JECFA Experts on Systematic Literature Searches

Prepared by

WHO JECFA Secretariat

Jan 2017

CONTEXT.....	1
INTRODUCTION	1
STEPS OF A SYSTEMATIC LITERATURE SEARCH:.....	2
1. Defining your Research Question	2
2. Determining Inclusion and Exclusion Criteria.....	2
3. Selecting Your Database/Sources	3
4. Develop your Search Strategy	4
5. Run your Search.....	7
6. Screen your Results	8

CONTEXT

There is increasing discussion on the use of systematic review methodology in chemical risk assessment. While it is difficult to apply such rigorous methodology on a routine basis for broad risk assessment questions as they are addressed by JECFA, there are elements that can improve transparency, objectivity and reproducibility of the work undertaken by experts. One of these elements is undertaking and documenting literature searches in a more systematic manner. This document is a brief guidance on how to undertake such literature searches in the context of JECFA work.

INTRODUCTION

A systematic review is a scientifically robust method based approach to collecting, analysing and interpreting all available data on a defined research question. Systematic reviews are a valuable tool for informed decision making and evaluate all available evidence in a transparent and clearly documented manner. The aim of conducting a systematic review,

as compared to a narrative review, is to minimize error and bias, which is of particular importance in areas of uncertainty or disagreement.

One key element in undertaking a systematic review in relation to a specific question is a thorough literature search. A simple literature search can use informal methods and the authors may be (often unintentionally) biased when selecting relevant data. A systematic literature search is a procedure based search to comprehensively identify data on a particular research topic, and clearly document each step of the search. These searches are conducted in such a way to increase transparency and reduce bias which helps to ensure that the findings are consistent and can be replicated. Such a transparent framework ensures when a conclusion is reached any disagreements can be reviewed and discussed, and helps to clearly identify gaps in knowledge for future research. The first step in your systematic literature search would be to define a protocol with the research question, criteria and databases. The purpose for having a protocol is so the process amongst the reviewers is standardized, and there are no introduced changes which may lead to bias. Any changes made to the protocol need to be documented and justified.

STEPS OF A SYSTEMATIC LITERATURE SEARCH:

1. Define your research question
2. Determine Inclusion and Exclusion Criteria
3. Select your search databases/ sources
4. Develop your search strategy
5. Run your search
6. Screen the results

1. Defining your Research Question

The first step to guiding the search process is to identify your research question. One way of doing this can be by breaking the question down into its components or using the acronym PICO, or PECO. P = Population, I/E = Intervention/Exposure, C = Comparator, O = Outcomes.

For example:

Does long term exposure to fumonisins cause cancer?

P = population exposed, E = long term exposure to fumonisin, C = population not exposed, O = cancer induction

In the context of JECFA with broad risk assessment tasks such a question can simply be: 'what is the toxicity of exposure to compound x' or 'at what level of exposure do adverse effects (or limited to one specific effect such as cancer or reproductive effects) occur?

This is applicable to experimental studies, the 'population' can be e.g. a group of experimental animals or cell cultures.

2. Determining Inclusion and Exclusion Criteria

After defining your research question, you can begin to define criteria that will determine eligibility of the studies in the context of your review and research question. Pre-defined eligibility criteria help to ensure that your question is focused and decrease bias. Some

common inclusion criteria include study design and methodology, dose levels, and outcome measurements.

For example:

Research question: What are the effects of acute exposure to fumonisins?

Inclusion Criteria: Exposure < 21 days, only fumonisins used for exposure, dosing administered orally, use of control group, reporting original data

Exclusion Criteria: duration of exposure longer than 21 days, exposure also to other mycotoxins, dosing other than orally, no control group, small sample size

3. Selecting Your Database/Sources

Common electronic search databases include [PubMed](#), MEDLINE, [AGRIS](#), [Cochrane Library](#), [Embase](#), [Web Of Science](#), BIOSIS, [Directory of Open Access Journals](#), [Global Index Medicus](#) (via Global Health Library), [CINAHL](#). See below for information on the content of each database. Not all databases are freely available like PubMed, AGRIS, etc. You may need to contact your local library to see about accessing subscription based databases such as Embase and CINAHL. Also be aware to use other sources such as grey literature, journals, and conference proceedings (can be accessed through Embase or Scopus). Grey literature includes reports and information that is either not published or inaccessible via commercial or academic databases. Grey literature can be found by accessing government or institutional websites directly or online through [GreyNet International](#), [Open Grey](#) or you can find a list of other resources at www.cadth.ca.

Database Content

PubMed is a database of indexed articles and abstracts of medical, veterinary, nursing, dental, health care, and preclinical journals provided by the US National Library of Medicine. Free access

MEDLINE is a subset of PubMed which also references biomedical and life science journal articles. MEDLINE is different from PubMed in that it uses MeSH to index its citations. If you limit your search to MeSH controlled vocabulary you will only see MEDLINE citations.

AGRIS is an agricultural science and technology database maintained by CIARD in collaboration with the FAO. It covers agriculture, forestry, aquatic sciences, human nutrition and animal husbandry. Included in this database is grey literature such as unpublished reports, conference proceedings, theses, government publications, etc. Free access

Cochrane Library is a collection of 6 evidence based databases for healthcare. It maintains up to date and accessible systematic reviews on the effects of healthcare interventions.

Embase is a biomedical and pharmacological literature database with an additional focus on drugs, pharmacology, medical devices, and clinical medicine. Not Free.

Web of Science is an interdisciplinary database that covers all scientific areas and is maintained by Thomson Reuters. It is limited to what is considered as top journals and English language journals. Access to some similar journals as PubMed.

BIOSIS, biosciences information services, is a database that indexes literature on biological and biomedical sciences. Not free.

Directory of Open Access Journals covers a wide range of subject areas and indexes peer reviewed open access research journals, periodicals and their articles metadata. Has access to some similar journals as PubMed, but others as well.

The Global Index Medicus (GIM) provides worldwide access to biomedical and public health literature produced by and within low- and middle- income countries. The main objective is to increase the visibility and usability of this important set of resources. Includes MEDLINE indexed references, and not all articles in English.

CINAHL stands for cumulative index of nursing and allied health literature and is a research tool for nursing, allied health professionals, biomedical and healthcare articles. Not free.

4. Develop your Search Strategy

Your search strategy needs to be broad enough to capture all of the relevant literature, but also narrow enough as to not include too much unnecessary literature which can be time consuming to navigate. There are numerous systematic reviews available on the web, so as a potential time saver check other search strategies for previously developed search blocks which you may be able to build upon. Your search strategy (syntax and controlled vocabulary) needs to be adapted to each database.

For example:

Search "Child" in PubMed vs CINAHL

PubMed - "Child"[Mesh] OR "Maternal-Child Health Centers"[Mesh] OR "Child Nutrition Sciences"[Mesh] OR "Child Health Services"[Mesh] OR "Child Nutritional Physiological Phenomena"[Mesh]

CINAHL- (MH "Child"+) OR (MH "Pediatrics+") OR (MH "Early Childhood Intervention"+) OR SU Infant OR SU Newborn* SU Baby* OR SU Babies OR SU Neonat**

PubMed has an advanced search builder where you can build your search block. This can be accessed on the PubMed website by clicking on Advanced under the search bar. For example:

(((mycotoxins[MeSH Terms]) AND fumonisin*)) AND (((("chronic toxicity") OR "chronic exposure") OR chronic toxicity tests[MeSH Terms]) OR chronic toxicity test[MeSH Terms]) AND ("2011"[Date - MeSH] : "2017"[Date - MeSH])

[Edit](#) [Clear](#)

Builder

All Fields (mycotoxins[MeSH Terms]) AND fumonisin* [Show index list](#)

AND All Fields (((("chronic toxicity") OR "chronic exposure") OR chronic toxicity tests[MeSH Terms]) OR c [Show index list](#)

AND Date - MeSH 2011 to 2017 [Show index list](#)

[Search](#) or [Add to history](#)

History [Download history](#) [Clear history](#)

Search	Add to builder	Query	Items found	Time
#4	Add	Search (mycotoxins[MeSH Terms]) AND fumonisin*	2092	09:27:54
#3	Add	Search (((("chronic toxicity") OR "chronic exposure") OR chronic toxicity tests[MeSH Terms]) OR chronic toxicity test[MeSH Terms])	15203	09:27:27

Medical subject headings (MeSH) are specific to health sciences and are important to understand when conducting a search. MeSH terms are a National Library of Medicine controlled vocabulary used for indexing articles in PubMed (or Medline). They allow you to search in a hierarchal structure from which you can go up or down a level depending on the specificity of your search. When conducting a search it is important to use both MeSH terms and key words because the indexer is not perfect. Using only keywords in your search can produce false hits, synonyms aren't included, and you can get lots of results that barely mention your search term. To make your search more specific, attach subheadings to MeSH terms.

Pharmacologic Action:

- [Poisons](#)

[All MeSH Categories](#)

[Chemicals and Drugs Category](#)

[Biological Factors](#)

[Toxins, Biological](#)

Mycotoxins

[Aflatoxins](#)

[Aflatoxin B1](#)

[Aflatoxin M1](#)

[Amanitins](#)

[Alpha-Amanitin](#)

[Citrinin](#)

[Cytochalasins](#)

[Cytochalasin B](#)

[Cytochalasin D](#)

[Fumonisin](#)

Shows hierarchal structure of MeSH terms



Mycotoxins

Toxic compounds produced by FUNGI.
Year introduced: 1967

PubMed search builder options

[Subheadings:](#)

- | | | |
|---|--|--|
| <input type="checkbox"/> administration and dosage | <input type="checkbox"/> classification | <input type="checkbox"/> pharmacology |
| <input type="checkbox"/> adverse effects | <input type="checkbox"/> drug effects | <input type="checkbox"/> physiology |
| <input type="checkbox"/> agonists | <input type="checkbox"/> economics | <input type="checkbox"/> poisoning |
| <input type="checkbox"/> analogs and derivatives | <input type="checkbox"/> etiology | <input type="checkbox"/> radiation effects |
| <input type="checkbox"/> analysis | <input type="checkbox"/> genetics | <input type="checkbox"/> secretion |
| <input type="checkbox"/> antagonists and inhibitors | <input type="checkbox"/> history | <input type="checkbox"/> standards |
| <input type="checkbox"/> biosynthesis | <input type="checkbox"/> immunology | <input type="checkbox"/> statistics and numerical data |
| <input type="checkbox"/> blood | <input type="checkbox"/> isolation and purification | <input type="checkbox"/> supply and distribution |
| <input type="checkbox"/> cerebrospinal fluid | <input type="checkbox"/> metabolism | <input type="checkbox"/> therapeutic use |
| <input type="checkbox"/> chemical synthesis | <input type="checkbox"/> organization and administration | <input type="checkbox"/> toxicity |
| <input type="checkbox"/> chemistry | <input type="checkbox"/> pharmacokinetics | <input type="checkbox"/> urine |

Subheadings that can be attached to your MeSH term when searching.

Exploding of terms will search for both your specific key word and more specific terms that are under it in the hierarchy. For example searching Mycotoxins [MeSH:NoExp] will find results that mention Mycotoxins in general and not each specific mycotoxin, which will increase the number of hits and can make your search more time consuming. For example, using No Explode when searching the MeSH term Mycotoxins will limit the hierarchal search to stop at mycotoxins, therefore there are less hits than if you explode the term.

Search mycotoxins [MeSH:NoExp]	8098
Search mycotoxins [MeSH Terms]	40359

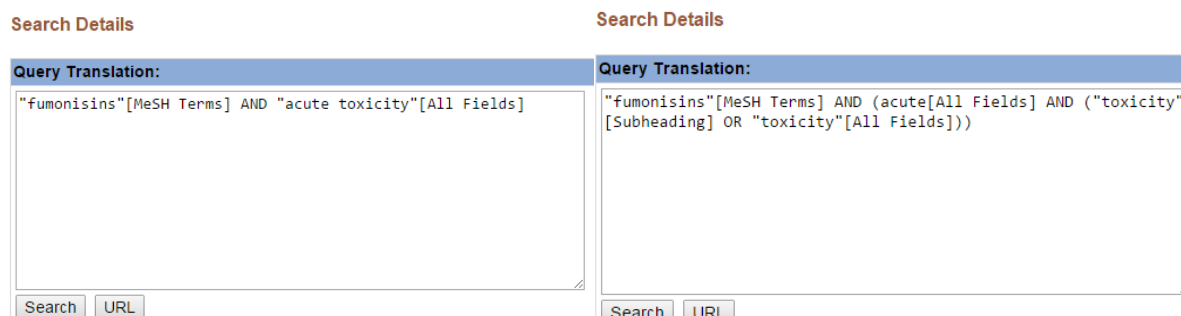
Truncation (*) can be used when you want to include all forms of a word. It may also be helpful to put together a list of synonyms, abbreviations, and alternative spellings of your search terms. Example below is searching for Fumonisin* [All Fields].

Query Translation:

```
fumonisin[All Fields] OR fumonisin's[All Fields] OR  
fumonisina[All Fields] OR fumonisin's[All Fields] OR  
fumonisinb[All Fields] OR fumonisinb1[All Fields] OR  
fumonisine[All Fields] OR fumonisenin[All Fields] OR  
fumonisin[All Fields] OR fumonisingehalt[All Fields] OR  
fumonisininducing[All Fields] OR fumoniskontamination[All  
Fields] OR fumonisinmycotoxins[All Fields] OR  
fumonisinogenic[All Fields] OR fumonisin[All Fields]
```

Be careful when using truncation with quotations as it may not work, and you cannot truncate MeSH terms. Term mapping and exploding a MeSH term will also stop when using truncation. Remember to put phrases in quotations, if you do not the search engine will breakdown the phrase into its components.

Example of how PubMed will break down “acute toxicity” into separate components without quotations.



For more precision in your search you can include tag words such as [TIAB] or [TI] which will find your key word in the title or abstract, or just the title. If no tag is added the search database will automatically search for your word in [All Fields]. Check your search string by looking at the details and make sure there are no unexpected terms included in the search. Example below shows a sample of search results for: (Aflatoxin[TIAB]) AND Exposure[TI]

[An effective self-control strategy for the reduction of aflatoxin M₁ content in milk and to decrease the exposure of consumers.](#)

Kerekes K, Bonilauri P, Serraino A, Giacometti F, Piva S, Zambrini V, Canever A, Farkas Z, Ambrus Á.
Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2016 Oct 3.
PMID: 27690758
[Similar articles](#)

[Evaluation of Efficacy, Acceptability and Palatability of Calcium montmorillonite Clay used to reduce aflatoxin B₁ dietary exposure in a Crossover study in Kenya.](#)

Awuor AO, Montgomery J, Yard E, Martin C, Daniel J, Zitomer N, Rybak M, Lewis L, Phillips T, Romoser A, Elmore S, Oyugi E, Amwayi S, Bii C, Vulule J.
Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2016 Sep 7. [Epub ahead of print]
PMID: 27603954
[Similar articles](#)

[Exposure Assessment of Infants to Aflatoxin M₁ through Consumption of Breast Milk and Infant Powdered Milk in Brazil.](#)

Ishikawa AT, Takabayashi-Yamashita CR, Ono EY, Bagatin AK, Rigobello FF, Kawamura O, Hirooka EY, Itano EN.
Toxins (Basel). 2016 Aug 31;8(9). pii: E246. doi: 10.3390/toxins8090246.

5. Run your Search

Once you have put together your search terms it is important to keep a record. This can be done using a reference management system such as [Endnote](#) or other open access software like [Zotero](#) or [Mendeley](#). This will help you keep track of your searches as well as determine duplicates among your searches. This information can then be put into a standardized recording document (see below). A thorough recording document is essential for systematic searches as it facilitates reproducibility and can help with updating reviews when new data is available. It is a good suggestion to copy your search strategies into a Word document so that you can go in and modify the search block.

It may be useful to try several search queries and strings to find the best combination of term, and clearly document the results. Also the date of the search and each step needs to be recorded.

The below table is how to document your search:

Systematic Literature Search	
Principle Investigator:	
Research Question: (PECO?)	
Inclusion criteria:	
Exclusion criteria:	
SEARCH 1	
Database/Resource Searched	
Date	
Search Terms	
Number of Records Retrieved	
SEARCH 2	
Database/Resource Searched	
Date	
Search Terms	
Number of Records Retrieved	
TOTAL SEARCH RESULTS	
Total Number of Records Retrieved	
Duplicate Records (Identify by who, ex. EndNote, or Researcher, etc.)	
Total Records to Screen	
SCREENING	
Number of Records to Screen	
Records Excluded	
Exclusion Criteria	
ELIGIBILITY	
Full text articles assessed	
Articles excluded	
Exclusion Criteria	
Studies Included in Review	

6. Screen your Results

The screening is usually done in two steps, first step is screening based on title and abstract (TIAB), second step is based on the full text. It is important to save all steps in a reference management system, so you can always go back to the previous step. At the TIAB step, in case of doubt based on inclusion criteria, always include the record for the next step (screening based in full paper).

Go through the title and abstracts of your search results and specify the limits put on your search criteria. Common limiting criteria include a set publication date range, language, or species. Be aware when using certain filters such as species or article types, for example when using the species filter, human, it can exclude recent studies that have yet to be indexed. For any limiting criteria there should be a sound rationale given otherwise the review could be susceptible to bias. *Example below shows a PubMed search for aflatoxin[TI] AND exposure[TI], when using the filter Humans, it reduces the amount of articles from 233 (top image) to 138 (bottom image) and also changes the top results.*

It would be advisable to do a quality check of the screening, ideally by another scientist (on the total number of record or only a part of it) but if not possible, you can do it yourself to see if you arrive at the same number of records.


Items: 1 to 20 of 233

<< First < Prev Page 1 of 12 Next > Last >>

- [An effective self-control strategy for the reduction of aflatoxin M₁ content in milk and to decrease the exposure of consumers.](#)
 1. Kerekes K, Bonilauri P, Serraino A, Giacometti F, Piva S, Zambrini V, Canever A, Farkas Z, Ambrus Á.
Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2016 Oct 3.
PMID: 27690758
[Similar articles](#)
 2. [Evaluation of Efficacy, Acceptability and Palatability of Calcium montmorillonite Clay used to reduce aflatoxin B₁ dietary exposure in a Crossover study in Kenya.](#)
Awuor AO, Montgomery J, Yard E, Martin C, Daniel J, Zitomer N, Rybak M, Lewis L, Phillips T, Romoser A, Elmore S, Oyugi E, Amwayi S, Bii C, Vulule J.
Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2016 Sep 7. [Epub ahead of print]
PMID: 27603954
[Similar articles](#)
 3. [Exposure Assessment of Infants to Aflatoxin M₁ through Consumption of Breast Milk and Infant Powdered Milk in Brazil.](#)
Ishikawa AT, Takabayashi-Yamashita CR, Ono EY, Bagatin AK, Rigobello FF, Kawamura O, Hirooka EY, Itano EN.
Toxins (Basel). 2016 Aug 31;8(9). pii: E246. doi: 10.3390/toxins8090246.
PMID: 27589799 [Free PMC Article](#)
[Similar articles](#)

Items: 1 to 20 of 138

<< First < Prev Page 1 of 7 Next > Last :

 Filters activated: Humans. [Clear all](#) to show 233 items.

- [Aflatoxin M₁ in pasteurized, UHT milk and milk powder commercialized in Londrina, Brazil and estimation of exposure.](#)
 1. Santos JS, França VR, Katto S, Santana EH.
Arch Latinoam Nutr. 2015 Sep;65(3):181-5.
PMID: 26821490
[Similar articles](#)
 2. [Mitigating aflatoxin exposure to improve child growth in Eastern Kenya: study protocol for a randomized controlled trial.](#)
Hoffmann V, Jones K, Leroy J.
Trials. 2015 Dec 3;16:552. doi: 10.1186/s13063-015-1064-8.
PMID: 26634701 [Free PMC Article](#)
[Similar articles](#)
 3. [Risk Assessment on Dietary Exposure to Aflatoxin B₁ in Post-Harvest Peanuts in the Yangtze River Ecological Region.](#)
Ding X, Wu L, Li P, Zhang Z, Zhou H, Bai Y, Chen X, Jiang J.
Toxins (Basel). 2015 Oct 15;7(10):4157-74. doi: 10.3390/toxins7104157.
PMID: 26501322 [Free PMC Article](#)
[Similar articles](#)

Once you are done with your searches and you have screened all the results, it is important to keep a record of the title and abstracts that were included in your systematic search.

EXAMPLES:

Below is an example of a simple search done on Brilliant Blue FCF and a more complex search on Fumonisin.

Brilliant Blue FCF

Systematic Literature Search	
Principle Investigator:	
Research Question: What is the toxicity of the food additive Brilliant Blue FCF?	
SEARCH 1	
Database/Resource Searched:	PubMed
Date	12 October 2016
Search Terms	("brilliant blue") AND toxicity
Number of Records Retrieved	166
TOTAL SEARCH RESULTS	
Total Number of Records Retrieved	166
Duplicate Records (Identify by who, ex. EndNote, or Researcher, etc.)	No Duplicates- only 1 search
Total Records to Screen	166
SCREENING	
Number of Records to Screen	166
Records Excluded	154
Exclusion Criteria	Brilliant blue used as a stain or dye, exposure to retinal cells or nonrelevant cell type for oral exposure, use for ocular surgery, phytotoxicity, photodegradation, not using brilliant blue
ELIGIBILITY	
Full text articles assessed	12
Articles excluded	4
Exclusion Criteria	Last JECFA assessment 1984, exclude studies done before then
Studies Included in Review	8

Fumonisin

Systematic Literature Search	
Principle Investigator:	
Research Question: Chronic Toxicity or Carcinogenicity of Fumonisin with a focus on studies after 2010	
SEARCH 1	
Database/Resource Searched	PubMed
Date	12 October 2016
Search Terms	("fumonisins"[MeSH Terms] AND (chronic[All Fields] OR "carcinogens"[MeSH Terms])) AND ("2011"[MHDA] : "2016"[MHDA])
Number of Records Retrieved	52
SEARCH 2	
Database/Resource Searched	Toxline search via Toxnet
Date	12 October 2016
Search Terms	Fumonisin chronic
Number of Records Retrieved	22
SEARCH 3	
Database/Resource Searched	Toxline search via Toxnet
Date	12 October 2016
Search Terms	Fumonisin AND cancer
Number of Records Retrieved	76
SEARCH 4	
Database/Resource Searched	Scopus (Elsevier)
Date	12 October 2016
Search Terms	Fumonisin chronic
Number of Records Retrieved	77
SEARCH 5	
Database/Resource Searched	Directory of Open Access Journals
Date	12 October 2016
Search Terms	Fumonisin AND chronic
Number of Records Retrieved	4
TOTAL SEARCH RESULTS	
Total Number of Records Retrieved	245
Duplicate Records (Identify by who, ex. EndNote, or Researcher, etc.)	
Total Records to Screen	
SCREENING	
Number of Records to Screen	
Records Excluded	
Exclusion Criteria	
ELIGIBILITY	
Full text articles assessed	
Articles excluded	
Exclusion Criteria	
Studies Included in Review	