Explanatory note on literature searching conducted in the context of GMO applications

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Explanatory note on literature searching conducted in the context of GMO applications for (renewed) market authorisation and annual post-market environmental monitoring reports on GMOs authorised in the EU market

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Abstract

Guidance of the Panel on Genetically Modified Organisms (GMOs) of the European Food Safety Authority (EFSA) assists applicants in the preparation and presentation of their market registration applications by describing elements and information/data requirements for the risk assessment and

Scope of the explanatory note

Recommendations are directed to applicants to conduct literature searching in the context of their:

- GMO market registration applications (APs) submitted under Regulation (EC) No 1829/2003 **before** and **after** the Implementing Regulation (EU) No 503/2013 (IR) entered into force [**GMO APs**]
- Annual post-market environmental monitoring reports on GMOs authorised for commercial cultivation in the EU [**annual PMEM reports**]
- GMO APs for the renewed market authorisation of authorised GM food/feed under Regulation (EC) No 1829/2003 [**renewal APs**]

Scope of the explanatory note

Requirements in regulation, guidance:

- GMO APs *after* IR

Systematic review

- GMO APs *before* IR
- Annual PMEM reports
- Renewal applications

Literature searches

Aim of the explanatory note

- To clarify the scope and methodology for literature searching
- To give recommendations on how to conduct, report systematic/extensive literature searches, and present the results of any scoping reviews
- To complement EFSA (2010) on the application of SR methodology to food/feed safety assessments to support decision making, with GMO-specific guidance

Strategy of the explanatory note

- GMO APs *after* IR

Scoping review

Determine whether it is useful to perform SR

- GMO APs *before* IR
- Annual PMEM reports
- Renewal applications

Systematic/extensive literature search

Literature, scoping and systematic reviews

	Systematic review	Scoping review	Literature review
Question	Focused and explicit	May be broad and explicit	Broadly defined
Sources and search	Explicit and extensive literature search	Explicit and extensive literature search	May or may not be explicit and extensive
Selection	Pre-defined in protocol	Pre-defined in protocol	Not always stated
Appraisal	Formal quality assessment using CATs	No formal quality assessment	No formal quality assessment
Data extraction	Pre-defined in protocol, detailed	Chart high level data	Variable
Synthesis	Quantitative synthesis when possible	Narrative and tabular Overall volume, strength and direction	Typically narrative, sometimes selective

Steps proposed for the scoping review

1. Identifying review questions and clarifying their purpose
2. Searching for/identifying relevant studies
3. Selecting studies
4. Extracting high level data from the relevant studies
5. Summarising and reporting the data, and considering the implications of the findings

1 Identify review questions/clarify their purpose

Problem should be addressed in the form of clear, unambiguous and structured **questions**

- Review questions should be broken down into **key elements**:
  - 1.1. Structured frameworks (e.g. PECO, PIT, PO)
  - 1.2. Based in information/data requirements

1 Identify review questions/clarify their purpose

1.1. Structured questions (e.g. PICO, PECO)

"Does either the GMO and derived food/feed products, or the intended trait(s), have adverse effects on human and animal health and the environment?"

Population	Intervention/Exposure	Comparator	Outcome
Humans Animals Environment	GMO Derived food/feed products Intended trait(s)	N/A	Adverse effects

1 Identify review questions/clarify their purpose

1.2. Information/data requirements outlined in relevant GMO Panel GDs, EFSA explanatory notes and Implementing Regulation

- Protein expression data
- 90-day feeding studies in rodents
- Laboratory/greenhouse feeding bioassays with representative non-target organisms
- …

2 Search for/identify relevant studies

Extensive/systematic literature **search** in order to find as many relevant studies in the most unbiased way possible to support the risk assessment

- Literature search involves:
  - 2.1. Construct the search strategy
  - 2.2. Identification of information sources to search

2 Search for/identify relevant studies

2.1. Construct a search strategy

- Decide the approach:
  - Use a single search strategy (lumping)
  - Use a series of search strategies (splitting)
- Select the search terms:
  - Free-text search
  - Subject indexing terms (where provided)
- Functions and operators
- Language and time period
- Reference study searches:
  - Test the search with a set of references

2 Search for/identify relevant studies

2.2. Identify sources of scientific literature

	Bibliographic databases	Internet searches	Manual searches
Mandatory	At least two multi-disciplinary/large (Scopus, WoS, CAB Abstracts…)	Internet sites key organizations involved GMO risk assessment (FDA, EPA, USDA…)	Reference list from recent reviews, scientific opinions, etc.
Optional	Subject specific databases (Agris, Agricola…)	Search engines, web-based databases (GS…)	Hand-searching journals Citation search

2 Search for/identify relevant studies

Set	Field	Search string	Concepts/key elements
#1	Topic	MON810 OR "MON 810" OR monsanto810 OR (monsanto NEAR/3 810)	Event
#2	Topic	Yieldgard* OR "yield gard" OR maizegard* OR "maize gard"	Trade names
#3	Topic	Cry1ab* OR "cry 1 ab" OR "cry 1ab" OR "cry1 ab" OR cryIab* OR "cry I ab" OR "cry Iab" OR "cryI ab"	Newly expressed protein
#4	Topic	GMO OR GMOs OR LMO OR LMOs OR GM OR GE OR transgen* OR (genetic* NEAR/3 (modif* OR transform* OR manipulat* OR improv* OR engineer*)) OR "living modif*"	GMO general
#5	Topic	Maize OR corn OR "Zea mays" OR "Z mays"	Plant species
#6	Topic	((Insect OR insects OR pest OR pests OR Lepidoptera* OR Noctuidae OR Crambidae OR borer* OR cornborer* OR stalkborer* OR earworm* OR "ear worm*" OR armyworm* OR "army worm*" OR cutworm* OR "cut worm*" OR Ostrinia OR "O nubilalis" OR Sesamia OR "S nonagrioides" OR Diatraea " OR "D grandiosella" OR "D crambidoides" OR Helicoverpa OR "H zea" OR Spodoptera OR "S frugiperda" OR Papaipema OR "P nebris" OR Elasmopalpus OR "E lignosellus" OR "D saccharalis" OR Striacosta OR "S albicosta" OR Agrotis OR "A ipsilon" OR "S cretica" OR Mythimna OR "M unipuncta" OR ECB OR MCB OR SWCB OR SCSB OR CEW OR FAW OR SCB OR WBC) NEAR (resistan* OR protect* OR toleran*)) OR "Bacillus thuringiensis" OR "B thuringiensis"	Intended trait
#7	Topic	"Bt maize" OR "Bt corn" OR Btmaize OR Btcorn	GMO general × intended trait
#8	Topic	(GMO OR GMOs OR LMO OR LMOs OR GM OR GE OR transgen* OR (genetic* NEAR/3 (modif* OR transform* OR manipulat* OR improv* OR engineer*)) OR "living modif*") NEAR (maize OR corn OR "Zea mays" OR "Z mays")	(GMO general NEAR Plant species)
#9		#3 AND (#4 OR #5)	(Newly expressed protein AND (GMO general OR Plant species))
#10		#6 AND #8	Intended trait AND (GMO general NEAR Plant species))
#11		#1 OR #2 OR #9 OR #10 OR #7	

3 Select studies

Screen the results to **identify** those studies that might be **relevant** using pre-defined eligibility/inclusion criteria

- Process
  - 3.1. (pre-)Establish eligibility/inclusion criteria
  - 3.2. Screen the results
  - 3.3. Classify the studies

3 Select studies

3.1. (Pre-)establish eligibility/inclusion criteria

Concepts	Criteria	Comment
Key elements of review questions with PICO/PECO structure		
Intervention/exposure	The GMO, derived food/feed products, and/or the intended trait(s) (e.g., newly expressed protein(s)) addressed in the study are identical or similar to those under regulatory review	This enables the selection of studies that address the GMO, derived food/feed products, and/or the intended trait(s) under consideration
Population	Human and animal health, and/or the environment (including biodiversity, ecosystem services, service providing units, and endangered species) are addressed as general protection goals	From the studies that address the GMO under consideration, those that address protection goals relevant to the risk assessment of the GMO are eligible
Outcomes	Effects/impacts on human and animal health, and/or the environment are addressed	Studies that address the GMO under consideration will also need to address effects/impacts on entities of concern, and potential determinants of exposure that place these entities at risk relevant to the risk assessment of the GMO

3 Select studies

3.2. Screening the results

- The selection is undertaken in two stages:
  - Rapid assessment based in title and abstracts
  - Detailed assessment of full text documents
- Studies should be assessed by more than one reviewer
  - Pilot to guarantee inter-reviewer agreement
  - Process to resolve disagreement

3 Select studies

3.3. Classification

- Relevant studies → To summarise and consider those for reliability
- Non-relevant studies → Give reason(s) for exclusion based on eligibility/inclusion criteria
- Unobtainable studies & studies with unclear relevance → Describe methods used to try to obtain a copy of the study; give justification of why relevance cannot be definitively determined

4 Extract high level data of relevant studies

The information to extract from each relevant study should **enable** to describe the **overall volume, strength and direction** of the evidence [**only applicable to scoping reviews**]

Category of information/data requirement(s)[a]	Study (Author(s) and year)	Intervention/test materials used	Adverse effects reported	Which adverse effect reported
[Example of how to fill the table: Assessment of interactions with non-target organisms]	[Example of how to fill the table: Dupont et al., 2017a]	[Example of how to fill the table: Purified protein (e.g., Cry1Ab); Plant material (e.g., maize MON810 pollen); Farm management practices: glyphosate-based herbicides]	[Example of how to fill the table: Yes; No]	[Example of how to fill the table: A 30% increase in larval mortality following exposure to the intended intervention compared to the negative control group]

5 Summarise, report, consider implications

- Summarising and reporting the data

  Applicants should report the **methods** as well as the **results**

  - Search methods and outcomes
  - Results of study selection process
  - Narrative synthesis/summary of relevant studies, describing their overall volume, strength and direction [**only applicable to scoping reviews**]

5 Summarise, report, consider implications

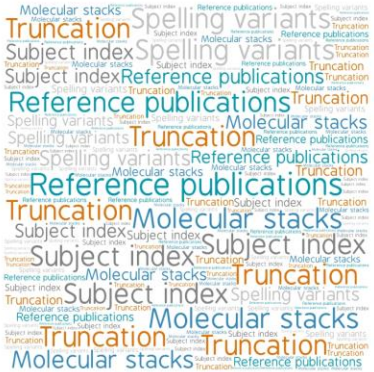
- Considering implications of the findings

  Applicants should consider the **meaning** of the the **results**
  - Value of undertaking SR [**only applicable to scoping reviews**]
  - Implications for risk assessment:
    - To assess the reliability and implications for the risk assessment of all relevant studies retrieved after detailed assessment of full-text documents for relevance

Future updates of explanatory note

Explanatory note may/will be revised:

- Experience is gained in its application
- In view of any amendments to the IR



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