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Developing a good practice for the review of evidence relevant to GMO risk assessment

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Abstract: Recent controversies over peer-reviewed papers on potential impacts of genetically modified organisms underline the necessity for an explicit, transparent and unbiased reviewing of published results. Evidence synthesis approaches represent powerful tools to collect, evaluate and summarize such research results in a transparent, reproducible and unbiased manner. The EU-funded project GRACE (GMO Risk Assessment and Communication of Evidence) aims to explore, adapt, apply, and promote these tools to enhance accountability in decision-making by providing policy makers with comprehensive, science-based information on potential impacts (scenarios) of genetically modified plants and their derived products. Furthermore, GRACE will establish an open-access database in order to support the review process, to mirror the evidence synthesis, to assist the dissemination of results and conclusions, as well as to act, in more general terms, as an information resource on biosafety of genetically modified plants.

Key words: Evidence synthesis, systematic review, impact assessment, genetically modified organism (GMO), genetically modified plant (GMP)

Introduction

Within the concept of a "knowledge-based economy," knowledge and information are increasingly being recognized as drivers for innovation, productivity and economic growth in modern economies. In line with this, policy decisions on new technologies, such as genetically modified organisms (GMOs), should be informed by comprehensive, science-based information on the potential impacts of these technologies on human and animal health, the environment, and society at large. In a recent call issued by the European Commission for proposals for research on such impacts of genetically modified (GM) plants, it was noted that, although many biosafety research projects have been conducted, "…a comprehensive review of national, EU and international research activities …is missing" while the "collection and

review of information must take account of scientific quality…" (Call: KBBE.2012.3.5-04 Verification of GMO risk assessment elements and review and communication of evidence collected on the biosafety of GMO). Recent controversies over findings of potential adverse impacts of GMOs published in peer-reviewed research papers highlighted the value of an explicitly transparent integration of results from all (accessible) studies in the field (Álvarez-Alfageme *et al*., 2011; EFSA, 2012; Parrott, 2008; Romeis *et al*., 2011; Rosi-Marshall *et al*., 2007; Schmidt *et al*., 2009; Seralini *et al*., 2012).

The EU-funded project GRACE (GMO Risk Assessment and Communication of Evidence) aims to collect, evaluate and analyze available studies dealing with potential impacts, including both risks and benefits, caused by the deliberate release of GM plants and products derived thereof on human and animal health, the environment and socio-economy in a transparent, reproducible and unbiased manner. The ability to update such a review process in order to incorporate any new and relevant information in the future has also to be guaranteed. Evidence synthesis approaches meeting these demands have already been established in other scientific areas (Bragge *et al*., 2011; CEE, 2010; EFSA, 2010; Green *et al*., 2008; Hetrick *et al*., 2010) and will be adapted by GRACE – namely Systematic Reviews (SR) and Evidence Maps (EM). Both approaches are well established in medical and social sciences and enable the defensible synthesis of outcomes by minimizing the introduction of bias whilst ensuring transparency of the methods used. The major methodological differences distinguishing them from traditional reviews are shown in Table 1.

Table 1. Major methodological differences between systematic reviews, evidence maps and traditional reviews (adapted from Bragge *et al.*, 2011; EFSA, 2010).

	Systematic Review	**Evidence Map**	**Traditional review**
Review question	Focused and explicit	Broad or focused and explicit	Often broad in scope
Criteria for inclusion or exclusion of studies	Pre-defined and documented; objectively applied	Pre-defined and documented; objectively applied	Not always explicitly stated
Review method	Reported and also predefined in a protocol	Reported and also predefined in a protocol	Seldom reported
Literature search	Structured to identify as many relevant studies as possible	Structured to identify as many relevant studies as possible	Not always extensive and transparent
Methodological quality assessment of included studies	Included, typically using a quality assessment tool	Variable	Variable
Reporting of study outcomes	Full reporting of relevant outcomes	Full reporting of relevant outcomes	Selective reporting; often of study author interpretation
Synthesis	Quantitative synthesis (meta-analysis) when possible	Usually narrative	Usually narrative, sometimes selective

Active stakeholder involvement is key to guaranteeing a broader acceptance of the conducted review by ensuring for its thoroughness and its relevance from a societal perspective. Thus, stakeholders are involved in the planning stage and, if appropriate, in the interpretation of review outcomes, to assure the quality of the process and the relevance of the scientific issues addressed.

Within GRACE, the establishment of an open access database will further increase the level of transparency by documenting and supporting the evidence synthesis process. The database will be hosted and maintained by the Julius Kühn-Institut beyond the lifetime of the project.

In the following sections, both evidence synthesis approaches (SR and EM) will be briefly introduced and major methodological differences affecting their integration in the impact assessment process will be highlighted.

Evidence synthesis for GMO impact assessment

Systematic review

A SR is based on a specific review question and integrates existing evidence by using pre-specified and standardized methods to identify, critically appraise, collect, report, analyze and, if possible, synthesize data (meta-analysis) from the studies that are included in the review (EFSA, 2010). It is especially valuable for impartially synthesizing evidence relating to contentious topics for which stakeholders may hold differing views. It forms the basis for providing a defensible answer to a critical question and the outcomes may directly inform the risk assessment process about a possible impact caused by the deliberate release of a given type of GMO. The procedure of a SR can be generally subdivided into eight core steps as shown in Figure 1.

Starting from a well-defined and specified research question, a review protocol is developed. The review protocol determines *a priori* the detailed procedure to be used for evidence synthesis. The protocol may be evaluated by stakeholders, if appropriate, and should undergo a peer-review process. This helps to minimise the introduction of a bias originating from methodological errors.

In the next step, relevant information sources, e.g. bibliographic databases, web-pages etc., are screened for possibly eligible reports using an extensive search strategy. The development of a proper search strategy is an iterative process aiming to retrieve the maximum amount of relevant evidence (CEE, 2010). It is a key step in the review process further aiming to minimize possible bias, originating from the published data *per se* (publication bias) and from indexing (EFSA, 2010). Once the pool of reports is obtained, they are screened using specific criteria to determine their suitability for inclusion in the SR. Any report not meeting the eligibility requirements are noted and removed from further evaluation, with the reasons for their ineligibility also recorded. The criteria thus used are so called inclusion/exclusion criteria and must be defined *a priori* in the review protocol to ensure that the boundaries of the review question are clearly defined (CRD, 2009).

In the following step, all necessary information is extracted from the eligible studies. As the value of the conducted SR depends on the quality of the included data/studies, a comprehensive quality assessment has to be performed. The quality criteria have to be developed and a determination made regarding the susceptibility (tendency) of each study to bias. Possible biases introduced into scientific studies can be caused by: discrepancies in the selection of the study subjects, the performance of the study, the detection and reporting of outcomes, and the handling of missing data. The quality assessment is then followed by a data

synthesis step, which can include a quantitative pooling of outcomes e.g. via meta-analysis. In the final step, results are objectively discussed and interpreted, taking the entire evidence base into account. A well-structured and solely evidence-based discussion is essential to drawing sound conclusions suitable to inform the decision-making process regarding possible impacts of specific GMOs and their derived products.

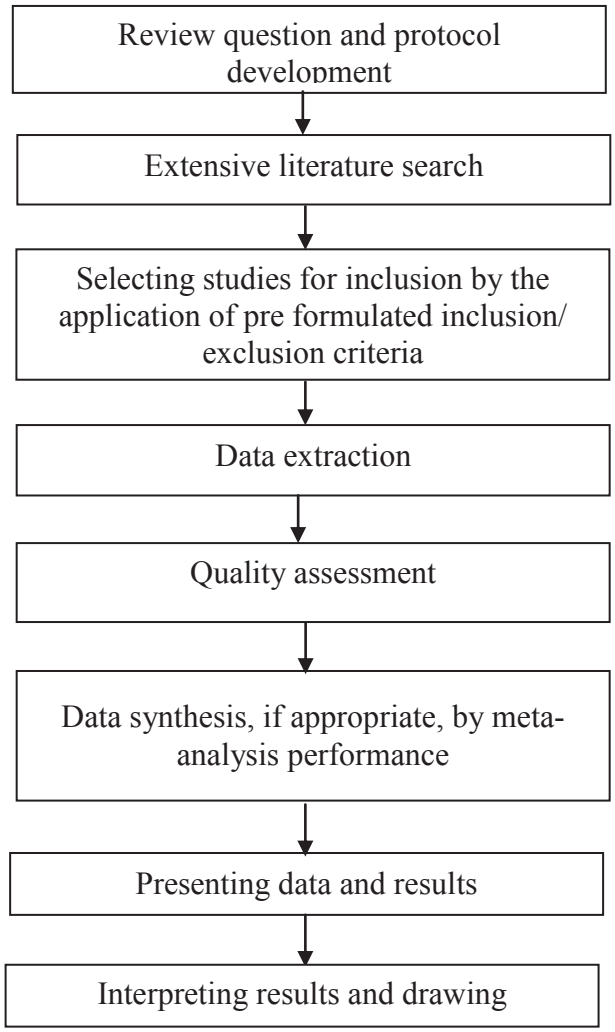

Figure 1. Core steps of a SR (adapted from EFSA, 2010)

Evidence map

An EM aims to identify all the literature relevant to a specific question in order to provide a comprehensive overview of both what is known and where gaps in evidence exist (Hetrick *et al*., 2010). Compared to SR, it employs the same methodological stringency for study identification and selection but typically provides a less detailed synthesis of the evidence. There are no firm rules about when an EM should be used. An EM may also have two, more general functions:

- To provide an overview of the extent, range and nature of research activities in a particular field (Hetrick *et al*., 2010);

- As a tool to inform stakeholders and risk assessors of the types of evidence available so that they can decide whether a specific synthesis of outcomes would be valuable, in one or more SRs (Bragge *et al*., 2011).

The reviewing approach for GMO impact assessment proposed by GRACE

The evidence synthesis framework proposed by GRACE can be subdivided into four distinct steps: i) the development of specific research questions, ii) the assessment of the need and feasibility for evidence synthesis for each question, iii) the selection of an appropriate evidence synthesis approach (SR or EM) and development of protocols, and iv) undertaking the evidence synthesis.

Special emphasis will be placed on the involvement of stakeholders, either directly by the organization of stakeholder workshops or indirectly e.g. via email correspondence or online questionnaires (see below). Furthermore, a transparent dissemination of review outcomes will be guaranteed by an open access database currently developed.

The status of the reviewing process currently developed by GRACE

Developing research questions about environmental impacts

Specific research questions have been developed through the use of conceptual models (CM). CMs help to develop a logical relationship between a specific concern and its relevant assessment endpoint. Questions which can be answered by a SR are characterized by a precise description of their scope and are thus referred to as being "focused". Key elements of focused questions are directly related to the impact assessment. The most commonly used type of question follows a "PICO" or "PECO" structure, where the key elements are defined as followed:

- Population of interest (P): Can be represented by a group of people, animals, plant species, a particular taxon or a sector of agriculture at a particular geographic scale (EFSA, 2010).
- Intervention/Exposure (I/E): The factor to which the population is exposed (EFSA, 2010).
- Comparator (C): The reference entity with which the intervention/exposure can be compared (EFSA, 2010).
- Outcome (O): Measurable consequences of a certain intervention/exposure (EFSA, 2010).

Examples of review questions considered within GRACE for dealing with potential environmental impacts caused by the deliberate release of GMPs (HT and *Bt* crops) are listed in Table 2. Besides the listed topics, additional reviews will be performed on the mode of action of Cry toxins and on insect resistance management.

At this stage of the project, the available evidence (quality and quantity of existing data) for answering each question is unknown. An initial estimate for the number of available studies can be made using an informal scoping process to assess the availability of data pertinent to a specific review question. Scoping results may trigger a decision to refine, specify or re-evaluate the original question and guide the selection of the most adequate evidence synthesis approach. The preference for one or another approach might further depend on the intended purpose of evidence synthesis (SR versus EM), already discussed above. As both approaches are highly labour intensive, the derived review questions may need to be prioritized in order to adapt the work load to the availability of resources, such as

time and personnel. For each finalized review question a protocol will be developed, guiding the entire evidence synthesis procedure. In line with the transparency pursued by GRACE, the protocols will be made accessible via the GRACE database as well as from independent third-party publication platforms upon acceptance of the submitted protocol.

Table 2. List of review questions addressing possible environmental impacts caused by genetically modified herbicide tolerant (GMHT) and insect resistant (*Bt*) crops.

GMHT crops
1. Is plant diversity (P) changed (O) by GMHT herbicide regimes (I) compared with conventional herbicide management (C)?
2. Are animal populations (P) changed (O) by GMHT herbicide and management regimes (I) compared with conventional management (C)?
3. Are soil microbial endpoints (P) changed (O) by GMHT herbicide and management regimes (I) compared with conventional management (C)?
4. Are population abundances (O) of soil invertebrates (P) changed by GMHT herbicide and management regimes (I) compared with conventional management (C)?
5. Do weed populations (P) exposed to HT herbicide regimes (I) compared with conventional herbicide regimes (C) become resistant to herbicides (O)?
Bt crops
1. Does the growing of Bt maize (I) change populations or ecological functions (O) of non-target animals (P) compared to the growing of conventional non-GM maize (C)?
2. Are population abundances (O) of soil invertebrates (P) changed by Bt crops (I) compared with conventional crops (C)?
3. Are soil microbial endpoints (P) changed (O) by Bt crops (I) compared with conventional crops (C)?

Stakeholder involvement

As mentioned above, special importance is given to the involvement of stakeholder groups in the review process. In the course of the GRACE project, stakeholders are consulted at three distinct stages: 1) the formulation of the review questions and their prioritization; 2) the review protocols, and; 3) the interpretation of the review results.

In April 2013, the first stakeholder workshop took place in Berlin to discuss and prioritize the proposed review questions. A broad range of stakeholders, including representatives from academia, competent authorities, industry, professional organizations and non-governmental organizations participated in the workshop and/or submitted written comments. Stakeholders were subsequently consulted via online questionnaire to prioritize the proposed review questions by ranking them against three relevance dimensions (RD) (adapted from Clavisi *et al*., 2013; O'Connor *et al*., 2012):

RD 1: Relative importance for the impact assessment of GMOs. Is the review question of high importance for the impact assessment of GMOs?

RD 2: Disagreement/controversy among experts. Is there expert disagreement on the review question?

RD 3: High public scrutiny. Is the review question the subject of high public awareness?

For each RD a scale (1-5) was applied to reflect the importance of the review question for the respective domain, with 1 = low importance and 5 = high importance. No answer was also possible.

Based on the outcome of this consultation step a final set of review questions will be selected and the review protocols will be elaborated. Following another consultation step on the draft review protocols the reviews will be initiated according to procedures described above.

Tentative timeline of GRACE

- The peer-reviewed protocols are envisaged to be available within the first quarter of 2014.
- The open access database is currently under development and will be available approximately by the middle of 2015.
- Finalized reviews and recommendations will be available by the end of 2015.

Conclusions

Based on a well-established, transparent and rigorous methodology, evidence synthesis approaches represent powerful tools to impartially summarize and assess the existing evidence base in order to efficiently inform decision-making processes. Their adaption and use in GMO impact assessment will increase the traceability and reliability of information dealing with possible adverse and/or beneficial effects on human and animal health, the environment and socio-economy caused by the deliberate release of GMOs and derived products.

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