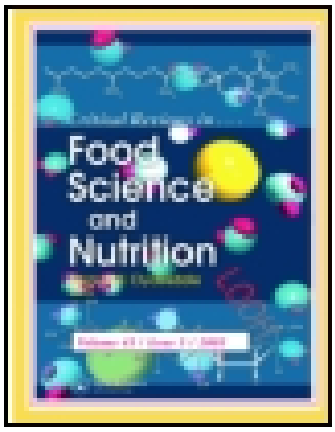

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Applicability and feasibility of systematic review for performing evidence-based risk assessment in food and feed safety

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Abstract

Food and feed safety risk assessment uses multi-parameter models to evaluate the likelihood of adverse events associated with exposure to hazards in human health, plant health, animal health, animal welfare and the environment. Systematic review and meta-analysis are established methods for answering questions in health care, and can be implemented to minimise biases in food and feed safety risk assessment. However, no methodological frameworks exist for refining risk assessment multi-parameter models into questions suitable for systematic review, and use of meta-analysis to estimate all parameters required by a risk model may not be always feasible. This paper describes novel approaches for determining question suitability and for prioritising questions for systematic review in this area. Risk assessment questions that aim to estimate a parameter are likely to be suitable for systematic review. Such questions can be structured by their "key elements" (e.g., for intervention questions, the population(s), intervention(s), comparator(s) and outcome(s)). Prioritisation of questions to be addressed by systematic review relies on the likely impact and related uncertainty of individual parameters in the risk model. This approach to planning and prioritising systematic review seems to have useful implications for producing evidence-based food and feed safety risk assessment.

Keywords

Evidence synthesis, Meta-analysis, Risk model, Transparency, Uncertainty.

1. INTRODUCTION

Systematic reviews have been widely used in clinical research to support evidence-based practice and policy decision making and they are increasingly used in other research areas of evidence-informed policy formulation and practice, for example in the fields of social welfare, international development, education and crime and justice (http://www.campbellcollaboration.org/) and environmental management (http://www.environmentalevidence.org). The use of systematic reviews in various aspects of food and feed safety is increasing (e.g. Sargeant et al., 2005; Lichtenstein et al, 2008; CEBC, 2010; Marvier, 2011; NNR5 working group, 2011). Risk assessors in food and feed safety face two particular challenges when considering the use of systematic review methods: i) how to refine broad food and feed risk assessment multi-parameter models into specific, reviewable questions suitable for systematic review; and ii) how to prioritise questions for systematic review, given that a risk assessment may generate multiple potentially reviewable questions.

In this article we contextualise the systematic review methodology developed by The Cochrane Collaboration (Higgins and Green, 2011) and other research groups (Sargeant et al., 2005; CRD, 2009; CEBC, 2010; EFSA, 2010) to illustrate the relevance of systematic reviews to food and feed safety risk assessment. To address the challenges of applying systematic review in this area, we present a framework for determining the suitability of food and feed safety risk assessment questions for systematic review and a set of criteria for prioritising questions for formal systematic reviews.

2. WHAT IS A SYSTEMATIC REVIEW?

A systematic review is an overview of existing evidence pertinent to a clearly formulated research question, which uses pre-specified and standardised methods to identify and critically appraise relevant research, and to collect, report and analyse data from the studies that are included in the review (EFSA, 2010). A meta-analysis is a statistical analysis to combine results across multiple, similar studies, and is usually undertaken within the context of a systematic review. Systematic reviews and meta-analyses are widely used in evidence-based health care to develop clinical and public health practice guidelines (Guirguis-Blake et al., 2007; WHO, 2010), set research priorities (NICE, 2009; Rylance et al., 2010), formulate scientific consensus statements (ADA, 2012) and in health technology assessments (Busse et al., 2002). Unlike traditional (narrative) reviews, systematic reviews follow an explicit process that aims to minimise bias and maximise transparency, thus providing more reliable and documentable findings from which conclusions can be drawn and decisions made (Higgins and Green, 2011). In particular, in a narrative review the research question is often broad in scope, the criteria for selecting studies are seldom stated, the literature search process is not always extensive and assessment of the methodological quality of the studies included in the review is variable and may not occur. On the other hand, in a systematic review the question is always focused and explicit, eligibility criteria are pre-defined, documented and objectively-applied, the literature search is often structured to identify as many relevant studies as possible and the included studies are critically appraised, using predefined quality assessment tools. Furthermore, in a systematic review the method is predefined in the review protocol and clearly documented and reported,

along with the results of each step of the process, to support transparency and enhance reproducibility (EFSA, 2010) (Table 1).

3. THE PARADIGM OF EVIDENCE-BASED FOOD AND FEED SAFETY RISK ASSESSMENT

Food and feed safety risk assessment uses multi-parameter models to estimate the likelihood of occurrence of adverse effects to human health, animal health and welfare, plant health and the environment, as a result of exposure to hazards. A model is a (simplifying) representation of the essentials of a system (e.g. scenarios, parameters, relations, processes and mechanisms), which incorporates existing knowledge and/or assumptions about the relationship between all system components in an explicit form (EFSA, 2009a). In general, food and feed safety risk assessment models follow an accepted methodology consisting of four fundamental pillars: (i) hazard identification; (ii) hazard characterisation; (iii) exposure assessment; and (iv) risk characterisation (Codex Alimentarius, 2003; WHO, 2009).

The overall scope of risk assessment is to provide, insofar as is possible, a complete set of information to risk managers, so that a systematic, comprehensive, accountable decision can be made concerning a potentially hazardous situation (Asante-Duah, 2002). The information presented in the risk assessment model facilitates decisions about the allocation of resources for safety improvements via hazard/risk reduction; provides decision makers with a justifiable basis for determining risk acceptability; and aids in choosing between possible corrective measures for risk mitigation programmes.

Pre-requisites of risk assessment are a high degree of transparency and the full use of all available scientific information. The extent to which a risk assessment model is useful in a

specific situation is determined largely by the validity of the method used to identify, select, appraise, and synthesise the best available evidence underpinning the questions generated by the model. However, in food and feed safety risk assessment there is no current standard for transparently combining and incorporating evidence, making it difficult to determine the evidence base for parameters in a risk assessment. This lack of transparency can reduce trust in the outcomes of food and feed safety risk assessments. In human health care, health technology assessments serve a similar purpose for decision makers as food and feed safety risk assessment, aiming to enable decision makers to understand the benefits, harms and resource allocation implications (Busse et al, 2002). The need for transparency is also similar. In health technology assessment, one commonly used framework for transparent evidence synthesis is that of systematic review and meta-analysis.

When feasible and justified, the systematic review approach can also be applied to minimise bias in the assessment of the parameters required by each step (pillar) of the risk assessment process in food and feed safety, to ensure an evidence-based overall risk estimate. However, not all parameters required by the risk assessment process can be estimated using meta-analysis and the systematic review process may be time- and resource- intensive.

4. A FRAMEWORK FOR IDENTIFYING QUESTIONS SUITABLE FOR SYSTEMATIC REVIEW IN FOOD AND FEED SAFETY RISK MODELS

We propose a framework for identifying questions that are suitable for systematic review (including meta-analysis where appropriate) from among the questions generated during development of risk assessment models. More specifically, we identify questions that are suitable for systematic review without change, those that are suitable for systematic review after

appropriate reformulation, and those that are not answerable by systematic review. This involves first clarifying the objective(s) of the questions generated by the risk assessment model, that is whether the questions aim to estimate a parameter or to gather other type of information necessary to inform the risk assessment model; and, second, for questions that aim to estimate a parameter, determining whether the question structure is completely specified (referred to as a "closed-framed" question) or incompletely specified (an "open-framed" question).

4.1 Step 1: Define the objective of the questions generated during development of the risk assessment model and identify questions that aim to estimate a parameter

We consider systematic reviews to be suitable for clearly specified questions aiming to estimate parameters such as might be evaluated in well-defined primary research studies. The risk assessment approach involves the identification of scenarios, formal representation as a mathematical model and finally parameterisation of the model. Systematic review might therefore be expected to support the latter step only. Assessment of the suitability for systematic review of the questions generated by a risk model involves defining the objective(s) of each question and determining whether or not they aim to estimate a parameter. For instance, questions like: "What analytical techniques are available to determine the concentration of chemical *x*" or "What countries have implemented a specific meat inspection method" aim to develop scenarios of a risk assessment, rather than to estimate a parameter and are not suitable for systematic review. They are more likely answerable by scoping the literature and mapping the relevant information, using expert knowledge or via direct enquiry (e.g. by running a survey or interrogating databases).

Most questions in food and feed safety risk assessments that aim to estimate a parameter fall into three main types: i) questions on the effect of an exposure or intervention; ii) questions on the sensitivity or specificity of a test; or iii) questions on the prevalence of a condition or the incidence of an outcome. These parameters can be estimated in primary research studies, and these primary research studies can be identified, appraised and synthesised using systematic review. A useful way to identify and classify these three question types within a risk model is to look at the *structure* of the questions and in particular at their *key elements*. These are the components of the question that specify what information must be provided in a primary study to estimate the parameter under assessment and hence answer the question. Common key elements of questions on the efficacy of an intervention include the population (P), intervention (I), comparator (C) and outcome (O), and such questions are widely known as "PICO" questions in the health care literature (Higgins and Green, 2011). The primary research studies answering the review question will have similar key elements (Glasziou and Henegham, 2009). In contrast, in questions that aim to develop scenarios of a risk assessment, the structure in key elements is not present (e.g. a question about what countries use a particular vaccine or what diagnostic tests are available for determining a virus).

The key elements in a PICO-type question are also applicable to intervention questions in food and feed safety risk assessment. For instance, in a question about the efficacy of a vaccine, the key elements would be the species under assessment (population), the vaccine (intervention), other vaccines or absence of vaccination (comparator) and the measure used to measure the effect, such as change in disease prevalence or incidence (outcome). For questions on the effects of exposure to a potential risk factor, the key elements are the population, the exposure, the

comparator and the outcome ("PECO" questions). For example, in a question about the genotoxic effect of a defined chemical on rats, the key elements are: rats (population); the chemical under assessment (exposure); the absence of chemical (comparator); and genotoxic effect (outcome).

A different type of question, frequent in the food and feed safety area, refers to the accuracy of a method of detection or diagnosis. For example: "What is the most sensitive method to detect condition *x* in an animal species?". The main elements of this question are: the population (P) on which the test is performed, the index test (I) and the target condition (T). We refer to this as a "PIT" question type. A third type of question structure is a question about a specific descriptive parameter for a population, such as: "What is the frequency of occurrence of condition *z* in animal species *x*?". The key elements in this question are the population (the animal species, P) and the condition of interest (i.e. the outcome, O); we refer to this as "PO" question type (Table 2).

In summary, in food and feed safety the three questions types suitable for systematic review are the intervention or exposure questions, with "PICO" or "PECO" structure; test accuracy questions with "PIT" structure (population, index test, and target condition); and questions on population parameters with the "PO" structure (population and outcome or condition of interest) (Table 2).

The key elements of a question to be addressed by a systematic review may be determined by the risk assessment process. For instance, the population of interest when performing human risk assessment of chemical contaminants occurring in the food chain is clearly the human population. However, human epidemiological data are not often available, or unattainable due to

experimental or ethical constraints. Hence, in the majority of cases, the risk assessment is based on experimental data from a test animal species (e.g., rat, mouse, dog, rabbit), which becomes the population of interest for the systematic review. Consideration of whether extrapolation of findings from animal studies to the assessment of risk in humans is appropriate would be addressed prior to conducting the systematic review, to ensure that the evidence will be relevant to the risk assessment.

Some examples of question types suitable for systematic review in the context of risk assessment of chemical contaminants in the food chain are given in Figure 1. The Figure illustrates question types suitable for systematic review according to the PECO/PO/PIT system in the context of the human risk assessment of a chemical contaminant in the food chain. Question types are illustrated for each step of the risk assessment process as follows: for the hazard identification step, examples of questions relate to the mutagenicity of a chemical or induction of cancer in humans and/or animals; hazard characterisation questions relate to the toxicokinetics of the compound in humans and/or animals exposure assessment with outcomes related to the fate of the compound (absorption, distribution, metabolism, excretion) such as half-life or clearance, the toxicity (toxicodynamics) dose-response of the chemical in its target organ in humans and/or test species; exposure assessment is related to questions dealing with occurrence of the chemical, food consumption and limit of detection of the analytical technique. The risk characterisation step is a broad consideration, which integrates answers from questions on hazard identification, hazard characterisation and exposure assessment, each of which may be separately answerable by systematic review.

Note that we have used the term “exposure” in two different contexts: in hazard identification and characterisation, exposure occurs as part of the PECO concept, corresponding to exposure to an identified hazard (e.g. a chemical at defined dose-levels); exposure assessment, on the other hand, is part of the risk assessment framework, aiming to estimate exposure levels in real-world scenarios based on empirical occurrence data and consumption data (both variations on the PO question type).

4.2 Step 2: Determine whether a question is open- or closed-framed and reformulate open-framed questions

For questions that aim to estimate a parameter for a risk assessment model and are suitable for systematic review, it is necessary to determine the question type and to clearly specify the key elements, because the actual elements of a systematic review will vary accordingly. If the key elements of the review question are specified in such a way that at least one study design can be envisaged that would answer the question in a primary research setting, then all elements of the systematic review can be immediately defined without further refinement of the review question. We define review questions where all key elements are clearly specified as *closed-framed* questions.

In broad policy problems that require risk assessment, the questions included that are amenable to systematic review are often formulated in a way that their key elements are not all clearly specified, i.e. are *open-framed*. For instance, in the questions "*what* chemicals have genotoxic effect *x* on humans?" or “does nutrient *x* reduce cholesterol?”, respectively the exposure (i.e. the chemicals) and the population (e.g. adults, obese people) are the missing key elements. The absence of specification of the key-elements makes it difficult to identify the most

appropriate study design that would provide reliable evidence and thus to perform a systematic review to answer the question. In PICO/PECO questions, however, the fact that the comparator is not explicitly specified in the review question does not mean that the question is open-framed. Often the I/E and C elements are implicitly considered together, for instance when comparisons need to be made between different levels or types of exposure/intervention in order to assess their effects on the outcome.

Open-framed questions can be addressed by performing extensive literature searches (or relying on expert knowledge), specifying the missing key elements (and converting them into closed-framed questions) and conducting a systematic review of the modified questions. Thus while closed-framed questions are immediately suitable for systematic review, open-framed questions must be converted into refined closed-framed questions to be addressed using systematic review. Broad policy problems and food and feed safety risk models may comprise a mixture of closed-framed and open-framed questions. The reviewer should explore the questions carefully to choose the right approach for answering each.

5. CRITERIA FOR PRIORITISING QUESTIONS FOR SYSTEMATIC REVIEWS IN FOOD AND FEED SAFETY RISK ASSESSMENT

The systematic review methodology can be time- and resource- intensive. When conducting food and feed safety risk assessment in support of decision making, urgency may be the most important concern and performing a systematic review to estimate all risk assessment parameters may not be practical. Consequently, it is important to prioritise, within the risk model, the

questions suitable for systematic review that are worth addressing using systematic review, taking into account the practical constraints.

Best practice in risk modelling requires the assessment and reporting of uncertainty (EFSA, 2009a). We propose a procedure for prioritising the parameters that should be estimated using systematic reviews. The method is based on a set of criteria, listed in Table 3, that consider the related uncertainty and likely impact of the individual parameters in the risk assessment model. Applying these criteria, the risk assessor can produce a priority list of model parameters for which the reliability of the estimate is considered most important. Systematic review (and meta-analysis) could then be considered to estimate these important parameter(s). In cases when the evidence necessary to estimate a parameter is scarce or of low quality and the uncertainty is high, the systematic review methodology can be particularly helpful to formally identify knowledge gaps or to document the limitations and flaws of the existing evidence. This in turn supports informed proposals for future research.

Our criteria for prioritising questions for systematic review in the context of risk assessment models are similar to those used to assess the uncertainty of model assumptions (Van der Sluijs et al. 2005, Table 3). This framework for prioritising questions for SR represents a preliminary attempt and, after some practical implementation, it would be helpful to define whether these criteria should be applied using a qualitative or quantitative approach.

We provide an example of criterion 4b ("anticipated structural effect of the parameter in the model") in Figure 2. In this example, various pathways were identified to assess the risk of introduction and spread of porcine brucellosis in a pig herd (EFSA, 2009b). In the analysis of the risk model, the diagnosis of porcine brucellosis at import was identified as common to all

pathways; thus the sensitivity and specificity of the diagnostic assay (RF5) were the most important model parameters. This importance justified the use of systematic review to estimate RF5. To estimate the parameters (sensitivity and specificity of the diagnostic essay RF5), the risk assessor first must identify the available diagnostic tests for porcine brucellosis, thereby addressing the question "what diagnostic tools are available to determine porcine brucellosis in pigs?". The answer to this question will produce a list of available diagnostic tests (and not an estimate of the parameter), and this answer might be obtained by performing an extensive literature search and mapping the relevant information. When the available diagnostic tools are identified, their sensitivity and specificity can be assessed by performing a systematic review. The question to answer using systematic review will be "What is the diagnostic sensitivity of tests *i*, *j*, *k* to determine porcine brucellosis in pigs?", which is a closed-framed question (population = pigs; index test = sensitivity of diagnostic test *i*, *j*, *k*; target condition = porcine brucellosis).

CONCLUDING REMARKS

Systematic reviews follow an explicit process that aims to minimise bias and maximise transparency, thus providing more reliable findings on which conclusions and decisions can be based (Higgins and Green, 2011). The implementation of the systematic review methodology for estimating risk assessment parameters in food and feed safety risk modelling can therefore contribute towards minimising biases in the risk estimates. However, implementation of systematic review in food and feed safety risk assessments requires thorough consideration of the actual suitability for systematic review of questions generated during development of risk models. Feasibility of systematic review, especially in case of limited resources or time

constraints (as it is often the case when conducting risk assessment in support of decision making) is also an important consideration.

The framework for assessing question suitability for systematic review and the set of criteria for prioritising questions for systematic review in food and feed safety risk assessment presented in this article represents a preliminary attempt to contextualise systematic review to food and feed safety risk assessment. The method presented can contribute to effective implementation of the systematic review methodology for estimating risk assessment parameters. Systematic reviews can enhance scientific soundness and transparency in food and feed safety risk assessments, and their use should be considered when the conceptual risk assessment model is built. This methodological framework is expected to continue to evolve as experience is gained through initial implementation.

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DISCLAIMER

The authors Elisa Aiassa, Ana Afonso, Jean-Lou Dorne and Didier Verloo are employed with the European Food Safety Authority (EFSA). However, the present article is published under the sole responsibility of the authors and may not be considered as an EFSA scientific output. The positions and opinions presented in this article are those of the authors alone and are not intended

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LIST OF FIGURES

Figure 1. Examples of question types (in terms of their structure in key elements) embodied in the four pillars of the risk assessment of chemical contaminants in the food chain

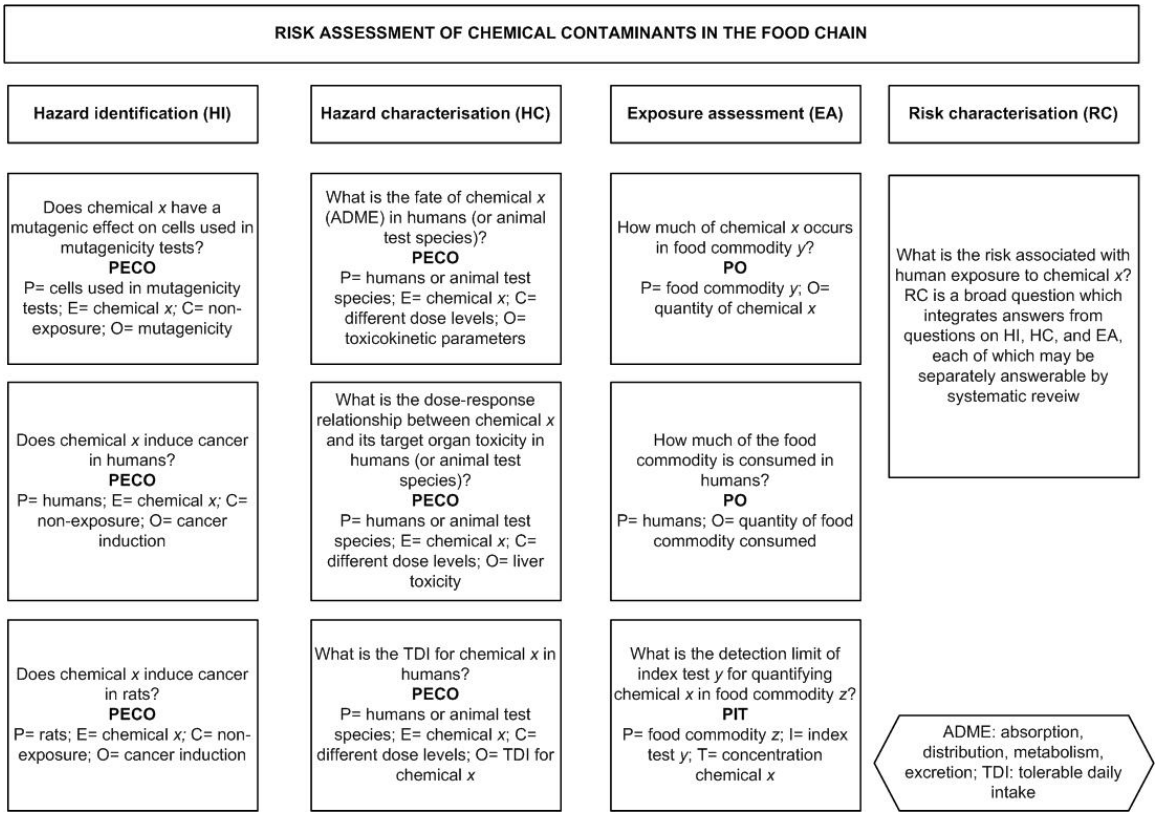

Figure 2. Criterion for prioritising questions for systematic reviews in import risk assessment in animal health: "anticipated structural effect in the model" (from EFSA, 2009b).

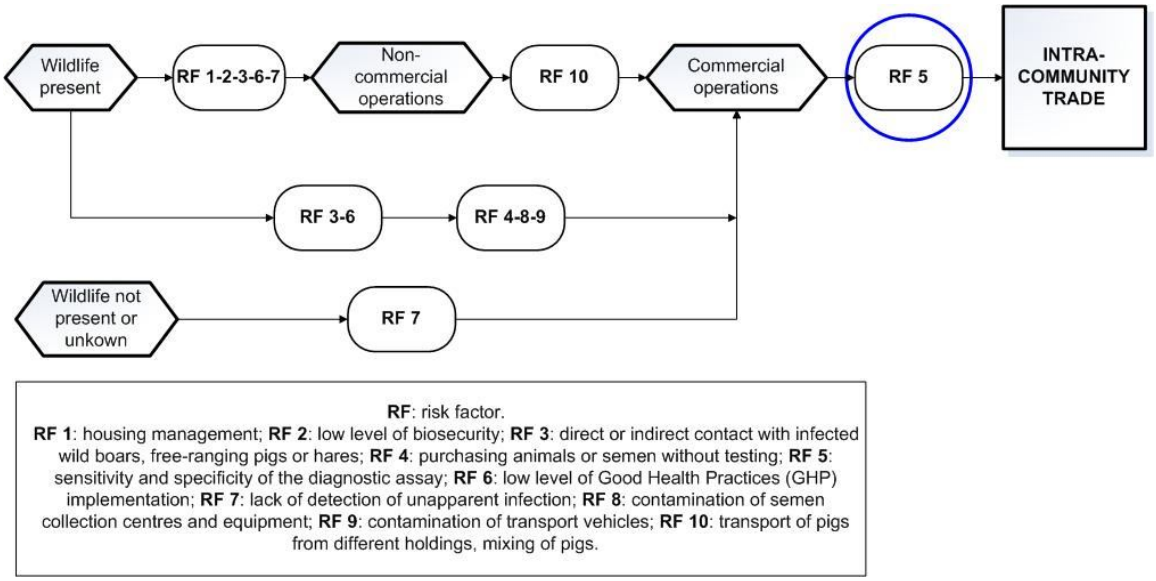

Table 1. Main steps of the systematic review process (based on EFSA, 2010 and Higgins and Green, 2011)

Step of the systematic review process	Description
Preparing the review protocol, including formulating the review question and developing the eligibility criteria for study selection	The review protocol contains the method foreseen for all steps of the review, which is made explicit *a priori*, to reduce the risk of introducing biases in the review. Question formulating consists of the clear specification of the review question. For instance, for a question on the effects of an intervention, question formulating implies the detailed specification of the relevant population(s), intervention(s) comparator(s) and outcome(s). Question formulating is crucial as all aspects of the review flow directly from it and is fundamental for defining the eligibility criteria for study selection. The eligibility criteria specify the types of research study that are considered appropriate to answer the question, including aspects of the review question as well as appropriate study designs.
Searching for studies	A thorough and extensive literature search is performed to identify as many studies as possible that meet the eligibility criteria. This implies the use of as many relevant information sources as possible (i.e. bibliographic databases, websites and sources accessible via hand-searching such as journals tables of contents as well as research groups to be contacted) and the development of search strategies (i.e. combinations of search terms and Boolean operators[1]) tailored to capture in the search some fundamental aspects of the review question.
Selecting studies for inclusion in the review	The studies are selected for inclusion in the review using the pre-specified criteria. Normally the selection process is undertaken by mutually independent reviewers in two stages: screening of titles and abstracts and examining the full-text documents.
Collecting data from included studies	Data are systematically collected from the included studies to ensure reproducibility of the systematic

[1] Boolean operators are used to combine terms when conducting electronic searches. Examples include "AND" (used to narrow a search), "OR" (used to broaden a search) and "NOT" (used to exclude terms from a search).

included studies	review. The guiding principle for collecting data is to determine study findings and to report study characteristics that influence heterogeneity across studies, study methodological quality and relevance of the findings.
Assessing the methodological quality of included studies	Each study included in the review undergoes a standardised assessment, to check whether or not it meets a predefined list of methodological characteristics, to assess the degree to which it is susceptible to bias (e.g. selection, performance, detection, attrition or reporting bias).
Synthesising data from the studies	The data generated through the systematic review are synthesised, when possible using meta-analysis[2]. If meta-analysis is not feasible, the results of the included studies are discussed narratively.
Interpreting the results and drawing conclusions	The discussion and conclusions include description of the quantity and quality of evidence underpinning the review question; interpretation of the results; any potential limitation of the review process; and consistency with other research beyond the scope of the SR.

[2] The use of statistical methods to combine results from previous separate but related studies (published or unpublished) in order to determine the presence, direction, consistency and magnitude of effects across the studies.

Table 2. Common review questions in food and feed safety risk assessment that are suitable for systematic review and their structure in key elements (based on EFSA, 2010)

Review question	Examples of what the question seeks to assess	Structure in key elements (question type)*
Effect of a deliberate intervention	• Nutritional properties of an additive in a food or feed • Efficacy of a vaccine in preventing a disease	PICO
Effect of exposure to a potential risk factor	• Mutagenic effect of a chemical on cells used in mutagenicity tests	PECO
Assessment of a dose-dependent fate of a substance or dose-response relationship (toxicokinetics and toxicodynamics)	• Changes in toxicokinetic parameters as a function of the dose of a chemical in animals or humans • Changes in physiological parameters or biomarkers as a function of the dose of a chemical in animals or humans (toxicodynamics)	PECO
Environmental fate	• Changes in the environmental distribution, degradation, leaching, or run-off of a substance into surrounding areas as a function of its concentration	PECO
Diagnostic test accuracy	• Ability of a test to indicate whether a condition is present or absent	PIT
Analytical accuracy of a test or measurement	• Extent to which a measurement technique correctly determines what the investigator intends to measure	PIT
Prevalence of a disease or condition	• Proportion of animals infected with a virus	PO
Incidence of a disease or event	• Number of new infections in a given time period	PO
Occurrence of a substance	• Level of e.g. a chemical in food, feed or the environment	PO
Consumption of a substance	• Average intake of e.g. a foodstuff	PO

*PICO: population(s), intervention(s), comparator(s), outcome(s); PECO: population(s), exposure(s), comparator(s), outcome(s); PIT; population(s), index test(s), and target condition(s); P: population(s) and outcome(s) or condition(s) of interest.

Table 3. Criteria to identify candidate questions for formal systematic reviews in the context of food and feed safety risk assessment (based on Van der Sluijs et al., 2005)

Criteria to prioritise questions for systematic review within a risk assessment model	Explanation
1. Plausible parameter space	Broad plausible ranges for parameters, when assessed on the background of their use in the model, may indicate the need for estimating such parameters using systematic review. Example: storage temperature of a food commodity may be more variable compared to certain intrinsic factors (e.g., salt contents, water activity, pH) and thus it may be appropriate to estimate it by performing a systematic review.
2. Intersubjectivity	Presence of variability among preliminary expert opinions about the parameter may indicate the need for systematic review.
3. Sensitivity to interests	Presence of stakeholders' interests on parameter(s) (e.g. citation of own work; anchoring on previous opinion; adherence to pessimistic scenarios out of a precautionary principle; etc.) may indicate the need for a systematic review to estimate the parameters for which there is a strong interest.
4a: Anticipated local effect of the parameter in the model	Due to its magnitude and direction, a parameter can have an important direct impact in the model and therefore it may be worthwhile to improve the parameter estimate by doing a systematic review. Example: the prevalence of a disease x in the country of origin has a considerable impact on the assessment of the probability of importing disease x into a defined (animal) population or (geographic) region. Therefore, assessing prevalence of disease x in the country of origin by performing a systematic review may be appropriate.
4b: Anticipated structural effect of the parameter in the model	Depending on its position in the model and the number of pathways involved, the parameter can have higher impact (many pathways involved) or lower impact (few pathways involved). Example: see Figure 2.