

The Director General

Maisons-Alfort, 25 July 2016

OPINION **of the French Agency for Food, Environmental** **and Occupational Health & Safety**

regarding the progress report on the assessment of the weight of evidence at
ANSES: critical literature review and recommendations at the hazard identification
stage

ANSES undertakes independent and pluralistic scientific expert assessments.

ANSES's public health mission involves ensuring environmental, occupational and food safety as well as assessing the potential health risks they may entail.

It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with the necessary information concerning these risks as well as the requisite expertise and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its opinions are made public.

This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 25 July 2016 shall prevail.

On 31 March 2015, ANSES issued an internal request to conduct a critical analysis of the approaches to assessing weight of evidence at the hazard identification stage.

1. BACKGROUND AND PURPOSE OF THE REQUEST

1.1 Background

ANSES contributes to safeguarding human health in the areas of the environment, work and food, as well as protecting animal health and welfare, and plant health. The Agency is responsible for conducting independent and multi-disciplinary scientific expert assessments, in order to assess risks and make recommendations to the competent authorities on measures likely to protect public health.

The Agency identifies and characterises biological, chemical, or physical hazards by mobilising all the available scientific data, and assesses the risks to human, animal or plant populations taking into account the diversity of types of exposure of individuals to different hazards. ANSES also assesses products (plant protection products, biocides, veterinary drugs, novel foods, chemicals, etc.) and processes (treatment of water or food, etc.) with respect to the regulatory requirements, for a decision on their marketing or authorisation for use by the ministries in charge of the regulations.

The topics examined by the Agency are dealt with in the framework of the health risk assessment process, which consists of four steps: hazard identification, hazard characterisation (including establishment of the dose-response relationship), exposure assessment and risk characterisation.

These topics may be of different types, for example: "Does consumption of dietary fibre have an influence on the risk of colorectal cancer?", "Are prion diseases transmissible to humans?"

The data used to answer these questions come from multiple sources (databases of the scientific literature, expert appraisals by professionals), are varied in nature (*in vitro*, *in vivo*, toxicological, epidemiological, etc.) and may be contradictory. They need to be analysed in depth in order to assess their relevance and validity, and then systematically integrated to address the questions asked. In the literature, the methodology for assessing the relevance and quality of the data, and then combining heterogeneous data, is called "assessment of the weight of evidence"¹. The literature mainly refers to the assessment of the weight of evidence at the hazard identification stage. The aim of this step is to identify the type and nature of adverse effects that an agent (biological, chemical or physical) can have on a body, a system or a population (IPCS 2004).

1.2 Identification of the issues and needs

To guide public policy, public authorities and stakeholders require evidence of different natures for a wide range of areas (NRC 2014, OECD 2015, US EPA 2014). Recently, differences between the conclusions reached by different organisations on the toxicity or risk associated with exposure to various substances (for example, between EFSA and the IARC on glyphosate²; between EFSA and ANSES on Bisphenol A³) have highlighted the impact on the final result of the assessment of health effect classification systems and conceptual models explaining the emergence of a health effect. Assessing the evidence in the framework of the scientific expert appraisal is therefore receiving growing interest from health agencies, at national and international level, for improving the robustness and transparency of the expert appraisal work (Hardy et al. 2015, OHAT 2015). This transparency is essential to ensure the credibility and confidence of the scientific community, along with other stakeholders, with respect to the public authorities.

Although frequently used, the concept of "weight of evidence" is ambiguous, often poorly defined, and does not always cover a transparently and coherently presented methodology (NRC 2014, Weed 2005). Historically, assessment of the weight of evidence was developed in the medical sector as a clinical decision support tool for prioritising knowledge of medical research (Sackett et al. 1996). Initially, the methods focused mainly on the critical review of the literature. After having been used in the framework of evidence-based medicine, these methods were adapted to address environmental health issues (Mandrioli and Silbergeld 2015, Krimsky 2005). Subsequently, the methods evolved to combine different sources of information in a transparent and systematic manner, in particular in the framework of collective expert assessments.

A review of ANSES's practices showed that a diversity of weight of evidence methods was used to deal with several formal requests for assessment. The choice of methods differed according to the theme of the requests (physico-chemical, biological, nutrition-related risks, etc.), and even within the same theme. The level of formalisation of these methods and the expression of the conclusions also varied among expert groups.

¹ The National Centre for Language Resource and Processing gives a general definition of the term "evidence": fact, testimony, reasoning likely to establish conclusively the truth or the reality of (something).

² See <http://www.efsa.europa.eu/en/press/news/160113>

³ (ANSES 2015b)

1.3 Purpose of the request

With the aim of improving the transparency of the expert assessment process required for an ISO 9001-certified organisation, ANSES asked the Working Group on the "Methodology of risk assessment" (MRA WG) to conduct a critical analysis of approaches to assessing weight of evidence at the hazard identification stage.

The main objectives of this internal request were to:

- Describe ANSES's current practices and compare them with those of other health organisations/agencies.
- Carry out a critical review of weight of evidence approaches.
- Propose harmonised procedures for assessing the quality of studies and available data, as well as the levels of evidence in relation to the questions or assumptions made.
- Propose harmonised procedures for assessing and communicating the overall level of evidence associated with all the available data and studies.
- Demonstrate the applicability of the recommendations through case studies.

The results of this request will contribute to improving the transparency and reproducibility of the assessment of the weight of evidence at ANSES.

2. ORGANISATION OF THE EXPERT APPRAISAL

2.1 Procedure for handling the request and purpose of the report

This internal request was examined in three steps:

- Review of current ANSES practices,
- Review of the literature on weight of evidence and formulation of recommendations aimed at harmonising ANSES's procedures,
- Assessment of the recommendations through case studies, in close collaboration with the ANSES expert groups, and drafting of a guide.

The first step was carried out by the "Review" Action Team (AT) set up by the MRA WG. This AT conducted a review of ANSES's practices regarding the analysis of uncertainty and the assessment of the weight of evidence, which was presented to and discussed by the Scientific Board on 22 September 2015.

This report presents the results of the second step. It was conducted by another AT on "Weight of evidence". This report details the literature review carried out by this AT and makes a series of recommendations aimed at harmonising ANSES's practices. This progress report was validated by the entire MRA WG.

The third step mentioned above will be the subject of a specific study, to be conducted with the ANSES expert groups in 2016-17. A methodological guide will be prepared at the end of this last step. It will propose methods adapted to different practical situations, for assessing the quality of the available studies and data, and assessing and communicating the weight of evidence.

The expert assessment work presented in this report was conducted by a group of experts working in the Agency's different fields and with competence in risk assessment methods.

This report was submitted to the Scientific Board for comments at a specific meeting on 29 February, and then on 1 March 2016. The MRA WG drafted a new version of the report taking into

account the comments of the Scientific Board and responding to the questions asked. This final version was sent to the members of the Scientific Board and validated by them on 1 April 2016.

The expert appraisal was carried out in accordance with French Standard NF X 50-110 "Quality in expertise activities – General requirements of competence for an expertise activity (May 2003)" (AFNOR May 2003).

2.2 Prevention of risks of conflicts of interest

ANSES analyses interests declared by the experts prior to their appointment and throughout the work, in order to avoid potential conflicts of interest with regard to the matters dealt with as part of the expert assessment.

The experts' declarations of interests are made public via the ANSES website (www.anses.fr).

3. ANALYSIS AND CONCLUSIONS OF THE SCIENTIFIC BOARD

The Scientific Board endorses the conclusions of the collective expert assessment report by the MRA WG:

3.1 Definitions

In this report, the MRA WG has proposed definitions for three key terms: weight of evidence, line of evidence and systematic review.

"The **weight of evidence** is the structured synthesis of lines of evidence, possibly of varying quality, to determine the extent of support for hypotheses.

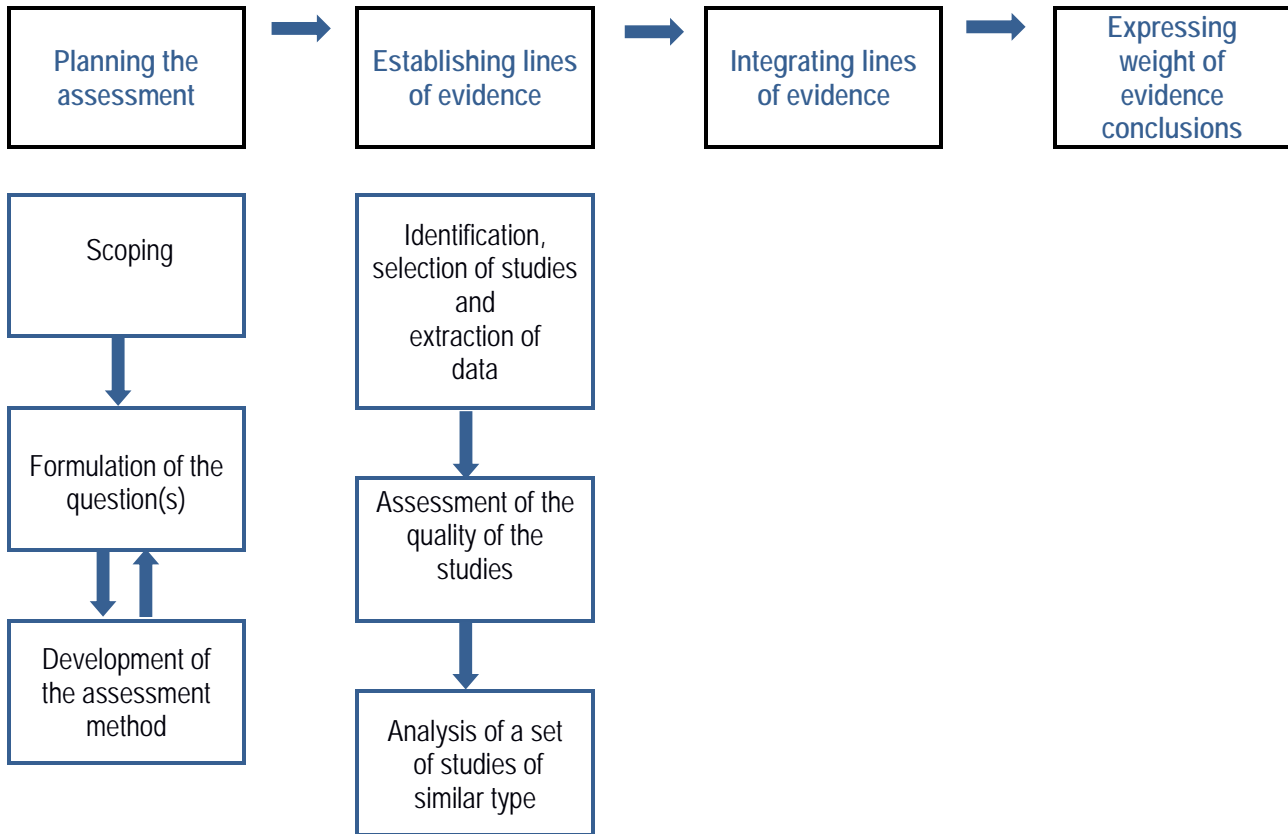
"A **line of evidence** is a set of relevant information of similar type grouped to assess a hypothesis".

"A **systematic review** of the scientific literature involves assembling, assessing and summarising in a comprehensive manner all the relevant studies, sometimes contradictory, addressing a specific issue. A systematic review is based on the prior drafting of a detailed protocol promoting the transparency and reproducibility of the process."

3.2 The steps in assessing the weight of evidence

The MRA WG recommends organising the weight of evidence assessment process into four main steps (Figure 1).

Figure 1: Weight of evidence assessment approach



The aim when **planning the assessment** (step 1) is to define the scope of the risk assessment, describe the issues and identify the methods to be implemented, including those for assessing the weight of evidence. This first step has three operational sub-steps:

- scoping,
- formulation of the question(s) to be assessed,
- development of the assessment method.

Establishing lines of evidence (step 2) also has three operational sub-steps:

- Identification, selection of studies (individual or synthesis) and extraction of data,
- assessment of the quality of the studies (individual or synthesis),
- analysis of a set of studies of similar type (epidemiological, toxicological, etc.) in order to establish lines of evidence.

The purpose of **integrating lines of evidence** to establish the weight of evidence (step 3) is to combine the available lines of evidence in order to determine the level of validity of assumptions or to estimate quantities of interest.

The step of **expressing conclusions on the weight of evidence** (step 4) serves to express the weight of evidence in the form of a clear and explicit result to assist with decision-making.

3.3 Critical analysis of the methods identified in the scientific literature

The MRA WG identified 25 methods for assessing the weight of evidence in scientific articles or methodological guides. The methods were examined using analysis grids for each of the steps described above. The methods were compared with each other using three criteria:

- The **prescriptive nature**: degree of formalisation of the method making the expert assessment transparent and reproducible.
- The **relevance**: degree of coherence of the method in light of the expected objective. The relevance should be placed in the context of the planning of the assessment (with regard to the question asked).
- The **feasibility**: degree of mobilisation of time and material/human resources, as well as specific methodological skills (modelling, statistics, etc.).

The results of this assessment were then used to formulate recommendations.

3.4 Recommendations

The methods identified in the literature review were compared to those inventoried in the review on the analysis of uncertainty and the assessment of the weight of evidence at ANSES, in order to define areas for progress. The documents in ANSES's quality system relating to the assessment of the weight of evidence were also considered in order to evaluate the benefits of including the assessment of the weight of evidence in the expert assessment process.

The report makes methodological recommendations, taking into account simultaneously the prescriptive nature of the methods, their relevance, and the feasibility of their implementation.

Recommendations for assessment planning

At ANSES, the assessment is planned when drafting the scoping document. ANSES does not have a specific document that states the assessment methods and the wording of questions for the expert groups. The MRA WG recommends setting up a complete process for planning the assessment in three sub-steps, each with an appropriate form.

Sub-step 1 (scoping) would be carried out by ANSES employees. The following two sub-steps would mobilise the expert committees and the experts involved in responding to the request. The MRA WG recommends adopting an iterative approach between sub-steps 2 (formulation of the question or questions to be examined) and 3 (development of the assessment method) in order to refine the wording of the questions to ensure that they can be properly addressed.

The MRA WG recommends conducting a preliminary review and, if necessary, hearings to:

- Identify the health, environmental, societal and economic issues in conjunction with decision makers (and, ideally, stakeholders).
- Assess the extent of available data.
- Formalise the question by means of a description structure presented in the literature (PICO, PECO, etc.).
- Formalise the sub-questions to be dealt with by the expert group, if possible in the form of a conceptual model.
- Draft a plan for developing the assessment method before it is carried out.

- Define the conditions for communicating the findings in the framework document.

In the framework of assessing the weight of evidence, for sub-step 3, the MRA WG recommends specifying at least the:

- Choice of the type of literature review: a systematic review or in-depth review to address the questions identified in sub-step 2. This choice must take into account elements from the framework document, the socio-economic analysis by ANSES and the criteria proposed by EFSA: assessing the likely impact of the evidence; assessing the quantity and quality of available evidence; considering the source and potential confidentiality of the evidence; considering the need for transparency and/or for integrating conflicting results; and evaluating the resources needed for carrying out the review.
- Criteria used to assess the quality of the studies by study type.
- Method chosen to assess a set of studies of similar type: meta-analysis, multi-criteria analysis, or qualitative approaches.
- Method chosen to integrate the lines of evidence: statistical modelling with or without expert knowledge elicitation, multi-criteria analysis, or qualitative approaches.
- Conditions for communicating the findings concerning the weight of evidence.

Recommendations for establishing lines of evidence

ANSES has conducted several systematic reviews of the literature, in previous assessments. However, they are still only carried out on an occasional basis within the Agency. Several of ANSES's groups use analysis grids to select studies and extract data, but these grids are not shared widely enough. In light of this observation, the MRA WG makes the following recommendations:

- Develop an analysis grid, or even a data extraction table, that can be adapted to the research question and the type of scientific study. This grid and table should be developed and tested on case studies in coordination with the expert committees. These grids should include elements regarding the relevance of the studies with respect to the question asked, descriptive elements of each study and criteria for assessing the quality of the studies.
- Consultation of at least two experts is desirable for completing the analysis grids.
- When a systematic review is carried out, a few major principles should be applied: the use of at least two databases, selection of the studies by two independent people, and definition of the study selection and exclusion criteria in advance.
- In cases where a systematic review is not carried out, the MRA WG recommends that the research, selection and extraction procedure be described as precisely as possible in the expert assessment report, keeping as closely as possible to the practices of a systematic review.

For assessing the quality of studies, the MRA WG recommends using lists of criteria formalised by type of studies (epidemiological, toxicological, etc.) so as to ensure the transparency of the assessment process. These lists should be developed in coordination with the expert committees. When studies are excluded, the exclusion criteria should be explicit and clearly stated by the expert group. When synthesis studies are considered in the expert appraisal process, the MRA WG recommends the use of the AMSTAR or R-AMSTAR method to assess their quality.

For assessing a set of studies of similar type in order to establish lines of evidence, the MRA WG recommends:

- For qualitative methods, defining as precisely as possible the assessment criteria and meaning of the scores assigned to these criteria by the experts.
- Using meta-analyses to establish lines of evidence on the strategic topics defined, taking into account the stakes in terms of health risks and the available resources (human resources, availability of data). These meta-analyses should be conducted using the available guidance documents, in particular the Cochrane Handbook.
- Analysing the sensitivity of the results to the input parameters when quantitative methods are used.
- Testing the benefits of multi-criteria approaches to assess their usefulness in the ANSES context.

Recommendations for integrating lines of evidence

The MRA WG recommends:

- Encouraging experts to describe and explain the choices made to ensure that the level of transparency is as high as possible. Certain methods for making the expert appraisal process more transparent could be used for this purpose (e.g. expert knowledge elicitation methods, integration of expert opinions in predictive models such as QSAR).
- Using qualitative methods such as those proposed by the IARC or the WCRF for the combination of lines of evidence, explicitly addressing the Hill criteria.
- Whenever feasible, using statistical modelling to combine different lines of evidence. As these approaches require specific skills and a relatively large time investment, the feasibility of their use needs to be assessed on practical examples.
- Analysing the sensitivity of the results to the input parameters when quantitative methods are used.
- Testing the benefits of multi-criteria analysis methods on practical cases in coordination with expert committees.
- Using a comparative weight of evidence assessment method in the specific field of mode of action analysis.

Recommendations for expressing conclusions on the weight of evidence

The MRA WG recommends:

- Providing an explanatory text to help interpret the numeric results when the weight of evidence is analysed with a quantitative method.
- Expressing conclusions concerning the weight of evidence in four levels of classification corresponding to increasing levels of evidence, when assessed based on a qualitative method. An additional category, "Assessment not possible", could also be considered. The MRA WG recommends that each level be defined precisely in the expert assessment reports. A classification on a numerical scale could be developed and tested on case studies in coordination with the expert committees.
- Organising the contents of the conclusion by adapting the work of the Cochrane Collaboration and the GRADE method to the Agency's areas. Closer ties with the Cochrane Collaboration could be considered in order to benefit from its experience.

- Characterising uncertainty in the conclusion, either qualitatively or quantitatively, depending on the weight of evidence analysis method used.

Operational recommendations

In order to facilitate the adoption by expert groups of the concepts and methods for assessing weight of evidence, the MRA WG recommends:

- Consulting the descriptions of methods and supporting references presented in this report.
- Making methodological support available to the expert groups to facilitate the implementation of methods for assessing weight of evidence. Methodological contact points could be identified to help expert groups carry out sub-steps 2 and 3 of the assessment planning, conduct the systematic reviews and apply the quantitative methods (meta-analysis, statistical modelling).
- Setting up an information system to share approaches adopted in earlier expert assessments. This information system could include the content of the analysis grids from the literature reviews and a description of the method of assessing the weight of evidence used in the expert assessment.

If they are adopted by the expert groups, these recommendations would help harmonise the Agency's procedures concerning the weight of evidence. However, in order to verify their relevance and facilitate their dissemination, the MRA WG suggests assessing these recommendations by conducting case studies in collaboration with the ANSES expert groups.

3.5 Conclusions and recommendations of the Scientific Board

The Scientific Board stresses the important work carried out by the Working Group on the "Methodology of risk assessment" and endorses this progress report. It insists on the need to implement case studies with the different ANSES expert groups in order to test the feasibility of the recommendations, and advocates the development of methodological tools for the expert groups (such as analysis grids) and provision of the necessary resources.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The French Agency for Food, Environmental and Occupational Health & Safety adopts the conclusions of the Scientific Board and the Working Group on the "Methodology of risk assessment" and recommends developing the quality system in the framework of continuous improvement.

The Director General

KEYWORDS

Weight of evidence, line of evidence, planning and scoping, expert assessment, systematic review, transparency.