

## SCIENTIFIC OPINION

# Guidance on Good Practice in Conducting Scientific Assessments in Animal Health using Modelling<sup>1</sup>

EFSA Panel on Animal Health and Welfare (AHAW)<sup>2, 3</sup>

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### ABSTRACT

The European Food Safety Authority (EFSA) asked the Panel on Animal Health and Welfare to develop a guidance document on Good Practice in Conducting Scientific Assessments in animal health using modelling. In previous opinions, the AHAW Panel has responded to two thirds of animal health related mandates using some kind of modelling. Every third opinion on animal health was supported by a quantitative model. These models range from simple to complex, employing a combination of scientific, economic, socio-economic, or other types of data. Hence, there is strong interest in the development of a guidance document to integrate modelling efforts into the routine process of EFSA working groups. In this document, an 'operating procedure' (OP) for the use of modelling within an AH working group is presented. The OP provides a detailed flowchart enabling modelling to be transparently and consistently integrated in the assessment. The OP is structured into several phases. These phases combine the standard operating procedures of EFSA with the modelling process. Each phase includes roles and actions to be taken, expected output and the sequence of agreements that need to be made between all partners in the scientific assessment. The development of a dynamic wiki-like web-based glossary for terminology used in modelling is recommended. The glossary, when maintained and continuously peer reviewed by EFSA experts, will support consistent use of terminology in a wide range of outputs. It is concluded that adherence to the OP will improve transparency and acceptability of models in EFSA outputs, and it is recommended to adopt the flowchart as a standard procedure when responding to AHAW mandates.

### KEY WORDS

Models, animal health, operating procedure, standard terminology, glossary, transparency, expert's roles, modelling techniques, model analysis.

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## SUMMARY

The European Food Safety Authority (EFSA) asked the Panel on Animal Health and Welfare to develop a guidance document on Good Practice in Conducting Scientific Assessments in animal health using modelling.

In the past, EFSA has used a range of models to inform opinions on important problems in animal health (AH), including: qualitative models, pathway-based decision tree models, epidemiological transmission or disease spread models, diagnostic test simulations on virtual hosts or host groupings. These models have ranged from simple to complex, employing a combination of scientific, economic, socio-economic, or other types of data.

Modelling was used during the preparation of approximately two thirds of past AH mandates (22/31). The use of modelling in this work is logical, providing a structured representation of our knowledge about the 'real world' underpinning each animal health problem. There is strong interest in the development of a guidance document to integrate modelling efforts into the routine work of EFSA working groups.

In this document, we present an 'operating procedure' (OP) for the use of modelling within an AH working group, tailored to support animal health decisions or to inform scientific risk or benefit assessments. A detailed procedure is presented, providing the chair and other members of a WG with a flowchart that lists the actions to be taken and the decisions to be made, to enable modelling to be transparently and consistently integrated, and objectives achieved.

The OP includes six main phases, which include the initial receipt of the mandate, the development of a strategic work plan, the implementation of the work plan, and the reporting for final adoption of the resulting opinion. Each phase includes actions to be taken, the contributing actors, the expected output and the relevant approval stages (i.e. sequence of agreements that need to be made between all partners in the steps towards a final scientific assessment). The OP highlights the points when agreement has to be achieved within the working group on key methodological issues. Therefore, within the OP relevant decision points are scheduled.

There is currently no standard inter-disciplinary glossary of terminology for modelling. The report recommends the development of a dynamic wiki-like web-based glossary, to be maintained and continuously peer reviewed by EFSA experts. This resource is recommended to support consistent use of terminology by AH opinion, at least to be consistent within the Panel and preferably across all EFSA outputs.

In conclusion, adherence to the OP will improve transparency and acceptability of models in EFSA outputs. The Panel recommends adoption of the flowchart in this report as a standard procedure for use when responding in an AHAW mandate.

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## **BACKGROUND AS PROVIDED BY EFSA**

During the process of assessing a potential risk for animal health, the use of models can be a prerequisite where mental simulation is not able to represent multiple causal links within a system. Models can help experts from different fields to interact and use all the available scientific evidence in order to answer with best confidence the risk management question. Models present a reflection of our understanding of the 'real world' and allow explaining or predicting effects.

Different types of models exist and different approaches can be used to categorise models, one being to group them into qualitative and quantitative models, and their roles in a scientific assessment process will vary according to the circumstances.

During scientific assessments, however, the danger may exist that good practice is overlooked whilst applying models under time pressure. Potential hazards to good modelling practice may be poor communication among subject experts and modelling experts, which may lead to poor understanding of the objectives for the modelling or its role in the report.

Considering the above, the aim of this mandate is to produce guidelines for the use of mathematical and statistical models to be provided to chairs and members of AHAW Working Groups (WG) as a support while conducting scientific assessments in animal health during their specific tasks and mandates. The goal is that models should be well-integrated into the scientific work and reflect the intention of the mandate, input of parameters into models and integration of model outcomes into the report.

## **TERMS OF REFERENCE AS PROVIDED BY EFSA**

1. A glossary should be created and definitions should be provided in order to establish a standard terminology for the use of mathematical and statistical models.
2. Description of the main types of models, including usefulness and limitations is needed.
3. A set of criteria or questions to guide a WG through the process should be developed, starting by the decision of using a model or not, choice of model and the possible objectives and roles of a model and recommended processes for model verification and validation.
4. Procedural guidelines for the proper integration of modelling into WG standard operational procedures should be developed. This may include effective communication among WG members and risk managers, common understanding of objectives and the role of the model in the report, as well as guidelines on the role of the subject and modelling experts within the WG.

## ASSESSMENT

### 1. Introduction

Models in general are a reflection of our understanding of the ‘real world’. The type of model used in a specific situation is determined by the purpose of the task, and by the availability and type of data, and often also by the available expertise and resources.

A model can be developed for one or several reasons including simplification of complexity, synthesis, optimisation, analysis, explanation, assessment, prediction, and simulation of complex systems. Considering these broad possible uses, models can assist:

- where multiple causal links within a system cannot be adequately represented by mental simulation (Lempert et al., 2003),
- when structuring available information or hypotheses about potential causal processes,
- in appropriately integrating available scientific evidence, and
- in explaining or predicting effects.

Hence, models (i.e. “modelling”) are likely to be at the core of the scientific assessment.

To assess the role of modelling in past EFSA AH opinions, a procurement was launched to systematically review the application of quantitative modelling in these documents. It was found that 21 out of the 31 used some kind of model and 12 included a quantitative assessment applying in total 21 different modelling tools.

Decisions on the development of new or use of existing models for a specific mandate has to be an essential element of the planning of the scientific assessment process. Experience with previous EFSA mandates has demonstrated some of the challenges faced when models are used as part of the scientific assessment. As a consequence of communication problems within the Working Group (WG) and beyond, some models have not been optimally integrated into the resulting WG report.

The main causes of communication problems between subject and modelling experts were (a) the unclear reasons for selecting different model types to deal with apparently similar risk questions, (b) a lack of understanding of the model development process by those not directly involved, (c) insufficient communication among all those involved in scientific assessment process (risk modeller, WG, Panel members, and requesting party), (d) a lack of documentation about the model structure, (e) the time constraints, and (f) lack of transparency in relation to decisions taken with respect to the modelling process. Consequently, discussions about the objective and purpose of the modelling, and of the appropriateness of selected tools and resulting outcomes have often only been held during the final phase of scientific assessment process, when adjustments to the modelling process is no longer possible.

The overall aim of this mandate therefore is to produce guidelines to chairs and members of AHAW WGs for the use of models in support of scientific assessments in animal health. The objective is to establish a structured process that results in models which are:

- more transparent,
- accepted by the majority of stakeholders,
- directly related to the scientific work,

- produced in a timely fashion, and
- consistent with the Terms of Reference laid out in the Mandate.

An enormous amount of literature is available on the topic of modelling (e.g. Scott and Smith, 1994; Mollison et al., 1995; Grenfell and Dobson, 1995; Hudson et al., 2002; Grimm and Railsback, 2005). It would be beyond the scope of this report to cover all the technical aspects of any modelling that could be useful for addressing future mandates. Therefore it was decided to include only a rather general description of main model types including their usefulness and limitations, as an Appendix - A (thereby specifically addressing ToR item 2).

The use of (formalistic) decision trees as a guide during model selection (part of ToR item 3) was not recommended. It was recognised that such a decision tree would (a) never completely reflect the scope of existing models, (b) not be agreeable to all modelling experts, and – most importantly - (c) reduce the flexibility of future WGs during the selection of model(s) that would be fit for purpose in achieving the specific objective. Often, there are several approaches that might be suitable when addressing a particular mandate (Philips et al., 2004).

The core of this report addresses items 3 and 4 of the ToR. It is comprised of a flowchart laying out the process of (a) deciding whether a model is needed early during acceptance and clarification of a given mandate, (b) assuring that all partners agree on the objective and scope before starting the modelling process and (c) establishing sufficient communication and feedback loops within the WG and between WG, Panel, Secretariat and Commission during the scientific assessment. This flowchart is annotated with explanations and accompanied by a short general glossary of technical terms used in mathematical and statistical modelling (ToR item 1) to establish a common level of understanding of the relevant terminology.

## **2. Standard terminology for the use of mathematical and statistical models**

For the report, the definition of a “model” includes a wide range of approaches from conceptual models (Dresner, 2008; Thulke and Grimm, 2009; i.e. verbal description or graphical representation of possible structures and relationships), to complex mathematical implementations (translations) of such conceptual models (i.e. computational models). The conceptual modelling is based on concepts and knowledge arranged to represent the processes and interaction in a disease-host-management problem explored without using technical tools, e.g. by mental simulation according to Lempert et al. (2003). The computational modelling refers to construction of technical tools (e.g. from semantic logical axioms, scoring-systems, semi-quantitative flow-diagrams, mathematical equations, or numerically simulated dynamic systems). Appendix A identifies characteristics of computational models that may enhance communication of a particular model in use. Moreover, the set of standard terms referring to the use of mathematical and statistical models was collated from previous AHAW documents.

While identifying standard terminology, a recurrent problem of the absence of universally agreed definitions in risk or benefit assessment terminology was faced. With the exception of some instances e.g. the OIE handbook on Import risk analysis (OIE, 2004) and some of the EFSA opinions, glossaries containing definitions in risk assessment for animal health are rare. One reason might be that the terms used in scientific assessments can vary between different disciplines such as “risk” in animal health and quantitative microbiology. This might explain why glossaries are rarely included in textbooks on quantitative scientific assessment. Further in qualitative risk and benefit assessment, the interpretation of the verbal grading of levels of occurrence and consequences may vary among different assessments.



## 2.1. Procedure followed to select the preliminary list of terms and definitions from previous AHAW opinions

In order to reply to the first ToR, it was decided to search for the relevant terms and respective definitions used in previous AHAW opinions and reports dealing with animal health issues. A total of 31 opinions have been analysed for terms related to risk assessment and modelling. The following terms were searched at the beginning: risk, assess, model, statistic, probability, prevalence, and epidemiology. An Excel table was developed with the terms found, the definition provided or the text related and the location in the document. Some terms were found in the opinions' glossary, some were retrieved from the text. A reference number was given to each term/definition. Experts were asked to evaluate these terms and the definitions provided and to classify them using the following criteria:

<b>G</b>	Generic	in context of modelling
<b>S</b>	Specific	in context of modelling
<b>NR</b>	Not relevant	in context of modelling
<b>D</b>	To be discussed	important concept for risk communication (to be included e.g. as recommendation)

It was decided to include in the glossary only those terms that were classified as "Generic" (G). Additional terms with definitions were included according to the expert's knowledge, e.g. if used in the current guidance. Terms and definition were provided with a source reference if the definition was cited without modifications from that reference. All the other definitions were elaborated and agreed by the experts (see Appendix B). Because the glossary will not be exhaustive, a wiki-based approach was recommended for an EFSA glossary on standard terminology for the use of mathematical and statistical models.

## 2.2. Proposal for a harmonised terminology using a wiki-based Glossary

Although there are some generally applicable terms in modelling, their precise interpretation may vary slightly according to the discipline or context of a specific scientific assessment. One option has been to define terms for each particular EFSA report/opinion. This, however, leads to an unstructured assemblage of relevant terms and concurrent definitions of the same term.

An electronic glossary is preferable, providing a dynamic approach to account for different disciplines, alternative modes of definition, and the evolution of methods, while also maintaining a general comprehension of the terms related to modelling or risk and benefit assessment. Such a dynamic glossary would facilitate the process of comparing outputs from different assessments e.g. by identifying the differences between different model types. The already existing definitions in the EFSA AHAW opinions as well as the glossary of this guideline could serve as a basis. Compound electronic glossaries, e.g. the "Thesaurus of Terms Used in Microbial Risk Assessment" provided by the USEPA, may enhance later extension (<http://www.epa.gov/waterscience/criteria/humanhealth/microbial/thesaurus/>; last visited Nov-12-2009).

The recommended dynamic glossary should be a central internal repository of EFSA containing standard terminology for the use of mathematical and statistical models in risk and benefit assessments. The access to the glossary should be limited to EFSA and its WGs. The formalities of updating the terminology should be specified, e.g. necessary expertise to certainly author definitions might be an issue.

The internally available compendium of agreed terms is recommended to be used as follows: (a) a self sustaining glossary is still required for each report but the general glossary should be considered as first source when definitions are provided, (b) if an exiting definition is found to need improvement, the WG can recommend an update.



As consequence, definitions used in EFSA communications would be consistent at least within the Panel and preferably should across all EFSA outputs.

### 3. Model characterisation, model selection and model transparency

#### 3.1. Model characterisation

Models can be classified according to different criteria. These criteria indicate whether a certain feature is present in the model. Typical examples are: quantitative vs. qualitative; analytic vs. simulation; complex vs. abstract; dynamic vs. static, strategic vs. tactical (Holling, 1966; May, 1973); top-down vs. bottom-up (Grimm and Railsback, 2005); associative vs. process (King and Soskoline, 1988); empirical vs. explanatory (Thrusfield, 2005); non-spatial vs. spatially implicit vs. spatially explicit; frequentist vs. Bayesian.

These approaches of categorising modelling approaches are often seen as competing or mutually exclusive. This can lead to non-productive discussions over which approach is right or wrong (Grimm and Railsback, 2005). Similarly, one might discuss whether a plumber should use a spanner or a wrench before starting work to stop a leak from a broken water-tap. There may not be a clear demarcation between different model classes, noting as an example that scoring systems during qualitative modelling can also be applied during quantitative modelling.

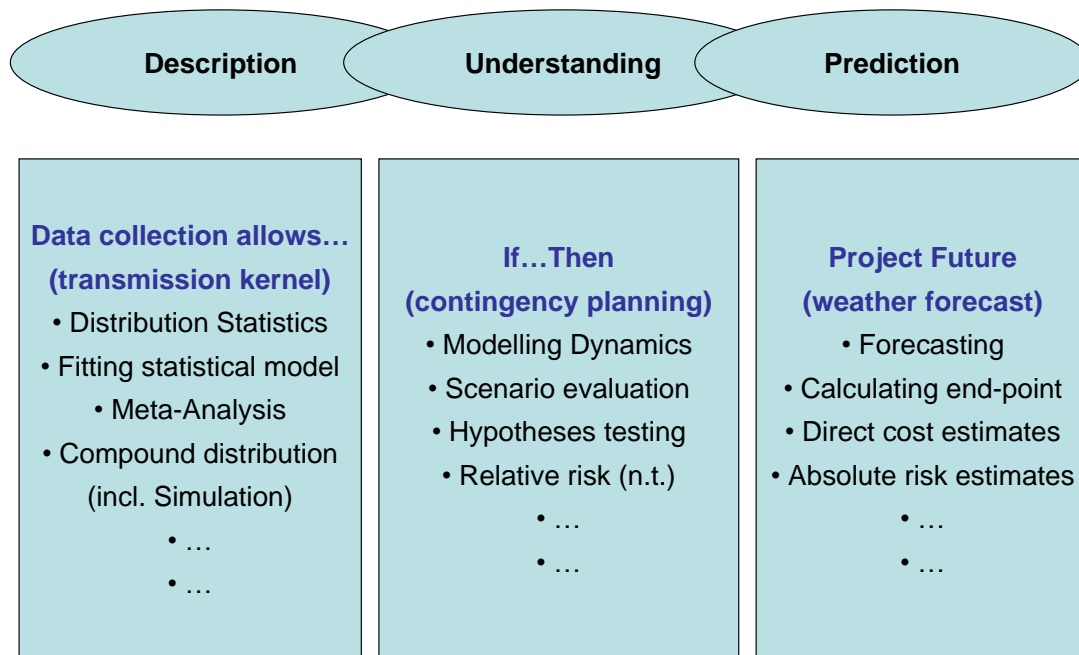
According to the scientific review done through the procurement (published in annex to this guidance), the previous EFSA AH mandates show that:

- Mandates, some with relatively similar terms of reference, differ in the type of modelling techniques that were used,
- Stochastic decision trees, constructed from conceptual pathways, were the most-frequently used modelling approach,
- Heterogeneous methods were applied to answer questions on specification of diagnostic test characteristics, and
- The spread or the transmission of diseases was seldom asked to be modelled.

The exhaustive model characterisation will assist in communicating the particular modelling approach adopted. For a selected model, the classification of modelling technique (Appendix A, Chapter 1) and the methods of analysing the model (Appendix A, Chapter 2) should be specified in the report to enhance transparency in communication.

#### 3.2. Model selection

The specific objective or purpose of a model-based scientific assessment will guide whether a particular modelling approach will be suitable (Starfield et al., 1990; Roughgarden, 1996; Philips et al., 2004; Grimm and Railsback, 2005). Three general objectives have been described in the literature (Figure 1). The purpose of modelling either focuses on more comprehensive **description** of collected data or aims at a systemic **understanding**, or the **prediction** of future events (Hall and DeAngelis, 1985).



Note: Overlapping ellipses symbolise potentially non distinct purposes of practical models

**Figure 1:** Identified purposes of modelling with typical examples

The purpose of models made for **description** is to clearly and systematically extract information from available data. It is important to gain an understanding of data availability, and of their inherent content and uncertainty. Models applied for descriptive purposes can provide important clues for explaining relationships. The purpose might relate naturally to the concept of “data-driven” modelling. The outcome of descriptive models may be hypotheses, which can then be challenged if new data become available.

The second purpose aims at improving our **understanding** of a system. The modelling can result in comparisons, and show variability in outcomes given different assumptions. Accuracy is often a less important issue when modelling relative or worst case scenarios in order to aid decision making. The complexity of a system and its internal relationships can generate emergent findings, and then lead to improved system understanding. This purpose can be related to the concept of “knowledge-driven” modelling.

The last group deals with **prediction/forecasting** of future consequences in the absence of data. Models intended for predictive purposes often attempt to mimic nature in great detail, leading to so-called “naive realism” (Grimm and Railsback, 2005). High accuracy, high predictive value and minimal uncertainty are desired but on the other hand unpredictable changes can have an impact on the precision of the forecast. This model category can be associated with both “data- and knowledge-driven” modelling.

The three categories reflect differences in the expected outcome of a modelling procedure. However, as the overlapping ellipses in Figure 1 indicate, in practice objectives of modelling reflect smooth transitions between the identified purposes. According to our observations in animal health, models made for description purposes are more frequently applied than those made for understanding or even prediction purposes.

### 3.3. Modelling process

The usefulness of a model can be enhanced by transparent and comprehensive communication of model structure, assumptions and outputs. Recent hierarchical schemes of model integration in

decision making outline the sequence of steps in a modelling process (e.g. Schmolke et al., unpublished manuscript). The process can be divided into three groups of activities that need to be completed in order to produce a transparent and comprehensive model:

- Model design & model formulation
- Model implementation & model evaluation
- Model application & output communication.

Correspondingly, the associated decisions and outcomes have to be documented along with the procedural steps to allow retrospective justification, the communication to external participants as well as guidance for methodological reporting.

### **3.3.1. Model design & development**

This activity comprises of two elements: a) the formulation of objectives to be addressed by the modelling, and b) the description of the model design.

The formulated objective, e.g. an identified risk question, is needed to focus the discussion amongst participants. Availability of data/information about the system to be modelled will be assessed, e.g. from systematic literature reviews, as described in the EFSA guidance document ‘Application of systematic review methodology to food and feed safety assessments to support decision making (Question No EFSA-Q-2008-717). Agreement needs to be reached amongst participants about what represents acceptable model outputs. A key question will be how the model output eventually will inform the conclusions expressed in the scientific opinion. Participants involved in the modelling process need to be made aware that the formulation of the objectives and data review can be one of the most time consuming steps in the whole modelling process.

The description of the model design refers to the joint specification of the conceptual model (i.e. verbal and graphical description). The conceptual model provides the basis for the model development process (Pascual et al., 2003; Philips et al., 2004). Based on this, the model type and its overall complexity can be justified considering available resources and time-lines. Here, the participants in the modelling process identify all important simplifying assumptions. The relationship between the model design and the model objectives needs to be documented. Written documentation should be provided at this stage because it will be essential for transparency and for communication with reviewers, Panel members, or requesting party.

### **3.3.2. Model implementation & model evaluation**

This activity comprises of two elements: a) model implementation, parameterization, and calibration; and b) model analysis and evaluation.

Model implementation refers to the physical realisation of the technical model. This is a technical task to be completed by a modelling expert. Modelling experts will use a variety of methods to translate a particular conceptual model into a formal mathematical representation, which ranges from functional equations to one-by-one sequences of conditional rules implemented in computer software. To support transparency and comprehensiveness, all model parameters, including their units, data source (e.g., own experiments, literature, expert estimations), and their variability/uncertainty should be documented. The technical component of model implementations includes qualitative and quantitative calibration of the model. All participants in the process need to be made aware that they can review any documentation associated with this step.

Model evaluation refers to a systematic technical analysis of an implemented model. This analysis does not target the resulting outcome of the modelling exercise but the detailed knowledge about the model and its properties. Accordingly, the analysis for a model evaluation can involve (Schmolke et al., 2009):

- Verification: to test whether the model is working according to its specification;
- Uncertainty analysis: to investigate the effects of lack of knowledge and other potential weak sources contributing to the model (e.g., the “uncertainty” associated with model parameter values, or model structure), essential for the assessment of the reliability of the model-based findings;
- Validation: to compare model output or output of sub-models with independent field data to strengthen confidence in usefulness of model for the specified problem;
- Peer review: Review of the model (including questions, conceptual model, and model evaluation) by a third party (not included in the modelling exercise) to increase confidence in model.

The documented outcome of the model evaluation activity provides the basis to reach acceptance of the implemented model by all participants.

### 3.3.3. Model application & communication

Once a model is accepted by the participants in the modelling process, it will be applied to produce outputs relevant to the objective of the modelling exercise. This activity comprises of two elements: a) model application; and b) communication of model output.

The application of the model generates output that lead to findings and recommendations. The modelling expert has to develop an appropriate pathway to analyse the model. Choosing a method of analysis still allows for some flexibility (although narrowed down by the existing model) to account for available technical resources and the agreed time horizon. Together with generating model output the analysis might include:

- Sensitivity analysis: to measure the effect of changes in input values or assumptions on a model's output; when conducted in combination with uncertainty analysis it allows a model user to be more informed about the confidence that can be placed in model-based findings (Pascual et al., 2003);
- Robustness analysis: to consider the impact on model output (e.g. estimates, scenario ranking, relative risk level) if changing certain structural aspects of the model;
- Threshold analysis: to specify the range of uncertain assumptions or parameters to which critical findings like breakpoints, thresholds and other quantitative or qualitative statements do not alter.

The communication of the output refers to the transparent and comprehensive explanation of model output based on the conceptual model and already demonstrated model properties. The communication enables the check whether initial questions could be answered. The communication facilitates the identification of findings and scientific conclusions as outcome of the modelling.

The next chapter will describe the recommended operating procedure for a WG in relation to the three stages of the modelling process. The resulting guidance will reflect the activities particularly for situations where the assessment requires the application of a modelling.

#### **4. Procedural guidelines for appropriate integration of modelling into WG standard operating procedure.**

##### **4.1. The roles of subject and modelling experts within the WG**

The roles of WG experts in the context of the modelling process need to be clearly defined. WG members may have one of two roles with regard to their responsibilities, particularly concerning the type of contributions to the draft report:

- Subject experts provide the scientific foundation for the problem to be addressed and identify the relevant scientific literature and data sources. If technical modelling is advised, subject experts provide scientific guidance and information for the development of the technical model. Based on their subject knowledge they support the modelling experts by putting the relevant information into a logical framework appropriate for addressing the mandate. This includes an identification of assumptions, limitations, and uncertainties, such as expert opinion as expressed in a semi-quantitative or quantitative manner. They should validate the output of models and derived findings in the light of their knowledge and experience. Subject experts will be responsible for ensuring state-of-art science with regard to the subject matter.
- Modelling experts select an appropriate modelling approach, which requires an understanding of the subject issues (with the support from the subject experts). Modelling experts are responsible for communicating their requirements to the WG (data, expert opinion, working time). This must be done in a timely and transparent manner to allow model verification and validation before application of the model in the assessment process. Modelling experts will be responsible for ensuring state-of-the-art with respect to the modelling techniques.

Table 1 specifies responsibilities for each of these two roles.

**Table 1:** Responsibilities of the subject and modelling expert(s)

<b>Responsibilities of the subject expert(s)</b>	<b>Responsibilities of the modelling expert(s)</b>
Review the mandate and determine the required relevant scientific literature and data sources;	Review the mandate and determine relevant needs for the type of model and its requirements
Contribute to laying out the conceptual model within the framework of the objectives of the ToRs	Contribute to laying out the conceptual model within the framework of the objectives of the ToRs
Determine the scientific soundness including its biological aspects of the proposed modelling approach(es) and their assumptions	Determine the relevant modelling options, considering time-frame, data and available resources; propose a structured model plan with required data.
Assess the reliability of the data sources and the quality of data;	Assess the feasibility of the intended modelling;
Assess the reliability of the practical model implementation	Provide proper implementation of the model tool
Assure transparency of the modelling process including reviewing the validity of assumptions, limitations and potential uncertainty together with the model experts;	Assure transparency of the modelling process including documentation of the model that identifies to the subject experts the underlying assumptions, limitations and potential uncertainty of the expected model output;
Provide scientific guidance and information for the justification of the model within the framework of the objectives of the TOR;	Provide sufficient evaluation of the model to demonstrate consistency with scientific guidance and information (e.g. correctness and validity) within the framework of the objectives of the TOR ;
Assess the scientific validity of the model output	Apply the model to answer the objectives
Review and assess critically the practical relevance of the model outputs aiming to derive sound findings as outcome from the modelling;	Present, explain, and justify the model output aiming for transparent communication of technical details and respond to questions from the subject experts.
Draft model findings and conclusions for the report	Draft final model description and model output for the report.
Being the advocate in promoting to the Panel members and others the scientific findings generated by the modelling process.	Confirm the conclusions and recommendation of the report derived from the model output.

#### 4.2. Operating Procedure

The recommended operating procedure for guiding a WG's response to a mandate has been formulated based on the combination of the EFSA SOP and personal experiences of experts as member of previous WGs. In the following the operating procedure is documented along sequential stages of a WGs work together with the required actions and expected outcomes. The stages are presented in Flowchart 1. The operating procedure was partitioned into 6 main phases. Each of the phases may comprise a series of steps. Moreover, within each step of the procedural sequence the reader's attention is called to the particular needs for appropriate integration of the modelling process (see Chapter 3.3). Agreements and final decisions are highlighted. And, involved participants and required communication between these are emphasised. Producing a decision tree to uniquely select a particular modelling approach, however, is not intended by the operating procedure (see Chapter 3).

The six phases of the recommended operating procedure are:

1. Acceptance and first clarification of the mandate with the Commission
2. Outlining the approach in response to the mandate
3. Acceptance of the modelling approach
4. Implementation of the working plan proposed in response to the mandate

5. Transversal meeting with the Panel
6. Acceptance of the “output” of the scientific assessment

The procedure is the same for self-mandates and Commission mandates, although the involvement of Commission in the former is informative and consultative in the latter.



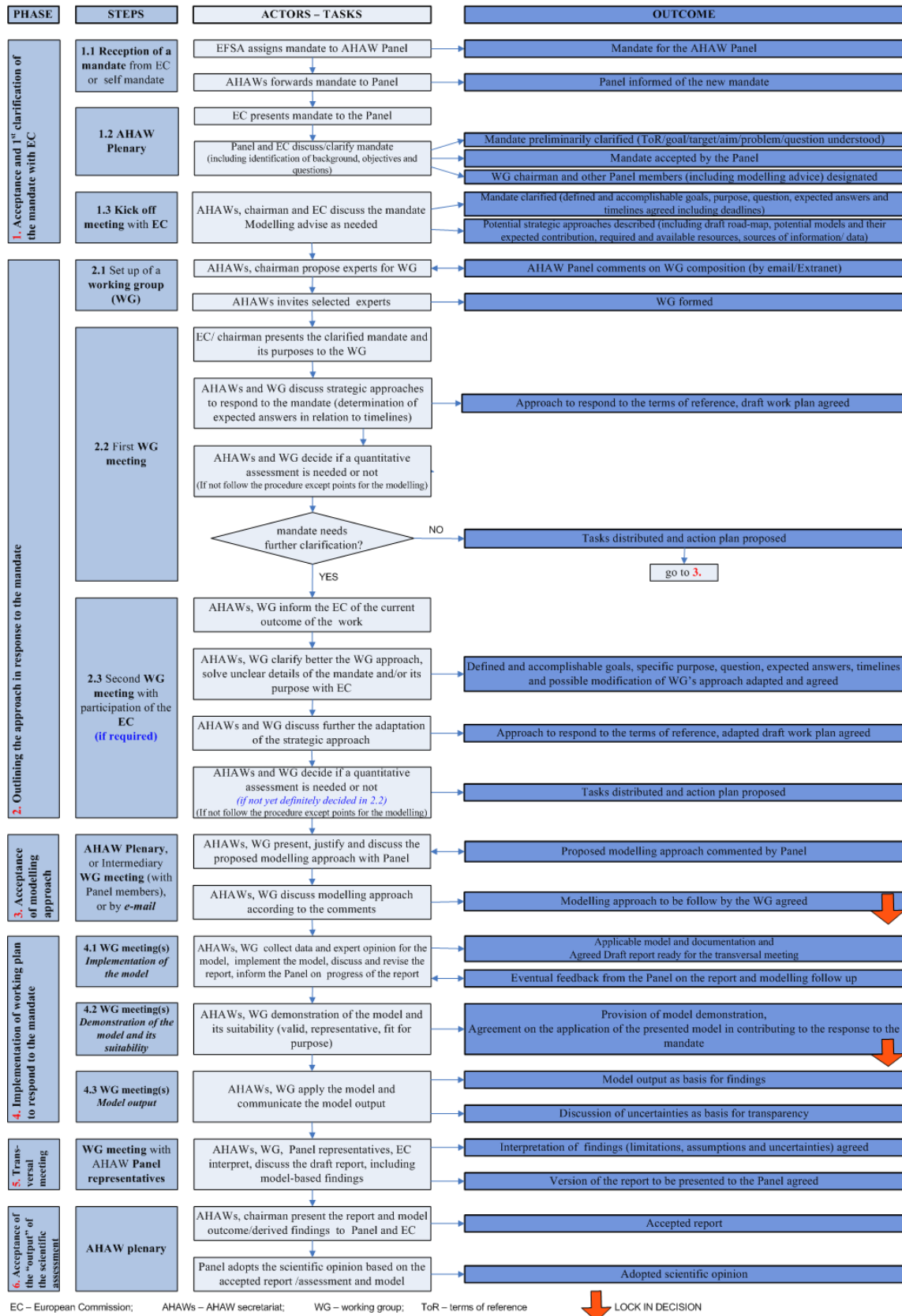


Figure 2: Procedural sequence to integrate modelling in the elaboration of risk assessments on animal health issues

## Phase 1: Acceptance and first clarification of the mandate with the Commission

Within this first phase, the animal health related background for addressing a specific mandate is presented, discussed and clarified within the AHAW Panel. If applicable, possible relationships with existing legislation used by risk managers are considered.

Step 1.2: If the AHAW Panel accepts the mandate, it subsequently selects an appropriate chairman. Additionally, the Panel assures modelling advice as needed to assist the discussions in the consecutive step, e.g. with the requesting party, tailored to clarify whether the achievement of certain objectives may be enhanced by a modelling study, and what realistic expectations are with regards to technical limitations or required resources.

Step 1.3: During the kick off meeting, the experts together with the AHAW secretariat and Commission representative draft a study plan for possible approaches. The study plan will identify possible questions where a model should be used; specify required expertise, data, and resources as well as time lines. Each Term of Reference (ToR) should be explicitly addressed.

The outcome of phase 1 is a **draft study plan** that proposes a strategy and has reached consensus among all participants. If a model in the technical sense is considered to address any of the ToRs, then the expected contribution(s) of this model to answer the ToRs should be documented. The resources in terms of time, data, methods and expertise, which are deemed necessary to implement the model, should be specified.

## Phase 2: Outlining the approach in response to the mandate

In phase 2, the working group members (experts) are invited, based on the requirements identified in the draft study plan. They review the mandate and the proposed strategy and define the roles and responsibilities of the respective WG members. The WG develops a strategic work plan from the draft study plan of phase 1. It is important that the strategic work plan is concise, clear, target-oriented and free from technical jargon which may compromise its readability.

Step 2.2: If the strategic work plan incorporates the use of modelling, then the WG has to formulate the objectives of the modelling (see 3.3.1.a) and to develop a conceptual representation of the model (see 3.3.1.b) that allows the modelling expert to propose a modelling approach (Pascual et al., 2003). The conceptual model represents structural relationships between all the knowledge the WG identifies relevant to answer those questions addressed by application of modelling. The conceptual model should be developed jointly by subject and model experts. The objectives and the respective conceptual model should be documented in the report, e.g. using flowcharts.

Step 2.3: The second WG meeting will be held with the Commission only if requested. Particularly, if during the first WG meeting unclear or impractical details were identified in the mandate or the draft study-plan, clearance and agreement should be achieved in this step.

The deliverables for phase 2 are an **agreed strategic work** plan that describes the tasks, the action plan, and reports on the WG's decision whether or not a technical model will be used. Without modelling the operating procedure is, however, the same but excluding the actions related to the modelling.

## Phase 3: Acceptance of the modelling approach

In this important feedback phase, the strategic work plan as agreed by the WG is presented to the Commission and finally should be approved by the Panel. After this phase, all partners should be in agreement on the interpretation of the mandate, the terms of reference (ToR), the scientific approach including, if applicable, the preferred modelling approach. The responsibilities of individual experts,

the expected outcomes, potential limitations, and resources (time, external support etc.) required to complete the task should have been accepted.

As the outcome of phase 3, the strategic work plan needs to be approved by all participants. The approval means that all partners are committed to follow the approved strategic work plan and further modifications are not expected. Particularly, Panel members might peer review the approaches foreseen by the WG, to raise their approval. The work plan is now **prepared for implementation** by the WG.

#### **Phase 4: Implementation of work plan proposed in response to the mandate**

In phase 4, the scientific approach including modelling is implemented by the WG, and results are generated. There is an ongoing communication between WG and the Panel members on the progress made. For example, continuous release of a WG progress report might be motivated by early discussions and peer review of the implemented approach by all partners. The review of the modelling may trigger iterative loops of gathering and quality assessment of data. Draft reports including output of the models are made available in the respective extranet workspace to the Panel in order to identify gaps in understanding of the structure, output and interpretation of the model, and to make the process as transparent as possible. If possible, selected Panel members should act as scientific reviewers. The milestone of these phases is the generation of a **report prepared to be presented to the Panel**.

If a technical model belongs to the work plan then phase 4 comprises three different steps related to the implementation, the evaluation and the application of the model (see 3.3.2 + 3.3.3):

**Step 4.1 - Implementation of the model:** This step refers to the technical realisation of the model that translates the conceptual model into mathematics or computer programming (see 3.3.2.a). To address a specific objective, usually, several modelling techniques are applicable. The technical task of model implementation is likely to become the responsibility of modelling experts. Selection of the appropriate technical approach may depend on the particular data structure, accessible expertise, available time-frame, resources and desired precision of model output. The outcome of this task is a functioning technical tool. Model documentation should be produced in parallel with the model implementation and a flowchart, formal or standardised model description (e.g. ODD-protocol) should accompany the model. To practical support the following, the level of model documentation should enable subject experts to conjecture on the model outcome.

**Step 4.2 – Demonstration of model suitability:** This step refers to the model evaluation (see 3.3.2.b). The modelling expert has to evaluate the correctness of the model realisation (verification) and the adequate representation of the underlying conceptual model (validation) and the uncertainty in model behaviour arising from: (a) scenarios, (b) modelling technique and (c) data or parameters.

The outcome of this step is a comprehensive demonstration of the usefulness and trustworthiness of the model. The documentation of the evaluation effort should identify critical assumptions in model structure, uncertain parameters, and secondary model outcomes that were used to validate the model. For transparency the source for model inputs and assumptions should be clearly stated. During the demonstration the WG and other partners need to decide whether the model is fit for purpose, that the model represents the relevant scientific knowledge adequately, and what kind of model(s) has/have been used by relevant sources to address similar problems; what are similarities and differences compared with other models. Documentation of the model and its evaluation should allow for independent reproduction. Particularly, the participants should be aware that technical documentation of the model implementation and of the evaluation steps can be provided by the modelling expert.

The evaluation of the model with successive communication and approval by all partners should be performed before application of the model to the mandate's question. The final goal of step 4.2 is a second approval, which means that all partners are committed to the approved model and further

modifications are not expected. The **model is now ready for application** to contribute to the WG's response to mandate.

Step 4.3 – Model output: As the final main task for the modelling, the tool is applied to the study question (Phase 2). The final model output has to be demonstrated and explained to the WG. The WG will use the resulting model output to derive findings and recommendations. Again, the individual steps of the model analysis should be documented to allow repeatability of the investigations. Model output has to be accompanied by associated uncertainty estimates and sensitivity of model outcomes in relation to uncertain model inputs or particular assumptions. WG, Panel and other partners might check whether the analysis provides a systematic knowledge gain concerning the system; whether the model output is consistent with expectations, and if not, whether deviations could be understood by the model assumptions.

The outcome of the phase will be a set of **justified findings** agreed between subject and modelling experts. It might be considered that although time constraints in practice may argue to weaken the sequential stepping forward through the operating procedure – in practise this should not be the case as already in phase 1 and 2 the approaches proposed should be adjusted to very strict time lines but not vice versa.

### **Phase 5: Transversal meeting with the Panel**

In phase 5, the interpretation of the findings is a matter of discussion and agreement between WG, Panel and other participants. Given agreement, the **draft report can be finalised** for possible acceptance.

The report should contain adequate documentation of the whole modelling e.g. as Annex. Recent standardised model documentation schemes (TCM, Grimm et al., unpublished manuscript) recommend going after the sequence of activities during the modelling process (see Chapter 3.3) when documenting for support in decision making:

- Model objectives, assessment questions, definition of outputs;
- Conceptual model including data presentation: crude data or references to data sources;
- Standardised model description, including the theoretical and empirical basis e.g. computer code of the model, including design concept;
- Assumptions regarding model inputs, ranges, distributions, other;
- Discussion and comparison of alternative model formulations and justification for choices made about model structure;
- Model verification, validation;
- Scenarios presentation: for example in the context of risk assessment one could include the temporal and spatial aspects of the exposure scenarios, the specific hazards addressed, exposed populations, and exposure pathways;
- Applied model analysis with sensitivity and uncertainty analysis.

The transversal deemed to be the final platform for constructive communication of interpretation of findings between WG and Panel. Often findings might be presented as conclusions. The Panel members already had approved the work plan including the model approach and the suitability of the implemented technical model based on the suitability demonstration and justified documentation. In consequence, during the transversal it is not expected to discuss the work plan or the way how

answers to the mandate's questions were achieved. In case, insufficient transparency of working plan implementation during phase 4 should be replaced by action of the Panel to implement regular updates during Panel meetings.

### **Phase 6: Acceptance of the “output” of the scientific assessment**

In this final phase, the report is accepted by the AHAW Panel and subsequently the **scientific opinion adopted**; the latter being the outcome for this phase and the completion of the task.

If the report might not be accepted, the report and model should be returned to the WG for further improvement. The revised report and models need to be presented again at the following Panel plenary.

## CONCLUSIONS AND RECOMMENDATIONS

### CONCLUSIONS

- Models have the potential to play an important role when addressing mandates, given their role in representing multiple causal links within a system, structuring available information, examining hypotheses about potential causal processes, integrating appropriately available scientific evidence, and explaining or predicting effects.
- Agreement among participants about the objectives and conceptual model(s) underpinning the mandate will strengthen decisions as to whether a technical model tool will be needed during the scientific assessment.
- Agreement among participants about the draft study plan and strategic working plan are integral to transparent communication between participants in the assessment process.
- There is a need for early and ongoing involvement and communication among all participants.
- There has been inadequately harmonised terminology in earlier mandates.
- There are many technical and practical terms used in the context of modelling, which makes it impractical to include a full glossary of terms in each report or opinion.
- It is not appropriate to predetermine a decision tree for model type selection.
- Evaluation of models from previous AHAW opinions in AH illustrated that:
  - There have been differences between opinions, some with relatively similar terms of reference, in the type of modelling techniques that were used to respond.
  - Stochastic decision trees analyses, constructed from conceptual pathways, were the most-frequently used modelling approach.
  - The ToR provided, were sometimes quite general, and available primary data, relevant to the requested assessment were often quite sparse.
  - The link between the modelling effort and the final opinion may have suffered from a lack of guidance during integration.
  - The documentation about model application was sometimes not sufficiently transparent to allow rigorous peer review by all participants.
- Guidelines produced for modelling in relation to AH may be helpful to WGs considering animal welfare topics.
- The operating procedure presented in this report was designed so that it can provide guidance to others (outside AHAW) on the development, evaluation and application of models.

### RECOMMENDATIONS

- When addressing mandate questions, it is important that a decision is taken early regarding the use of modelling.

- For each ToR, the use of modelling should be considered based on a conceptual representation.
- The conceptual model for each ToR should be presented in the report to allow judgment, justification and peer-review of any decision made with regard to modelling.
- All participants in a mandate (WG, Panel, and requesting party) should agree on the objectives and be actively and regularly involved in the development of the conceptual model, the strategic working plan, and the derivation of findings (regardless of whether modelling is used or not).
- Terminology should be harmonised to enhance transparency and clarity in assessments where modelling is used.
- A glossary of modelling terms should be established by EFSA, to be maintained by a system administrator and controlled by experts. A specific glossary is required for each report.
- Modelling definitions should be consistent, both for communications within the AHAW Panel, and more broadly. The adoption of these definitions should be explored with international organisations such as OIE and FAO.
- For those mandates where modelling is used, all partners should contribute to the transparent assessment process, as proposed in the operating procedure.
- No stage in the modelling process, apart from the technical implementation of model tools, should be addressed solely to the modelling expert(s).
- All partners should evaluate the output of models and derived findings in the light of their knowledge and experience.
- Standard protocols for reporting should be developed and used when describing models, model outputs and related findings.
- Priority should be given to the establishment of standard reporting protocols for (stochastic) decision tree models, noting that this has been the most commonly used modelling approach in previous AH mandates.
- The proposed operating procedure should be considered in relation to other disciplines within EFSA.



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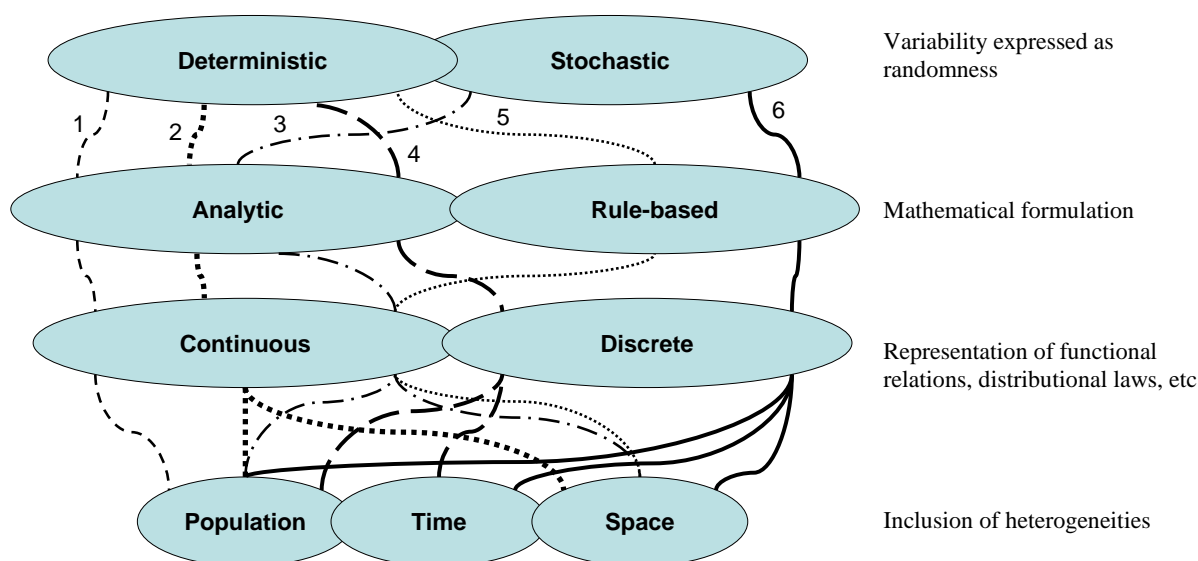
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## APPENDICES

### APPENDIX A - MODEL CHARACTERISATION

#### 1. MODELLING TECHNIQUES

Modelling techniques have defined characteristics. Examples are inclusion of randomness, mathematical formulation, representation of functional relations, distributional laws and inclusion of heterogeneities (entities, temporal, spatial). These basic features do not provide a unique hierarchy but help to identify the technical aspects of a model used (Hurd and Kaneene, 1993). None of these features alone can guide model selection in exclusively one way. Different features can be linked according to the problem the model should address. In the figure below connecting lines show available examples that may combine the respective features within a particular model.



None of the model features exclusively governs the choice of other model features. Numbers and line type identify model examples from research about rabies in foxes: 1- Anderson et al., 1981; 2 - Källén et al., 1985; 3 – Tyul'ko and Kuzmin, 2002; 4 – Garnerin et al., 1986; 5 - Thulke et al., 2004; 6 – Eisinger et al., 2005. (Note: Neither the scheme nor the selection of examples does intend completeness).

**Figure 3:** Representation of various combinations of model characteristics. Sample paths (lines) represent existing models from epidemiological or ecological studies. Horizontally, different forms of the same model feature are shown, overlapping represents possible mixtures or hybrid models.

In the following text the model features are presented. It is obvious that all of them could be combined according to purpose, expertise, time-frame and resources available. The list is not comprehensive.

##### 1.1. Variability expressed as randomness – Deterministic to Stochastic

Whether a model is classified as deterministic or stochastic depends on whether randomness is included in some way. Deterministic modelling is based on the assumptions that an average of some quantity (parameter describing a distribution or dynamic), is relevant and that uncertainty about the “average” can be neglected. Most existing political legislations, at the end, reflect deterministic thoughts. Deterministic models require that model inputs are single-valued, e.g. mean, median or percentiles of known distributions. In some applications, default values are used, which are either derived from data using standard methods or set by expert Panels. It has also been noted that the use

of upper percentiles for a large number of independent model input values ends up in a scenario which has virtually zero probability to occur in the real world (Greiner et al., 2007). Based on deterministic models different scenarios or concepts can be compared and a worst case scenario can be presented. Using “pessimistic” values in deterministic assessments may intentionally or implicitly introduce an element of precaution.

If variability of any input quantity is expected to matter, the model will include some parameters or processes that are modelled in a stochastic way, e.g. by randomly drawing values from a probability distribution, leading to a stochastic (probabilistic) model. Accounting for variability and/or uncertainty may increase confidence in the model outcome. However, this gain of stochastic modelling is offset by less unique outcome that requires interpretation of the joint contribution of variability and uncertainty on the endpoint of the model. For example: the arithmetic mean of a data set with or without deviance descriptors (e.g. confidence limits); and correspondingly the epidemic SIR model with or without randomized infections of spatially distinct individuals that might soften the theoretically sharp threshold value for mass vaccinations (e.g. Anderson et al., 1981 vs. Eisinger et al., 2008). In both examples the first provide the reader with a clear and decisive end-point, but only the second allows judging the strength of the end-point message and a plausible range of outcomes. The purpose of the modelling is the only way to decide which of both is relevant for the assessment.

## 1.2. Mathematical formulation – Analytic to Rule-based

Mathematical formulation is the favourite feature for characterising models, but often inadequate as a good indicator for the right model type for a given problem

Models can be formulated based on equations (e.g. SIR dynamic model with differential equations, or the normal distribution as probability model) or arbitrarily grainy (fuzzy) as sequence of logical rules (e.g. SIR dynamic model with explicit spatial movement of vehicles, daily decisions of farmers and infection depending on numbers of hosts and farm type; or using the empirical distribution as probability model). Examples from epidemiological literature can illustrate selection between the two characteristics (e.g. EFSA, 2009). Categorizing mathematical formulation may be confused with the description of functional relationships that are “continuous versus discrete” (see next point) or the topic of solving a model by an “analytic (closed) solution” or “simulation-based solution” (see subsection Methods of model analysis).

Analytic approaches have the advantage of describing the model in a concise way (in mathematical language e.g., a set of equations). But this simplicity presumes mathematical soundness which means that assumptions have to be agreed and accepted prior to model building. In other words, the dynamics of analytically formulated models are imposed top-down, for instance at the host population level. In the other approach, based on detailed and explicit rules, no assumptions on structural characteristics, functional shapes or characteristics of dynamics are required. In the extreme, everything will be progressively developed in the model. The dynamics of such rule-based models are implemented bottom-up, i.e. from the entities’ behaviour. However, the communication and documentation of such detailed models require a considerable effort, although standard protocols start to emerge (Grimm et al. 2006; Grimm et al. unpublished manuscript). This usually requires an element of translation between the technical jargon used on either side.

Most analytic formulations have well understood properties or dynamic behaviour. Rule based model formulations have usually rather unknown (i.e. emergent) properties or dynamic behaviour. Here, specific methods for verification and validation need to be deployed (e.g. Grimm et al. 2005; Wiegand et al. 2003; Kramer-Schadt et al., 2007).

Since more than one model type may be appropriate and different model types require different skills, experience has shown that the choice of the model depends strongly on the particular expertise of the modeller. Often modellers impose their favourite modelling technique (Schmolke et al., 2009). It may be beneficial to elaborate those identities between different model realisations if the reconcilability



and interpretation of given scientific literature is enhanced. Indeed, techniques do exist to align models from different mathematical formulations to each other, e.g. adding more differential equation to the system, or substituting sets of rules by an aggregated description and thus allowing a certain comparison or transition between analytical and rule based models (Levin and Durrett, 1996; Bolker and Pacala, 1997, 1999; Wilson, 1998; Fahse et al., 1998; Grünbaum, 1998; Picard and Franc, 2001; Law et al., 2003; Sato and Iwasa, 2000; Bolker et al., 2000; Dieckmann and Law, 2000).

### **1.3. Representation of functional relations and/or distributional laws - Continuous to Discrete**

The aspect is used to identify how model entities (Grimm et al., 2006), like random variates or their relation to each other are represented. Model entities can be represented continuous or discrete for example time scale, spatial structure, host population, transmission factors and many others. This model aspect is illustrated by probability distributions of random variables in a model (e.g. birth) with the examples of the normal and the binomial model – the first being continuous and the second discrete. Models also vary according to the use of continuous and discrete functions used to represent outcomes of real world processes (e.g. seasonal birth distribution). The choice of distribution in models often follows the nature of the input data which is being modelled (e.g., count data vs. measurement data) and the corresponding sample statistics.

### **1.4. Inclusion of heterogeneous entities in dynamic models – Population, Time, Space**

Stratification or factor levels in models are used to describe different states of a model entity, for instance all hosts are represented as one population number, several herds or numerous individuals (e.g. population dynamics model or individual-based model). If in epidemiological models, susceptible sub-population or intervention measures change with time the model can incorporate heterogeneous time (e.g. continuous or discrete changes). Studies that take into account spatial patterns as having an impact on for example disease spreading will represent heterogeneous space (e.g. geographic location of herds, habitat maps, patchy or regular grids with units representing changes in space or connectivity among farms by vehicles). The inclusions of these heterogeneous entities characterises a model and all combinations of heterogeneity in spatial, temporal and population units might be used in epidemiological modelling. However, a decision whether or not explicit heterogeneity will matter for the problem at hand has to be made with respect to the particular objective of the modelling.

Heterogeneity might be assessed in the context of the process generating the data. But if reasons for heterogeneity in data are known, this should be reflected by a stratified analysis or incorporation of factor levels.

## **2. METHODS OF MODEL ANALYSIS**

The way a model's output is calculated can be classed at least by two main types (Hurd and Kaneene, 1993): the analytical solution versus simulation-based solution (Fine, 1982). Related concepts feature either or both of these principal approaches. Stepwise analysis may for example use different techniques or even combine their application, e.g. if a model is analysed with simulations but stochastically formulated then techniques of statistics are applied to explain model output.

### **2.1. Analytical analysis**

Analytical analysis depends on mathematical manipulation to explore the relationship between different (dynamic) variables. Ideally, a solution is sought to describe the state of these variables at equilibrium (Hurd and Kaneene, 1993). Most classic epidemiological models employ this approach, which requires sound mathematical skills (Bailey, 1982). The great advantages are the ease of presenting closed-form solutions (e.g. comprised in some functional expressions) and the rigour of evaluation. Closed expressions can lead to the identification of functional relationships among model parameters, which may generate new insights. Examples include the relationship between prevalence

and incidence or the calculation of the basic reproduction number  $R_0$  from the parameters of a SIR model.

## 2.2. Numerical analysis

The numerical analysis concept incorporates algorithmic procedures combined with an analytic solution (today often computer-based routines). Examples include the Newton-Raphson (NR) or expectation-maximization (EM) algorithms for calibrating model parameters in generalised linear models through estimation (GLM). The importance of these algorithms in statistics arises from their use in ML estimation, when the likelihood function and its derivative cannot be written in closed form. The outcome is not necessarily of a closed form – that is a set of equations - and may be presented for instance as a graphic solution. The choice of numerical techniques depends on the complexity of the problem. NR and EM algorithms, for example, depend among others on starting values. The latter is especially an issue if the target function is a function in several model parameters and local maxima (or minima) exist. So-called life-science algorithms such as simulated annealing or genetic algorithms usually overcome the problem of multidimensional, multimodal target functions at the cost of long run-time. All these algorithms are examples of optimisation algorithms and therefore require an objective or target function. For statistical estimation, this is a function in the parameters given the data. In other applications (e.g. optimisation of surveillance sampling), the objective function may reflect utilities such as testing costs, risks and benefits of testing.

## 2.3. Statistical analysis

By statistical analysis the formulated model is fitted (parameters, factors or distributions) to optimise representation of the data. In that sense parameter estimation in statistics might be seen as model calibration using data. The accuracy of model fitting (e.g. in terms of maximum  $R^2$  or AIC value) might be seek with patterns observed on different data (e.g. temporal, spatial), different scales (herd and country or different hierarchical levels (population and individual). Ideally, different patterns are simultaneously considered as quality of model accuracy (Grimm et al., 2005).

### 2.3.1. Frequentist vs. Bayesian analysis

According to the classical, “frequentist” approach in statistical inference, all evidence about a parameter is derived from the data used in the estimation. Common estimation methods in this framework include maximum-likelihood (ML), least-squares, method-of-moments, minimum chi-square to mention a few. Bayesian methods, on the other hand, have in common with ML technique, that all information about a parameter is extracted from the data in form of the so-called likelihood. The latter expresses the probability of the data given a set of model parameter(s).

A particular feature of Bayesian analysis is that the unknown parameter is interpreted as a random quantity and that all existing (or non-existing) knowledge about this quantity can be expressed in terms of a probability density. Therefore, in the Bayesian framework, prior knowledge (the priors) exists about the parameter(s) of interest. Choosing “non-informative” or “flat” priors allows expressing that virtually no prior information exists. For example, the non-informative prior distribution of a prevalence parameter  $p$  may just state that the minimum is 0 and the maximum is 1 and that every value between and including these limits has the same chance to be correct. A statistical distribution reflecting this flat prior is the  $\text{beta}(1,1)$ , which is also equivalent with a continuous uniform distribution  $U(0,1)$ . In the Bayesian framework, prior distributions may be subjective or objective (empirical). An example for the first is to choose a beta prior based on expert opinion (e.g. “The most plausible value for  $p$  is 0.1 and I am 95% sure that  $p$  is less than 0.2”). An example for an empirical prior distribution based on count data such as “ $k$  out of  $n$  were positive” is a  $\text{beta}(k+1, n-k+1)$ . It is important to ensure that the prior is in fact independent of the data.

Bayesian estimation is a process of updating the prior using the likelihood. This process may be simple or computationally complex. In the example given above, the beta prior is said to be conjugate to the binomial likelihood of the data. Therefore, and due to the additive properties of the beta



distribution,  $\text{beta}(k+1, n-k+1)$  can also be interpreted as posterior of the likelihood  $L(k, n)$  and the  $\text{beta}(1, 1)$  prior. In other cases, the update requires iterative algorithms as those implemented in Markov-chain Monte Carlo (MCMC) methods (see A.2.6).

The advantage of frequentist methods is that the potentially controversy about valid prior information is avoided. ML estimators have favourable statistical properties, especially so for large data sets. The advantage of Bayesian methods is that they are applicable even for sparse data, that prior information can be combined with new study data and complex models or estimation of parameters with unknown sampling distributions can be more easily implemented. An additional advantage is the availability of the posterior (non-parametric) distribution of parameter estimates for further analysis.

#### **2.4. Simulation-based analysis**

Simulation-based analysis refers to the procedural solving of models by iterative evaluation of scenarios. Particular difference to numerical approaches is that the solution must not even have a form of a function e.g. when studying several management scenarios for the eradication of a disease. The technique might be used to derive a proxy solution for models that were formulated analytically (see A.1.2) if temporal and/or spatial dimension are made discrete by intervals or spatial segments. The technique may also be helpful for stochastic models. Then multiple simulations (repetitions) of the same model (constant parameters) accumulate to a frequency distribution as solution (this is not equivalent to Monte-Carlo simulations).

#### **2.5. Analysis using graph theory**

The method of analysis explores model properties using descriptors from graph theory (degree, betweenness and centrality). Recently, this analysis is applied to solve network models that reflect e.g. transport structures in animal industry or large-scale networks of transport and trade. The analysis enables the identification of specific structures like central nodes that are high risk with regard to disease spread. This will be relevant to perform exposure assessments in compartmentalised trading systems or to assess consequences after incursion of a disease.

#### **2.6. Monte-Carlo analysis**

Monte-Carlo analysis focuses on the explicit representation of uncertainties within the model outcome and relies on random sampling from distributions describing the ranges of these uncertainties. The technique is often applied to analyse models based on simulations. Usually the solution is derived from multiple analyses of the model with randomised sets of parameter values reflecting the associated uncertainties. Hence with Monte-Carlo techniques, the analysis outcome is again a distribution. The resulting probability distributions are typically non-parametric hence they cannot be described in analytically closed form. Rather the output is described using statistical techniques, e.g. based on moments and percentiles of the resulting distribution.

Monte-Carlo techniques allow functions of random variables being evaluated without need for analytical convolution of probability density functions. Therefore, in probabilistic risk assessments, where highly non-linear functions of random variables need to be considered as outcome functions such techniques are useful.

In Life-sciences the Monte-Carlo approach is used for models constructed with great detail (e.g. agent-based models). Latin-Hypercube sampling (LHS) performed to sample parameter combinations for which the model is solved can be used in combination with a Monte-Carlo approach. More technical, LHS enhances convergence to the specified sampling distributions by drawing values stratified for intervals with sampling weights proportional to the area over the respective intervals, e.g. simple random sampling might become cumbersome if lognormal distributions are involved – due to their heavy tail LHS will quicker represent extreme realisations and thus converge faster to the true distribution.

Often the Monte-Carlo concept is inconsistently called for if model outcome is compared for different sets of scenarios (as already discussed under 2.4.). This, however, is rather a simulation-based analysis as long as for each scenario a constant set of parameters applies.

## APPENDIX B - STANDARD TERMINOLOGY FOR THE USE OF MATHEMATICAL AND STATISTICAL MODELS

**Table 2:** Preliminary list of terms and definitions for the ToR 1 on terminology

<b>Accuracy</b>	<p>Generally, in modelling context accuracy describes the degree of agreement between the observation and the model outcome (e.g. <math>R^2</math>).</p> <p>In specific statistical models, accuracy of the model output in comparison to the observed data is often expressed as a summary value, and the objective in model fitting is to optimise this value. The smaller/larger it is the higher accurate the model is depending on the particular summary value (e.g. <math>\text{Chi}^2</math>, <math>R^2</math>, AIC).</p> <p>In the diagnostic test context, accuracy is defined as the overall (proportion of) agreement between a (new) test result and the true disease status (gold standard) in a sample of individuals.</p>
<b>Assumption</b>	<p>Assumptions, or working hypotheses, are important components of many models. They can be defined as propositions taken for granted. The validity of and therefore results from those models partly depend on these propositions (i.e. assumptions). Assumptions often are found to be the most plausible, reliable, or suitable (but often without formal proof).</p>
<b>Bayes' Theorem</b>	<p>A theorem developed by Thomas Bayes that is the backbone for Bayesian Inference and thus a Bayesian framework. Bayes' Theorem is a simple mathematical formula used for calculating conditional probabilities. The Theorem relates the "direct" probability of a hypothesis conditional on a given body of data, <math>P_E(H)</math>, to the "inverse" probability of the data conditional on the hypothesis, <math>P_H(E)</math>: With that the most general formulation of Bayes' Theorem is provided by: <math>P_E(H) = [P(H)/P(E)] P_H(E)</math></p>
<b>Bayesian framework</b>	<p>Within a Bayesian framework, Bayes' Theorem is used as a method to combine new evidence or observations (data) with prior (to data collection) probability of a certain condition or event into a new (posterior) probability for that condition/ event. This is to be contrasted to the frequentist framework in which the new probability of a condition or event is exclusively derived from the data (and the used model with inherent assumptions).</p>
<b>Classification of risks</b>	<p>The division of risk into classes according to specific criteria of both their probability to occur and their consequence. The classification will depend on the hazard, the risk assessment process as well as the risk management and communication needs.</p>
<b>Closed solving</b>	<p>Method of analysing a model resulting in a "closed solution". A closed-form solution solves a given model in terms of functions and mathematical operations.</p>
<b>Compartmental model</b>	<p>These models describe how materials/ energies/ individual units like animals or herds move between defined compartments (states) of a system on the basis of transition probabilities. One basic assumption is that all entities in a compartment are assumed in an identical status (homogeneous) with regard to the described dynamics.</p>
<b>Compound distribution</b>	<p>A secondary probability distribution specified by a first probability distribution in which one or more parameters that define this primary distribution are not fixed values but follow yet another (second) probability distribution. Compound distributions are sometimes used in stochastic models to describe specific probabilities. (Oxford Dictionary of statistical terms).</p>
<b>Conceptual model</b>	<p>Descriptive representation of a system based on current knowledge as well as on assumptions about its components, their inter-relationships, and system boundaries. Conceptual models often are depicted by visual methods (diagrams) that exhibit assumed causal relationships. They form the basis for further modelling approaches.</p>

<b>Confidence Interval</b>	An interval estimate statistically derived from a sample. The interval estimation is designed to include (capture) an unknown (true) population parameter with a certain level of confidence.
<b>Continuous variable</b>	Quantitative or metric variable measured on a continuous scale. It may take on any value within a given interval, and the meaning of unity does not change along the interval. The interval (valid data range) could be finite or infinite.
<b>Covariate</b>	A secondary variable that can affect the relationship between the dependent variable and other independent variables of primary interest in a model. (Wikipedia)
<b>Data-driven model</b>	Quantitative models where the relationships between the factors are directly determined/estimated from observed data. A simple example of a data-driven model is a linear regression model. Coefficients of the regression equation are identified ("trained") on the basis of the existing data.
<b>Decision tree model</b>	The model translation of a decision tree or risk pathway diagram. Usually applied as unidirectional evaluation of a sequence of alternative (stochastic) events that contribute to the final outcome of the tree (end-point calculation).
<b>Deterministic model</b>	A model (or system) in which no random process is involved in the derivation of future states of the model. Deterministic models thus produce identical outputs (results) for a given unchanged set of input values (starting conditions). (Wikipedia)
<b>Discrete variable</b>	Quantitative or metric variable that takes on selected values (typically equally spaced) within an interval; the interval could be finite or infinite. A qualitative or categorical variable may be converted into a discrete variable if the categories have a meaningful order (ordinal variable).
<b>Dose-response model</b>	A dose-response model describes the likelihood of a specified response resulting from exposure to a specified pathogen or hazard in a specified population, as a function of the dose. The result of such a model described the change in response with changing levels of dose (exposure).
<b>Estimate</b>	<b>Expert knowledge:</b> subjective indication of the value of a parameter based on the information available to the expert including his own "field experience". <b>Statistics:</b> Calculation of the value of an unknown parameter based on observed data from a sample of individual units using statistical functions and assumptions.
<b>Evidence</b>	Includes specific information that is used to demonstrate the truth of an assertion. <b>Scientific evidence</b> is generated through population studies or observations or through experiments and is used to support or reject a hypothesis. <b>Anecdotal evidence</b> is derived from unsystematic individual (case) reports, and is weaker than scientific evidence in supporting or rejecting hypotheses.
<b>Expert opinion</b>	Information on a specific question or the value of a parameter required for a modelling exercise that was provided by one or more experts based on their personal experience, opinion and (often) assumptions. Expert opinion is important in areas where data (for modelling) is needed but not readily available through other sources.
<b>Exploratory data analysis (EDA)</b>	Statistical techniques (mostly graphical) describing the distribution of values within variables, and subsequently exploring relevant relationships between factors or differences between population groups of interest. EDA is frequently used to identify potential research questions.
<b>Exposure assessment</b>	The quantitative and qualitative evaluation of the likelihood of hazards occurring in a given population as a result of exposure.
<b>Generic model</b>	Generalized format of existing models not yet adapted to a specific hazard (e.g. individual pathogen, disease, population, or combination of all). They incorporate standardised relation types, together with the entities or objects that may be related.
<b>Hazard characterization</b>	The qualitative and/or quantitative evaluation of the nature of the adverse effects associated with the hazard.
<b>Hazard identification</b>	The identification of any factor, from birth to end of life, capable of causing adverse effects on a studied subject / population.
<b>Import risk assessment</b>	Formal risk assessment to evaluate the probability of importing a specific hazard into a defined (animal) population or (geographic) region (to be checked with other risk assessment glossaries).

<b>Individual-based model</b>	Model with individuals as basic entity. Individuals differ in their status and exchange information between them or with the environment (e.g. host animals, farms, and free rooming herds). In such models, the history of individually identified units (animals, people) is modelled and thus can be followed.
<b>Input parameter (model)</b>	A factor/ component in a model which is provided with a value/ specification at the beginning of the calculation process (→ output parameter).
<b>Intermediate parameter value</b>	Intermediate output of a stepwise (iterative) model analysis that is necessary for the next analysis step but is not a model result.
<b>Knowledge-driven model</b>	Models where the system relationships, key parameters and their values are predominantly based on a synthesis of existing knowledge from various published and unpublished data sources as well as expert opinion, but not from sample-derived estimation (→ data driven models).
<b>Likelihood</b>	Probability. In statistics often used in the context of estimation, i.e. the “maximum likelihood estimator” as being the estimator of a certain value or model component which gives the highest probability (likelihood) to the observed data given the applied model.
<b>Linear regression model</b>	A <u>regression model</u> assuming a linear functional relationship between dependent and independent variables, i.e. assuming that there is a linear (straight line) relationship between those.
<b>Logistic regression model</b>	A <u>regression model</u> assuming a linear functional relationship between the logit (log odds) of an event probability ( $\ln(p/(1-p))$ ) as dependent variable and the independent variables.
<b>Mathematical model</b>	Models that are formulated (can be written down) by mathematical language.
<b>Meta-analysis</b>	A statistical analysis that combines the results of several studies that have addressed the same research question. As combination may increase statistical power of the estimation, results may be a more accurate reflection of the unknown property than those derived from a single study under one set of conditions. (Oxford dictionary of statistics)
<b>Metapopulation model</b>	The term metapopulation originates from ecology. A <b>meta-population</b> consists of a group of spatially separated populations of the same species that interact at some level. A metapopulation model links multiple sub-populations to represent spatial structures. Linkage of these population might be determined either explicit (e.g. landscape map) or implicit (e.g. intensity value of exchange).
<b>Model</b>	A (simplifying) representation of the essentials (parameters, relations, processes, or mechanisms) of an existing system (or a system to be constructed) which incorporates existing knowledge and/or assumptions about the relationship between all system components in an explicit form that can be investigated by systematic or manipulative experiments.
<b>Model input</b>	Any part of a model which is specified (e.g. by a value/ distribution/ functional relation / mechanistic rule) before model analysis (→ model output).
<b>Model output</b>	<b>General:</b> All output that is generated by the analysis of a model (e.g. qualitative or quantitative values/ distributions/ proportions).
<b>Model prediction</b>	A process where models, based on specific input, are used to forecast (predict) results for yet unobserved (unobservable, new or future) situations (→ predictive model).
<b>Modelling approach</b>	The methods used to construct, validate and analyse the model, including estimation techniques for the model analysis.
<b>Monte Carlo simulation</b>	Iterative technique applies in modelling (with Markov chain Monte Carlo or MCMC sampling as a common example) to estimate the range of possible output (i.e. a distribution) that involves repeatedly drawing random numbers from input (parameter) probability distributions. The technique usually is applied in stochastic models in which the exact parameterisation cannot be taken for granted (substantial uncertainty in input values).
<b>Multivariable model</b>	A model in which several independent (predictor/ risk factor) variables are assessed simultaneously for their relationship to a single dependent (outcome) variable (univariate model), thereby allowing control for confounding relationships between the independent variables.

<b>Multivariate model</b>	A model in which one (univariable) or several (multivariable) independent (predictor/ risk factor) variables are assessed simultaneously for their relationship to two or more dependent (outcome) variables; this relationship is often expressed in the form of matrices.
<b>Output parameter (model)</b>	<b>Output parameter:</b> factor / component in a model for which the final value is derived or estimated during the calculation process (as a function of the model structure and the model input). Consistent use only possible if the output structure is pre-specified and has itself ‘parameters’ to estimate/ evaluate (→ output value). <b>Output value:</b> qualitative or quantitative value of designated output parameters at the end of the model analysis (resp. a model run).
<b>Parameter</b>	Quantity that defines certain characteristics of a model element, system or function. Parameters can take a range of value from qualitative classes via single values to probability distributions, depending on their role in a model (→ input, intermediate or output parameter).
<b>Point estimate</b>	The single-valued result of the application of a point estimator to the data. In statistical models, this is often provided by the maximum likelihood estimation (MLE) of the (unknown) true population parameter. Point estimation usually is accompanied by its (→) confidence interval, i.e. the calculation of an interval estimate from the same data.
<b>Population dynamics model</b>	A model that represents dynamic processes of a system on the level of population changes, i.e. proportions of populations or sub-populations that change their “state”. From these models population averages can be derived, but no individuals fate can be “simulated” (→ individual based model).
<b>Prediction Interval</b>	An interval estimate in which future observations will fall, with a certain probability (e.g. 95%), given what has already been observed. Prediction intervals are often used in regression analysis.
<b>Predictive model</b>	→ Model prediction
<b>Probability distribution</b>	A model of occurrence of possible values (probabilities) of a random variable. There are theoretic probability distributions with defined shape (e.g. normal, exponential, binomial) and empirical distributions reflecting raw data on occurrence that have no defined shape.
<b>p-value</b>	The probability that a sample characteristic (e.g. difference between mean of two groups) might have been observed by chance, given that the null hypothesis (of no difference) is true in the population from which the sample was drawn. The p-value can range from 1 to 0. By specifying a threshold level of significance (often 0.05) sample characteristics (difference between means) are judged statistically significant (“not plausible by chance”) if the p-value is smaller than the threshold.
<b>Qualitative Risk Assessment</b>	An assessment that generates an estimate of categorical nature or based on an ordinal scoring system. The outcome of such an assessment is a classification of output into descriptive categories.
<b>Quantitative Risk Assessment</b>	An assessment that generates an estimate of a numerical nature directly tied to a measurement or calculation. Depending on the type of model tool used, an indication of the associated uncertainties - expressed either as extreme values, → confidence intervals or → prediction intervals are needed.
<b>Regression model</b>	A mathematical model that describes the relationship between an dependent (outcome) variable (y) and one or more independent (explanatory/predictor/risk factor) variables (x1, x2, x3 ...) using a specific functional form of the relation (e.g. → linear, → logistic, exponential).
<b>Relative risk</b>	The comparison of risk estimates from two samples or risk scenarios by dividing the two risks, i.e. expressing on risk as a relative value to the other (often denoted as baseline) risk value. Possible value range is 0 to infinity, with a relative risk of 1 indicating that the two compared risks were identical.
<b>Risk</b>	Epidemiology: Likelihood (probability) of a certain event (outcome) to occur in a cohort, where the event usually is considered “negative”. Risk assessment: A function of a probability of an adverse health effect and the severity of that effect, consequential to a hazard. General: subjective summary for a hazard, its probability of occurrence and the



	(negative) consequence.
<b>Risk Analysis</b>	A formal process consisting of three components: risk assessment, risk management and risk communication.
<b>Risk Assessments</b>	A systematic approach to assess the effect of an exposure to a hazard/stressor. The approach formally includes hazard identification, characterisation and consequences assessment. These steps are implemented in the risk assessment model, and respective procedural guidelines are available. (definition OIE / Codex Alimentarius).
<b>Risk characterization</b>	Element of an → Risk Assessment, determining/ describing the effect of an hazard qualitative or quantitative, including attendant uncertainties about the occurrence and severity of known or potential adverse effects on a given population.
<b>Risk factor</b>	A factor that influences the likelihood for the disease or health event to occur. Risk factors are often identified through epidemiological studies and related risk factor analyses (such as uni- and multivariable regression models).
<b>Risk mapping</b>	Diagrammed technique to prioritize risks according to frequency (alternatively likelihood) and severity (alternatively significance). For each risk, the severity is plotted on one axis and the frequency is plotted on the other axis. Geographical representation of spatial variation in risk.
<b>Risk pathway</b>	A (conceptual) representation that illustrates the sequential events of risks considered to be leading to the risk outcome. The risk pathway will serve as guidance for data collection, logical deductions, and any quantification required in the subsequent risk assessment e.g. using → decision tree models.
<b>Rule-based model</b>	Model that is constructed from simple and generic rules that reflect expert knowledge as close as possible. The method is purposeful if limitations due to structural assumptions have to be avoided and usually results in more complex models.
<b>Scenario</b>	A certain combination of input parameter values that is used in a specific model run. When there is uncertainty about the value of a specific input parameter, a range is considered (selected), and (randomly) chosen representatives are tested in separate model runs (“scenarios”). Alternatively, different hypotheses about the modelled system (control options) might lead to specific parameterisation of the model each reflecting a scenario.
<b>Scenario analysis</b>	Assessment of the model output depending on specified scenarios. Often the analysis includes at least a worst case scenario, i.e. with values selected for important input parameters that are assumed to (all) be at the maximum likely negative (adverse in the risk context) value.
<b>SEIR model</b>	Compartment model that incorporating four possible “states” (compartments) in which subjects can be found: S=Susceptible, E=latently infected but not (yet) infectious; I= infectious; and R=recovered/removed. (Wikipedia)
<b>Semi-quantitative or qualitative risk scale</b>	Within → Risk Assessment, probabilities of an event are assessed and described textually on a scale from negligible, indicating that the probability of an event or the estimated risk cannot be differentiated from zero (and in practical terms can be ignored) to extremely high.
<b>Sensitivity Analysis</b>	A method to qualify the output of a model by measuring the variation in model outputs resulting from changes in inputs. Through this, the “sensitivity” of a model to the respective changes can be assessed, and work can be focussed onto those input parameters that have substantial impact on the model output. Testing changes in model output caused by changing certain structural aspects of the model usually may be referred to as Robustness Analysis.
<b>Simulation model</b>	A model that is evaluated via explicit (e.g. step-by-step) simulation of the implemented structural processes and their interactions. Simulation as method of model analysis/model solution allows arbitrary complexity of the model. <i>Alternatively:</i> a mathematical representation of the essential characteristics of a real-world system or situation, which can be used to predict future behaviour under a variety of different conditions. The process of developing a simulation model involves defining the situation or system to be analyzed, identifying the associated variables, and describing the relationships between them as accurately as possible. <i>Alternatively:</i> Simulation is a computerized (iterative) approach to derive solutions



	(often in form of outcome distributions) for models that either do not have a closed mathematical solution or in which uncertainty in the input parameter values needs to be accounted for.
<b>SIR model</b>	Compartment model that incorporating three possible “states” (compartments) in which subjects can be found: S=Susceptible, I= Infectious; and R=recovered/removed. (Wikipedia)
<b>Spatial model</b>	Model that explicitly or implicitly incorporates the effect of spatial heterogeneity, i.e. spatial differences in either population density, outcome-related (risk) factors or both.
<b>Statistical analysis</b>	Any method applied to explore, describe or model the information contained in a given set of data, in most instances samples derived from larger populations, to make inferences from that sample to specific (source) population parameters.
<b>Statistical significance</b>	The a-priori fixed (threshold) level of maximum error probability (alpha, type 1 error) that one accepts when concluding – based on the results of a statistical test – that the alternative hypothesis (inequality) is correct. Depending on the nature of topic maximum error probability of alpha = 0.05, 0.01, or even less are used in statistical hypothesis testing, i.e. → p-value.
<b>Stochastic model</b>	A model in which randomness is involved in the derivation of future states of the model. Stochastic models thus produce distributions as output even for a given starting condition. Randomness might be incorporated via stochastic parameterisation i.e. accounting for variability and uncertainty of event occurrence.
<b>Systematic Literature review</b>	Conducting a literature review using prior criteria for searching/selection the literature with scientific tools to assess the findings from the published studies.
<b>Transmission model</b>	Specific models in which pathways describing the transmission of (infectious) diseases/ agents in populations are constructed, and values for the transmission probabilities along that pathway either entered (to simulate disease spread) or estimated based on observed population data.
<b>Uncertainty (statistical)</b>	Lack of knowledge in the exact value of a population parameter. Statistic methods derive estimates for that parameter as well as the associated uncertainty using fundamental concepts and theories of sampling, probability and randomness. In models uncertainty can be incorporated by probability distributions with information coming from either data or expert opinion.
<b>Uncertainty analysis</b>	Uncertainty analysis draws upon a number of techniques for determining the reliability of model predictions, accounting for various sources of uncertainty in model input and design such as input parameter values and assumptions. A related field is → Sensitivity Analysis.
<b>Univariable model</b>	A model in which a single independent (predictor/ risk factor) variable is assessed for its relationship to one or more dependent (outcome) variables.
<b>Univariate model</b>	A model in which one or more independent (predictor/ risk factor) variables are assessed for their relationship to a single dependent (outcome) variable.
<b>Validation</b>	Concept of checking the validity of the model formulation with regard to the intended purpose; ideally done with independently observed patterns. Checking correctness is intended task of model → verification.
<b>Variability (biological)</b>	True (inherent) biological, measurement or system-based variation in the possible values (value range) for a given parameter. In models that variability, similar to uncertainty, can be incorporated as probability distributions with information coming from either data (and classical statistics) or expert opinion
<b>Verification.</b>	Concept of checking the correctness of the model implementation; ideally done by measuring back any input pattern, code review, implausible scenarios (e.g. assuming no effect of a proven treatment). Checking appropriateness for purpose and consistency with conceptual thinking is the intended task of model → validation.
<b>Worst case scenario</b>	A situation where everything that can go wrong, does go wrong. Used in risk assessment to consider the worst predictable outcome by using extreme (risk increasing) model inputs.

## **ABBREVIATIONS**

AH: animal health

AHAW: EFSA Panel on Animal Health and Welfare

EFSA: European Food Safety Authority

OP: Operating procedure

ToR: Terms of Reference

WG: Working Group