Aim and expected outcome of EFSA training courses

EFSA has recognized a need for training of its Panel and Scientific Committee members and scientific staff to facilitate their understanding, uptake and use of the best risk assessment practices developed by EFSA. In addition there is a need to strengthen the cross-fertilisation of scientific discussion and support harmonization between the different scientific domains in EFSA.

The overall objective is to provide high quality training courses to meet the needs for BenchMark Dose (BMD) modelling and computational toxicology as identified by EFSA. The Training Coordinator and Tutors will make available their massive experience in organizing training courses in risk assessment, their unique expertise in the topics of the training courses and their extensive knowledge of the EFSA risk assessment practice.

The outcome will be:

1. Increased understanding of the basic principles of BMD modelling and computational toxicology;
2. increased implementation of best risk assessment practices related to BMD modelling and computational toxicology among Panel and Scientific Committee members and scientific staff;
3. hands-on training using the PROAST and BMDS software, and modelling tools used in the domain of computational toxicology;
4. increased awareness and uptake of risk assessment guidance and practises on cross-cutting risk assessment approaches among Panel and Scientific Committee members and scientific staff.

The contractors will organise the two types of training courses: (1) benchmark dose modelling and (2) computational toxicology and associated modelling tools.

1.1. Training course on Benchmark Dose Modelling

1.2. Objective

The objective of this training course is:

- To enable the understanding and practical implementation of best risk assessment practices amongst Panel/Scientific Committee members and EFSA scientific staff, in particular the horizontal aspect of evidence base for risk assessment.
- To strengthen the dissemination of guidance and to increase knowledge and understanding of BMD modelling.
- To make a link between the theory and practice by including practical sessions with examples of different types of scientific information from the work of EFSA.

1.3. Intended learning outcome
At the end of the course, participants should be able to understand and describe the following:

- general principles of the BMD approach;
- how to derive a BMDL from quantal as well as from continuous dose-response data, using the PROAST or the BMDS software;
- how to gain information by combining datasets;
- how to take litter effects into account;
- how to report a BMD analysis;
- how to derive a health-based guidance value from a BMD analysis.

The EFSA opinion on the BMD approach (2009) will be taken as the guidance on how to apply the BMD approach.

1.4. outline of the training course

The BMD module will be a mixture of lectures, discussions and practical sessions. The lectures will deal with the general principles of statistical analysis of dose-responses data, with focus on dose-response modelling. It will be discussed how a BMDL can be derived in the case of continuous and in the case of quantal data. Further, it will be explained how different comparable datasets can be combined in a BMD analysis, and thereby provide better information on the BMD. For developmental data, it will be shown how litter effects can be taken into account. In the practical sessions, datasets of different types will be offered as exercises in performing BMD analyses using the BMDS and the PROAST software. The intention is to use datasets from EFSA practice, to the extent possible.

In the practical sessions participants will actually work with the data and perform BMD analyses themselves to experience the challenges of different aspects of data analysis, including the interpretation of the results obtained. Throughout the training participants will be challenged to make links between what they have learned and their own work within EFSA.

1.5. Alignment of course content with learning outcomes

The table 1 below describes how the teaching and learning activities align with the intended learning outcome. For a detailed description of the training programme and the content of individual lectures and practical training sessions, see below.

Table 1: intended learning outcome of BMD course

<table>
<thead>
<tr>
<th>Intended learning outcome</th>
<th>Teaching and learning activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Understanding the general principles of the BMD approach.</td>
<td>Lecture discussing the general principles of statistical dose-response modelling, including reporting of results. The latter will be used by the trainees in the exercises to come.</td>
</tr>
<tr>
<td>How to derive a BMD with quantal data from animal studies.</td>
<td>Brief lecture on the use of BMDS, followed by exercises with quantal datasets using BMDS</td>
</tr>
<tr>
<td>How to derive a BMD with continuous data from animal studies.</td>
<td>Brief lecture on the use of PROAST, followed by exercises with continuous datasets using BMDS.</td>
</tr>
<tr>
<td>How to combine different datasets in a single BMD analysis.</td>
<td>Lecture on the general principles of combining datasets, followed by exercises with PROAST</td>
</tr>
<tr>
<td>How to take litter effects into account.</td>
<td>Lecture of litter effects, and statistical models to account for them, followed by exercises (either by BMDS or PROAST, to be decided by the trainee).</td>
</tr>
</tbody>
</table>
1.6. Presentation and use of relevant EFSA and other guidance documents

They will be in line with the EFSA opinion and scientific reports addressing BMD modelling.\(^1\)\(^2\)

2. Training course in computational toxicology

2.1. Objective

The objective of this training course is:

- To enable the understanding amongst Panel/Scientific Committee members and EFSA scientific staff of computational toxicology and software tools used for computational toxicology methodologies like QSAR, read across, grouping, Weight-of-Evidence.
- To make a link between the theory and practice by including practical sessions with examples of hazard assessments, screening and prioritization from the work of EFSA.
- To enable the understanding of harmonisation issues regarding QSAR models used at the international level.

2.2. Intended learning outcome

At the end of the course, participants should be able to understand and describe the following:

- Conceptual basis on construction of toxicity modelling tools:
  - overview of principles and different types of (quantitative) statistical modelling techniques, read across, trend analysis and various applications (e.g. OECD QSAR Toolbox, freely available tools developed by EU and US government);
  - assessing model reliability in a general (statistics, mechanistic basis, structure representation)
  - assessing model validity for a specific substance/prediction (with examples);
  - chemical applicability domains (with examples);
  - over fitting and quality issues (with examples).
- How to prepare and clean data sets for screening in computational toxicology tools, how to use the tools appropriately. Case studies shall be drawn from publically available European and international resources.
- How to verify that model predictions given in dossiers containing information from using such tools, has been generated appropriately.

2.3. Outline of training course

We will start with demonstrations of existing and available models such as DEREK, CAESAR, TOPKAT, MultiCASE, highlighting their similarities and differences in modelling approaches. By

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understanding the algorithms and logic behind the available models, things like model applicability domain and the quality issues related to predictions of specific substances (or classes of substances) will be made intuitively understandable. Validation as an indicator of general predictive power of a model will be discussed as opposed to the predictivity of a model for a specific prediction. Sampling the underlying databases, looking for toxicologically relevant analogues and subsequently validating a model for a specific type of substances will be illustrated using the OECD QSAR Application Toolbox. Both the applicability domain, or more importantly the limitations to applicability, of QSAR models and expert systems to different (human health) endpoints, and quality issues with these models will be demonstrated by discussing the data underlying the existing models and the assumptions (worst case, average etc.) used in establishing the models. By also discussing and giving examples from the concepts of Read Across and Grouping/Category approaches, issues with applicability domain and quality of a theoretical prediction will be additionally discussed more in general, instead of only addressing specific model issues.

Examples of issues related to preparation and cleaning of datasets for modelling purposes will be addressed, thereby highlighting issues such as choice of representative structure, ionization, mixture representation as well as metabolic transformation (precursors etc.). The course will not exhaustively cover this objective as the purpose of the course is understanding the principles of QSAR modelling, not to be able to derive new/own models. These issues will be dealt with when demonstrating the capabilities and possibilities of the OECD QSAR Application toolbox.

Usefulness and adequacy of predictions for dossier purposes is derived at by taking into account all validation, applicability and quality issues. This is especially relevant when theoretical predictions are used in conjunction with in vitro and in vivo experimental evidence. Some statistical as well as more qualitative approaches to performing Weight of Evidence (WoE) analyses will be explained using results of the EU FP6 project OSIRIS.

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The participants will get an overview of the possibilities of reproducing / validating model predictions provided in dossiers in order to evaluate their usefulness for risk and hazard assessment; and they will have an overview of the most important quality issues making model predictions less reliable or unusable.

The module course consists of four four-hour sessions, each a mixture of lectures, discussion and practical sessions. The session will include demonstrations of examples using one of the computational tools discussed (such as the OECD QSAR Toolbox, but also showing DEREK, TopKAT, MultiCASE), after which there will be a short hands-on session where a separate example is to be analysed by the participants, under supervision of the course tutor(s). All examples will be based on real data/dossiers.

The participants will be provided with an EFSA laptop/desktop computer with the OECD QSAR Toolbox software installed in advance, and the hands-on examples will make use of this software. Other tools will be demonstrated in the lectures, but no hands-on exercises with these other software tools will be given in the course.

2.4. Alignment of course content with learning outcomes

Table 2 describes how the teaching and learning activities align with the intended learning outcome.

Table 2: intended learning outcome of the QSAR course
<table>
<thead>
<tr>
<th>Intended learning outcome</th>
<th>Teaching and learning activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conceptual basis of construction of toxicity modelling tools:</td>
<td>Lecture demonstration available software and models, explain the concepts used in these models and compare them to each other.</td>
</tr>
<tr>
<td>- overview of principles and different types of (quantitative and qualitative) statistical modelling techniques, read across, trend analysis and various applications (e.g. OECD QSAR Toolbox, ToxTree, CAESAR/VEGA models, freely available tools developed by US EPA).</td>
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<tr>
<td>Conceptual basis on construction of toxicity modelling tools:</td>
<td>Lecture that will show the possibilities of the OECD QSAR application toolbox to reproduce predictions / reestablish models, thereby using (possibly) more or other data on the endpoint considered. Hands-on exercises will be provided where the participants will generate a prediction and evaluate the reliability/validity of this specific prediction using the OECD QSAR Toolbox software.</td>
</tr>
<tr>
<td>- Assessment of model prediction validity (with examples)</td>
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<tr>
<td>Conceptual basis on construction of toxicity modelling tools:</td>
<td>Lecture that will introduce different model applicability domain definitions (physico-chemical, descriptor space, chemical structure, multivariate). An example will be used to experience hands-on the relevance of applicability domain. Tools for evaluating the applicability domain of a given QSAR model (e.g. AMBIT software) will be demonstrated. Lecture that will combine all relevant issues influencing the prediction reliability from the previous parts, and discuss the possibility to use model predictions in a Weight of Evidence approach, instead of (often unwanted) 1:1 replacement of experimental evidence.</td>
</tr>
<tr>
<td>- Chemical applicability domains (with examples)</td>
<td></td>
</tr>
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<td>- How to prepare and clean data sets for screening in computational toxicology tools, how to use the tools appropriately. Case studies shall be drawn from publically available European and international resources</td>
<td></td>
</tr>
<tr>
<td>Conceptual basis on construction of toxicity modelling tools:</td>
<td>Throughout the sessions the participants will get an overview of the possibilities of reproducing and assessing the validity of specific model predictions provided in dossiers in order to evaluate their usefulness for risk and/or hazard assessment; and they will have an overview of the most important quality issues making model predictions less reliable or unusable.</td>
</tr>
<tr>
<td>- over-fitting and quality issues (with examples)</td>
<td></td>
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<tr>
<td>- verification of the correctness/reliability of computational tox model information in dossiers</td>
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</tbody>
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