Gesellschaft für Toxikologie

Combined Advanced Course 2021 „Computational/in silico Toxicology/QSARs – Implementation and Assessment in the Regulatory Context“ of the GT Working Groups Regulatory Toxicology and Computational Toxicology

Login

Many Thanks to the Programme Committee:

Lennart Anger

Jochen vom Brocke

Monika Batke

Andreas Czich

Susanne Dorn

Sylvia Escher

Heidrun Greim

Madeleine Joel

Oliver Licht

Michael Werner

Prosacon Product Safety Consulting

Gesellschaft für Toxikologie

Combined Advanced Course 2021 „Computational/in silico Toxicology/QSARs – Implementation and Assessment in the Regulatory Context“ of the GT Working Groups Regulatory Toxicology and Computational Toxicology

Login

Introductory Remarks
-
Coverage of Regulatory Data Requirements by Non-Animal Methods – Reality or Wishful Thinking?

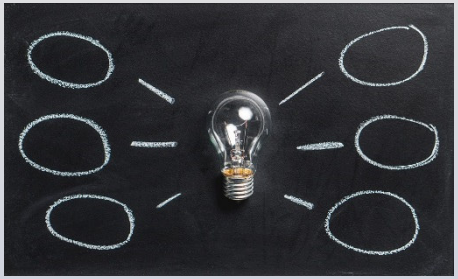
Dr. Michael Werner, Prosacon GmbH, Germany

Prosacon Product Safety Consulting

Aims of the Combined Advanced Course 2021

- **Overview of the application of non-animal methods/tools**
  - **in relation to assessing different (toxicological) endpoints**
  - **in relation to their capabilities and limitations**
  - **in different regulatory areas (industrial chemicals, PPPs, biocides, cosmetics)**

- **Familiarize „non-computational“ toxicologists with the tools available**
  - **Applicability domains (“Training Sets”)**
  - **Implementation in the regulatory context**
  - **Acceptance by regulatory bodies**



ProsaCon Product Safety Consulting

Analysis of viewpoints: Where are we?

Regulatory Toxicologist ⟷ **„Synergism“** / **„WoE “** ⟷ **Computational Toxicologist**

- Evaluation of **complete tox profile** → **mostly via animal studies** as per data requirements
- Note: **„Animal testing should be last resort“** → discrepancy to ECHA testing proposals and decisions of Board of Appeal
- **Desirable:** Generate all endpoints by „pressing the button“
- **Reality:** Non-animal testing methods limited and not applicable to all endpoints

- Modelling of tox-endpoints by in silico/QSAR tools → **full compliance with „3R principles“**
- **Desirable:** Full acceptance of results by regulatory bodies in the context of e.g. substance evaluations
- **Reality:** Tools are expert systems → outputs need to be well explained to be understood/accepted → further supporting evidence needed for in silico/QSAR results (**read-across/weight-of-the evidence approaches**)

ProsaCon Product Safety Consulting

Practical examples for the acceptance of QSARs in regulatory toxicology (I)

- **„VCI (Association of the Chemical Industry) Voluntary Self-Commitment of the Chemical Industry“ (mid/end 1990s):**

  - Use of **QSAR tools (preferentially EpiWin) general practice** for preparing „substance information short assessments“

    - **Phys-Chem:** $logP_{ow}$, vapour pressure
    - **Efate:** Biodegradation, BCF, Distribution (Mackay Level 1)
    - **Ecotox:** ECOSAR predictions for short-/long-term aquatic toxicity (fish, invertebrates, green algae)

  - **Pitfall:**
    - **Reliability/robustness of predictions**
    - **Large deviations between experimental and predicted ecotox endpoints**
    - **ECOSAR only applicable to assess relative toxicities vs. absolute estimates**

Prosacon Product Safety Consulting

Practical examples for the acceptance of QSARs in regulatory toxicology (II)

- **Art. 54 of the Biocidal Products Regulation (BPR, Regulation (EU) No. 528/2012): Assessment of Technical Equivalence of „alternative active substance sources“**

  - **Background:**

    - Demonstration of **technical (i.e. (eco)toxicological) equivalence (TE) of alternative source with reference source/reference specification**
    - **Direct comparison of purity/impurity profile(s)** with reference source **not possible → „CBI“** of the original review programme participant

  - **Approach:**

    - **Impurities** (identity and level) of alternative source **were known**
    - **QSARs (OECD toolbox, DEREK etc.)** were performed with a **focus on structural alerts and assessment of (ecotoxicological) profile of impurites**
    - **QSAR results + accompanying argumentation paper** were **accepted by ECHA → TE of alternative source** with reference source was **proven**

ProsaCon Product Safety Consulting

Symbiosis of Regulatory and Computational Toxicology (I)

❖ **„Vision“:**

- **Coverage of all (eco)toxicological endpoints/data requirements by non-animal methods,** i.e. *in silico*/QSAR tools + *in vitro* methods + read across approaches

- All tools are

  - **fully validated**
  - **scientifically reliable/robust**
  - **applicable for the prediction of „higher tier endpoints“ → repeated dose toxicity (RDT)/carcinogenicity + reproductive toxicity (CR), endocrine disruption (ED)**
  - **fully accepted by regulatory bodies** in the context of registration/authorization procedures of active substances, industrial chemicals and pharmaceuticals

Prosacon Product Safety Consulting

Symbiosis of Regulatory and Computational Toxicology (II)

❖ Status Quo

- Up to date, **performance of animal trials cannot completely be abolished** in the near future **(e.g. ED assessment of active substances; ECHA testing proposals** with a focus on OECD 414 and OECD 443 studies**)**

- **Focus** is presently on the **„3R Principle“** by **implementing an increasing portion of non-animal methods** in regulatory dossier submissions (e.g. local effects, skin sensitisation)

- **Applicability of in silico/QSARs:**

  - **Supplementation of animal studies with non-animal methods for validated endpoints**
  - **Evaluation of relative (eco-) toxicities** of e.g. parent compound and metabolites
  - ***In silico*/QSAR tools as supporting evidence when applying a weight-of-the-evidence (WoE) and/or read-across approach**
  - **Note on genotox assessment:** Requirement of **high congruence of in silico/QSAR results** with well established *in vitro* systems **in terms of predictivity**

ProsaCon Product Safety Consulting

Thank you very much for your attention

Enjoy the Combined Advanced Course 2021!

ProsaCon Product Safety Consulting