Gesellschaft für Toxikologie

GT Advanced Course 2025
„Computational Methodologies in Regulatory Assessments “
of the GT Working Groups
Regulatory Toxicology and Computational Toxicology

Login

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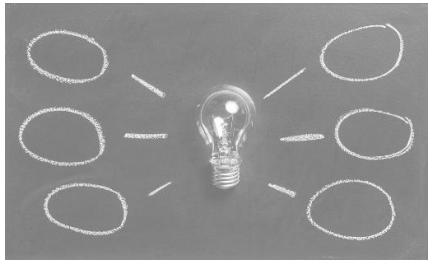
GT Advanced Course 2025 „Computational Methodologies in Regulatory Assessments “

10:00	Opening remarks: Introduction with a focus on the regulatory background	Chairs of the GT Working Groups.
Session 1:	**Application of CompTox Methods for Effect Assessment (Eco)Tox**	Moderation: Markus Frericks (BASF)
10:20	Metabolism Data Digitalisation - Metapath - IUCLID - Toolbox	Juan Parra Morte (EFSA)
10:50	Weight of Evidence and Confidence in in silico workstreams	Markus Frericks (BASF)
	11:20 Coffee break	
11:50	Omics-based grouping of substances for read across	John Colbourne (Birmingham University, UK)
12:20	Lunch Break + General Meeting WG RegTox	Working Group Regulatory Toxicology
Session 2:	**Application of CompTox Methods for Exposure Assessments (Human Health/Environment)**	Michael Werner, WG RegTox
13:30	Overview of human non-dietary exposure prediction and respective tools in different regulations.	Sven Ruhl (knoell)
14:00	Dietary Exposure (PPPs/Biozide/FCM) Advances in tools to estimate dietary exposure	Giulio Di Piazza (EFSA)
	14:30 Coffee break	
15:00	Principles and advancements in environmental exposure modelling under different regulations	Stefan Hahn (Fraunhofer ITEM)
15:30	Panel discussion	All Panellists Moderation: Markus Frericks, Michael Werner
16:30	End of Advanced Course	

Purpose of the Advanced Course 2025

- Gain an overview of the state of the play in animal-free hazard assessments using computational/in silico methods including read-across.
- Understand the scope and the limitations of computational/in silico methods in hazard assessment and their use/acceptance in the regulatory landscape.
- Getting insights into approaches/tools for (non-) dietary human as well as environmental exposure assessments as well as the needs in the development of new exposure models.



Session 1: Application of CompTox Methods for Effect Assessment (Eco)Tox

❖ Drivers for the increasing use of non-animal methods (I)

- **Objectives:**
  - **Animal welfare:** Complete **phasing out of animal tests → "cruel free" testing** for hazard assessment
    - see 2nd COM conference in October 2024 and 3rd COM conference in June 2025 outlining roadmap on present status and planned ways forward.
  - Complying with the **"mission" of the Chemicals Strategy for Sustainability (CSS) and the Green Deal**
    - Fostering innovation and promotion of the production/use of safe and sustainable chemicals that are safe and sustainable by design throughout their lifecycle
  - **Replacement of** available (OECD/OPPTS) ***in vivo* studies** by non-animal methods
  - **Hazard assessments, reference value deduction and risk characterization** on the grounds of ***in vitro* data.**

Session 1: Application of CompTox Methods for Effect Assessment (Eco)Tox

❖ **Drivers for the increasing use of non-animal methods (II)**

- **Challenges:**

  - Availability of **reliable and valid non-animal/in silico methods for all (eco-)tox endpoints**

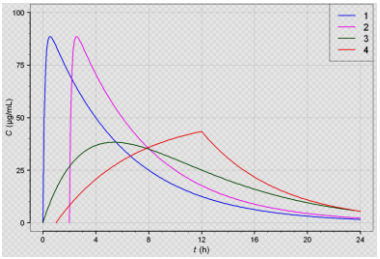
    - **Development of (NAM) methods for higher tier tox end**points (e.g. carcinogenicity/reproductive toxicity/(developmental) neurotoxicity) ongoing.

  - Results of **non-animal methods need to correctly map the (eco)toxicity profile** of substances.

  - **Animal testing should be the last resort → Reality: animal tests are still required by regulatory bodies** for fulfilment of data requirements in the Biocides/PPP/REACH regulation).

  - **"Paradigm change":** Quantitative *in vitro - in vivo* extrapolation (**QIVIVE**)

    - Need for **reliable "*in vitro – in vivo* conversion factors"** (e.g reliable **PBK modelling required** for conversion of ***in vitro* concentrations to *in vivo* doses**).



Session 1: Application of CompTox Methods for Effect Assessment (Eco)Tox

❖ Drivers for the increasing use of non-animal methods (II)

Use of in-silico- Tools and conduct of QSARs
(Qualitative or Quantitative Strucure – Activity- Relationship)

- **QSARs** (e.g. Danish QSAR Data Base, DEREK, MultiCASE, OECD Toolbox) **need to be validated**.
- **QSARs** are in the first instance **used for screening purposes.**
- **QSAR results** serve as **supporting information cannot be used** as **standalone tools** to fulfil data requirements .

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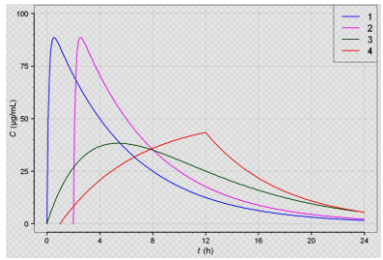

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Session 1: Application of CompTox Methods for Effect Assessment (Eco)Tox

❖ **Status of the use and regulatory acceptance of non-animal *in vitro* methods in toxicity testing**

- **Current approaches for the fulfilment of regulatory requirements:**

➢ **Mainly based on *in vivo* tests**, especially for endpoints like **repeated dose toxicity, reproductive and developmental toxicity, (developmental) neurotoxicity, carcinogenicity.**

➢ **„Mixed approach for the present toxicological hotspot „endocrine disruption“.**

- **Adversity** investigated by ***in vivo* studies.**
- **Endocrine activity** investigated by combination of ***in vitro* + *in* vivo (mechanistic) → additional** *in vivo* (mechanistic) studies often requested by evaluating authorities.

➢ ***In vitro* data accepted/required for**

- **Local effects** (skin + eye) including **skin sensitisation.**
- **Mutagenicity/genotoxicity.**

Session 1: Application of CompTox Methods for Effect Assessment (Eco)Tox

❖ Animal vs. non-animal methods in toxicity testing: Regulatory status (e.g. Biocides, PPPs, REACH)

In vivo studies	*In vitro/in silico* studies
 ○ Repeated dose toxicity (RDT) studies (subacute/subchronic/chronic studies) ○ Developmental and reproductive toxicity (DART) studies (fertility/development/teratogenicity) including pubertal assays ○ Combined chronic toxicity/carcinogenicity studies ○ Developmental neurotoxicity (DNT)/neurotoxicity studies ○ *In vivo* mechanistic studies on endocrine disruption	 ○ Skin irritation/corrosion ○ Eye irritation/eye damage ○ Skin sensitization (if substance fulfil requirements of OECD TGs) ○ Mutagenicity/genotoxicity (bacterial and mammalian cells) ○ *In vitro* mechanistic studies on endocrine disruption + QSARs ○ Dermal absorption through *human skin* → **relevant for exposure rather than hazard assessment!**

Session 1: Application of CompTox Methods for Effect Assessment (Eco)Tox

❖ **Reflection on the trust in non-animal methods**

➢ **Enhesa Weekly Newsletter 14 March 2025:**

"European citizens may trust NAMs more than animal testing, survey finds

The public may have more confidence in the predictive powers of in vitro toxicity testing than testing on animals*, according to a* ***survey of Swiss citizens*** *that mimicked a landmark series of* ***surveys conducted in the 1990s.***

However, ***the public's higher confidence in in vitro testing relative to animal testing contrasted with data from a sister survey of professional risk assessors, who were more confident in predictions made using whole organisms."***

Core question:

In vitro/in silico vs. In vivo **- which approaches map more accurately the „true" hazards of a substance?**

Session 2: Application of CompTox Methods for Exposure Assessments

❖ **Status of the use and acceptance of exposure models for regulatory purposes**

- **Current approaches for human and environmental exposure assessments:**
  - Use of (regulation specific) exposure models in all legislations.
  - **Monitoring** (workplace) and **background** (environment/food) **data** are often considered → **reliability** of data **crucial for regulatory acceptance.**
  - **Human exposure studies** are performed **in exceptional cases → robust and representative study design!**
  - Environmental exposure studies **usually not performed in practice.**

Session 2: Application of CompTox Methods for Exposure Assessments

❖ **Non-exhaustive overview of human and environmental exposure models in different legislations (e.g. Biocides, PPPs, REACH)**

Human health	*Environment*
○ Biocides: ART tool, BfR livestock calculator, BHHEM Document, ConsExpo, ECHA Guidance Volume III (Parts B+C), EFSA PRiMo, TNsGs 2202/2007, HEEG opinions, HEADhoc recommendations, RiskOfDerm ○ REACH: ART tool, CHESAR, ConsExpo, ECETOC TRA, EASY TRA ○ PPPs: EFSA Guidance (operators, workers, residents and bystanders), EFSA PRiMo, PHED	○ CHESAR (Biocides, REACH) ○ EUSES (estimation of the initial release of substances from biocidal products (or treated materials)) ○ FOCUS simulation models and FOCUS scenarios (e.g. ground water, surface water) ○ SimpleTreat (emission from sewage treatment plants and exposure in surface water) ○ Emission scenario documents (ESDs) for biocides ○ PELMO (leaching model) ○ PEARL (Pesticide Emission Assessment at Regional and Local scales)

Session 2: Application of CompTox Methods for Exposure Assessments

❖ Challenges ahead in exposure modelling

○ Reliability of exposure assessments:

- ➢ Exposure **estimations via modelling** are usually **very conservative/precautionary**.
  - **Modelled exposure** is usually **far higher than exposure in real world scenarios** (as shown by exposure measurements if available).
  - **Exposure modelling** generally **involves a number of refinements** to demonstrate safe uses.

○ Needs in exposure assessments:

- ➢ Development of **exposure models mimicking** as closely as possible the **true exposure** in different **real world scenarios**.
- ➢ **New exposure models** need to be **valid, sufficiently robust and accepted by regulatory bodies** for regulatory purposes.

The Working Groups “RegTox” and “CompTox” wish you an interesting and exciting Advanced Course 2025