Session 2 – Reflections from stakeholders

EFSA Workshop on implementing EC Roadmap on phasing out animal testing in pesticides and biocides

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Assessment of Active Ingredients

While data requirements foresee the generation of animal-heavy datasets, several areas require / could profit from **NAM**-based approaches:

- **N**on-**A**nimal **M**ethods
- **N**ew **A**pproach **M**ethodologies

Eg.

Acute Toxicity
Repeated dose (e.g. ~~dog~~)
Carcinogenicity Testing
(e.g. ~~mouse~~)

Assessment of impurities / metabolites (TTC, meaningful QSAR, Read Across)

Toxicokinetics (e.g. IVIVE)

Mechanistic understanding of effects seen in animal studies

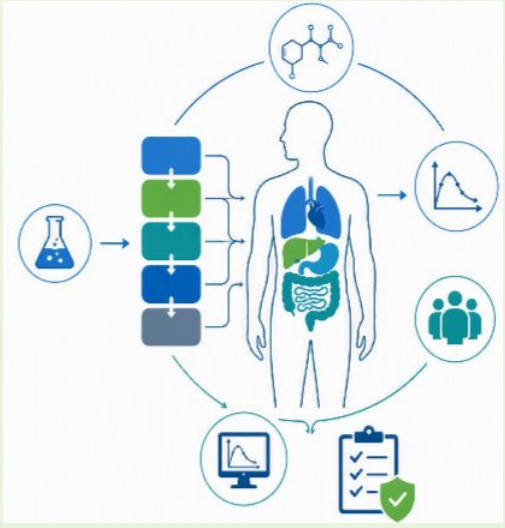
Endocrine Activity (e.g. thyroid)

Identification of species differences (e.g. human relevance)

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Toxicokinetics and PBK approaches

We know „everything“ about external doses in animals, but have limited knowledge on internal doses in animals or humans.



Dose extrapolation

- Forward dosimetry – from dose to internal concentration
- Reverse dosimetry (QIVIVE) – from concentration to dose

Species and population extrapolation

- Cross-species comparison – human equivalent doses
- Life-stage differences

Exposure and risk assessment

- Route-to-route extrapolation
- Concentration in target tissue

Input parameters

- Absorption
  - Caco 2 assay
- Distribution
  - Partition coefficient log P_{OW}
- Hepatic clearance
  - E.g. IVCM, …
- Plasma Protein Binding
  - Fraction unbound – in vitro or QSAR
- *Renal clearance*

We need an agreed PBK workflow!

httk

The High-Throughput Toolkit (*httk*) is a toolkit for preparing and running calculations, analyzing the results, and storing results in global and/or personalized databases.

GitHub | Twitter | Docs | Discussions | + Contribute

CERTARA

Simcyp® PBPK Simulator

CropLife EUROPE

efsa JOURNAL OPEN ACCESS

EDITORIAL | Open Access

TKPlate 1.0: An Open-access platform for toxicokinetic and toxicodynamic modelling of chemicals to implement new approach methodologies in chemical risk assessment



PKSIM

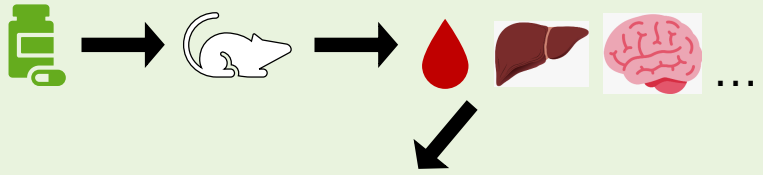
HIGH QUALITY FLIGHT SIMULATOR SCENERIES

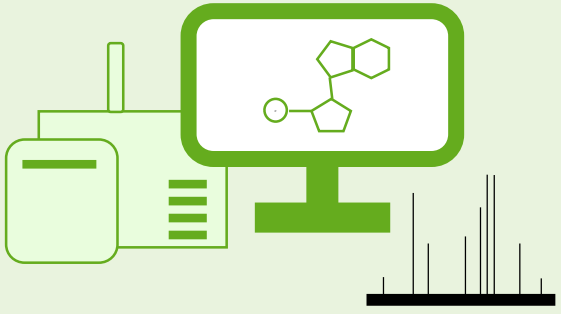
CropLife EUROPE **Comparability of different models**

From very simple to super-complex
- Different scopes and predictivity

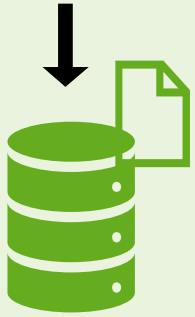
But ultimately needed in future / NGRA

Example: More information from animal studies





Transcriptome / Metabolomics

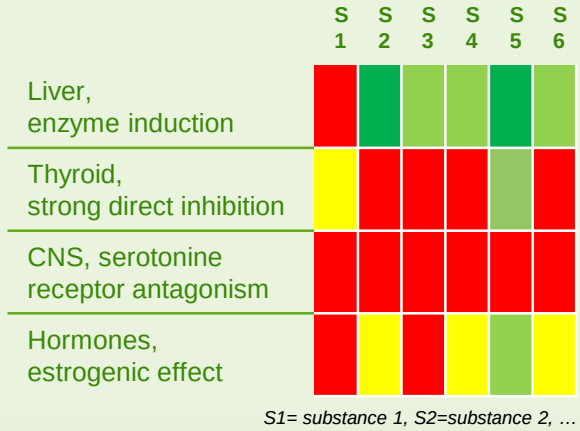


e.g. MetaMap®Tox database

Targeted ex-vivo investigations:

- Cell proliferation
- Hormones
- Specific Immunohisto-chemistry

1. The pattern ranking approach of MetaMap® Tox database identifies toxicological modes of action / MIEs



S1= substance 1, S2=substance 2, …

match	weak match	equivocal	mismatch
> 90% similarity	> 75-90% similarity	> 50-75% similarity	< 50% similarity

2. Read- across use of information from 'source' to predict properties of the 'target' substance

Metabolite → Read-across (**Similar patterns**) → Active Ingredient

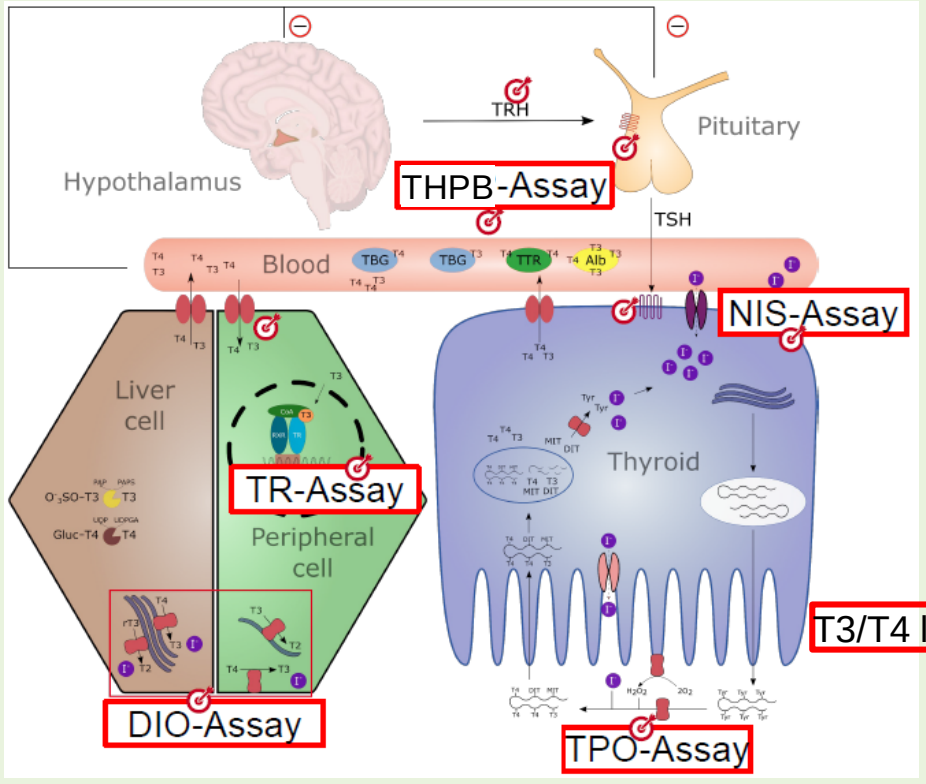
Applicable to Active Ingredients (eg. Carcinogenicity), Impurities, Metabolites

Helps reducing animal studies

Safe spaces

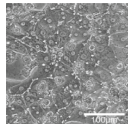
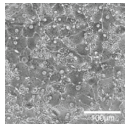
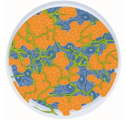
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Example: Thyroid Assessment (endocrine activity, non-human relevance)



Validation of *in vitro* assays (OECD, PEPPER)
Predictive QSARs
Organ models covering several MIEs

Focus Liver enzyme induction

2D-rat 2D-human 3D-liver

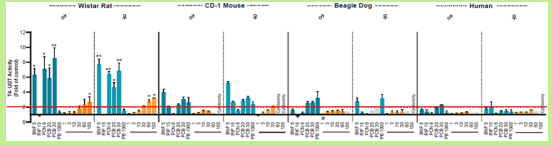


Multiorgan-chips

Human only

Rat vs human

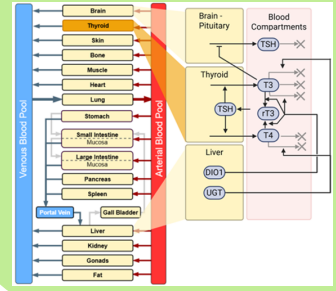
No or "serious doubt on" human relevance



Comparative liver enzyme induction assay

Acceptance criteria

Comparative PBK and TH-QST modeling (compare T3 / T4 / TSH levels in rat vs human blood)



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Thyroid Supermodel

Safe spaces

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