QSAR Toolbox in REACH registrations

Webinar: OECD QSAR Toolbox applications for REACH and beyond

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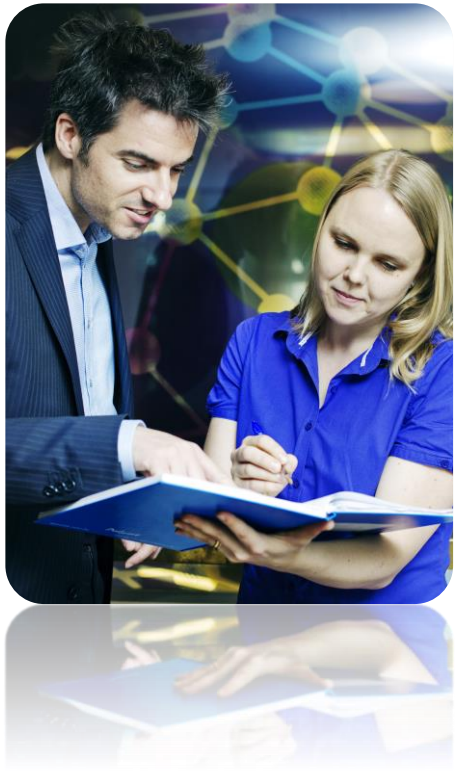
Objective

- Explain how we assess different types of results from the QSAR Toolbox when used by registrants to adapt REACH standard information requirements



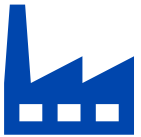
Content

Our assessment of different types of Toolbox results:

- Profilers and metabolic simulators
- Read-across
- Quantitative Structure Activity Relationships (QSARs)

REACH context

- Industry ensures safe use of their substances
- Minimum set of hazard information = standard information requirements
- QSAR and read-across as adaptations (Rules in REACH Annex XI)
- ECHA checks information in dossier evaluation



Industry

Submits REACH registrations incl. Toolbox results

Receives and assesses the information

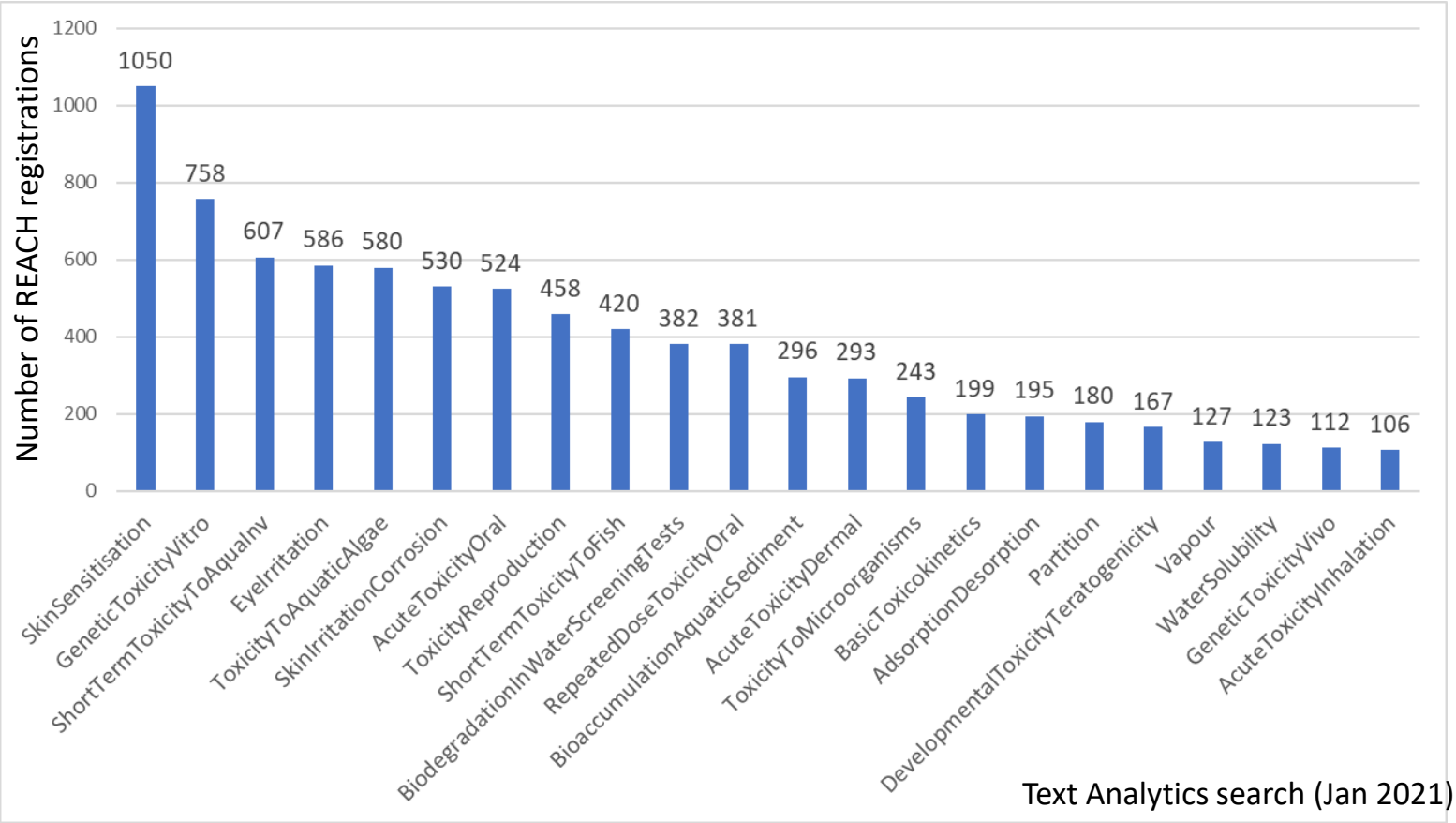
Statistics

- Registered users: **28 221** (November 2021)

Use in REACH dossiers (May 2021):

- **9 144** Endpoint Study Records
- **3 142** Registrations

Use of Toolbox per endpoint in REACH registrations



Text Analytics search (Jan 2021)

What are profilers?

- "Knowledge" in the Toolbox, linking structures to mechanisms of action and other properties
- Tools to identify analogues and group substances based on chemical and mechanistic similarity
- Also useful for screening purposes

What are metabolic simulators?

- Information on predicted and observed (bio)transformations of the target
- Allows identification of analogues with similar metabolic profile
- No quantitative information or predicted metabolic maps

Profilers and simulators

Can be used to:

- Search for relevant analogues (with experimental data)
- Cover elements of read-across justification:
  - Category description
  - Impact of impurities
  - Also for read-across cases built outside the Toolbox

Profilers and simulators - Don’ts

- Do not use profiler results to fill data gaps directly:
  - Lack of alerts from profilers cannot be used as negative predictions
  - Why? Profilers are not (Q)SAR models, may not fulfil the criteria for valid models such as a defined applicability domain, or appropriate measures of performances
  - E.g. lack of mutagenicity alerts cannot be used to conclude on lack of mutagenicity potential of a substance; but can be used to find suitable analogues with data to build a read-across case

Read-across

- Toolbox can make predictions using experimental data from analogues using read-across and trend analysis
- ECHA evaluates both approaches as read-across* using the Read Across Assessment Framework
- When used as key information, an adequate read-across justification is needed - submitting the Toolbox report alone is not sufficient
- Improved Toolbox reports will be available to facilitate this task

With the exception of ecotoxicological trend analysis predictions using a high number of analogues, which can be assessed as (local) QSARs.

Read-across

Use of Toolbox information (1)

Use Toolbox information in connection with read across assessment framework assessment elements when preparing justification

Common assessment element	Toolbox information
Characterisation of source and target	CAS#, EC#, structure, name, composition
Category description and supporting information	Category boundaries are defined by profilers used for analogue selection Category justification can be supported by explanation of profiling results
Link with structural similarity	Structural profiler results
Impact of impurities	Predicted mechanism, properties and experimental data for impurities
Consistency of the properties in the data matrix	Experimental (or predicted) data among different properties relevant for prediction
Source data quality	Metadata and original reference for experimental data
Bias	Prediction report documenting all steps and manually removed data points

Read-across

Use of Toolbox information (2)

Specific assessment element	Toolbox information
Formation of common and non-common compounds	Observed and predicted transformation products (kinetic not included)
Degradation	Degradation related profilers, data and QSAR models
Bioaccumulation potential	Bioaccumulation related profilers, data and QSAR models
Impact of common and non-common compounds	Profilers, data and QSAR model results for common and non-common compounds
Common underlying mechanism: qualitative aspects	Results from mechanistic and endpoint specific profilers related to target endpoint
Common underlying mechanism: quantitative aspects	Predicted and experimental data for target endpoint

Read-across
Work in progress

Improved Toolbox reports under development to address common deficiencies of read-across cases with Toolbox found in REACH dossiers:

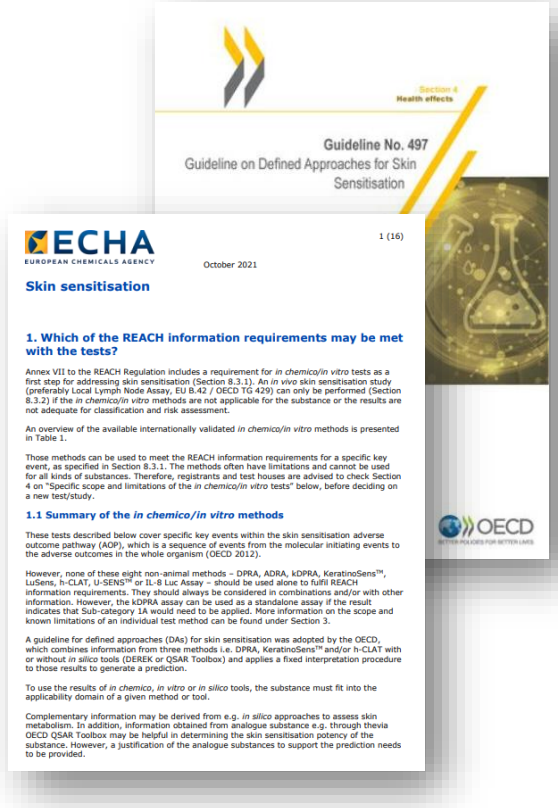
- **Differences** between analogues and target substance and their (lack of) impact on (eco)toxicological properties
- **Quality and reliability** of source experimental data. Toolbox may not include all information needed to assess quality of source data, and the original source might need to be consulted
- ECHA expects a justification in addition to automatically generated reports

QSAR models in Toolbox

- Many external QSAR models in Toolbox – results and some metadata
- Useful for screening or as supporting information for read-across
- Fulfilling information requirements for REACH: run QSAR models in their original platform and include all relevant information in your dossier
- QSAR results need to be valid. More information on our assessment of QSAR results: watch our webinar

Skin sensitisation

- Predictions from the automated workflow for defined approaches for skin sensitisation in the Toolbox include applicability domain information
- Part of the OECD Guideline for defined approaches for skin sensitisation (first and only free *in silico* tool part of an OECD Guideline)
- Can be used for fulfilling standard information requirements. Read our guidance on how to use the OECD guideline for REACH



Take home messages

- Toolbox results can be successfully used as key or supporting information for adapting information requirements in REACH registrations
- Adequate justification in addition to the Toolbox report is key for acceptance
- Toolbox results are more likely to be compliant for endpoints for which biological mechanisms are well understood and complexity of effects limited, i.e. for low tier endpoints

Thank you!

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