Persistence assessment in the regulatory assessment and management of chemicals

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Romanas Cesnaitis, Lale Carstensen (former trainee in ECHA), Anna-Maija Nyman, Doris Hirmann, Anne-Mari Karjalainen, Kostas Andreou, Marta Sobanska and Anu Kapanen
Content of the presentation

→ Alternative approaches in persistence assessment under REACH and CLP – Weight of Evidence
→ Modelling in persistence assessment
→ Prioritised groups of potentially PBT/vPvB and PMT/vPvM substances
Persistency in the regulatory assessment

→ Key property driving hazard, exposure and risk

→ Information on Persistence is needed for many purposes
  ✓ To fulfil regulatory information requirements
  ✓ PBT/vPvB and PMT/vPvM assessment
  ✓ Exposure assessment
  ✓ Risk assessment

→ Persistence is mostly assessed based on experimental data
  ✓ Data generation often time consuming and expensive
  ✓ How to use alternative non-testing methods to speed up the assessment?
Persistence assessment under REACH and CLP

Screening (indication) of (P) persistence

- ready biodegradation tests
- other degradation screening tests (e.g. enhanced ready test, tests on inherent biodegradability)
- predictions from adequate (Q)SAR models
- other adequate information

Assessment of persistence

- simulation testing on degradation in surface water, soil and sediment;
- other adequate information, such as information from field studies or monitoring studies

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<table>
<thead>
<tr>
<th>Thresholds in Persistence assessment</th>
<th>REACH/CLP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>Mineralisation (%)</td>
</tr>
<tr>
<td>Readily biodegradable</td>
<td>Not P/vP</td>
</tr>
<tr>
<td>Inherently biodegradable fulfilling specific criteria</td>
<td>Not P/vP</td>
</tr>
<tr>
<td>Assessment</td>
<td>Half-life (days)</td>
</tr>
<tr>
<td>Water fresh/estuarine</td>
<td>&gt; 40 (marine &gt; 60)</td>
</tr>
<tr>
<td></td>
<td>&gt; 60</td>
</tr>
<tr>
<td></td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>vP</td>
</tr>
<tr>
<td>Sediment fresh/estuarine</td>
<td>&gt; 120 (marine &gt; 180)</td>
</tr>
<tr>
<td></td>
<td>&gt; 180</td>
</tr>
<tr>
<td></td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>vP</td>
</tr>
<tr>
<td>Soil</td>
<td>&gt; 120</td>
</tr>
<tr>
<td></td>
<td>&gt; 180</td>
</tr>
<tr>
<td></td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>vP</td>
</tr>
</tbody>
</table>
Use of (Q)SARs in persistence assessment
(Q)SARs as part of Weight-of-Evidence in P-assessment

- (Q)SAR estimates may be used for a preliminary identification of substances with a potential for persistence.

- It is recommended to use combined results from three estimation models in the EPI Suite™
  - BIOWIN 2, 3 and 6.

- Degradation half-lives based on QSAR models using data from ready biodegradation tests should not be used for comparison with the P/vP criteria.

- (Q)SAR provide valuable information for:
  - screening potential P/vP substances,
  - supporting read-across assessment,
  - grouping of substances (similarity or trend analysis),
  - predicting degradation potential of constituents of a UVCB substances,
  - predicting formation of degradation products.
Use of (Q)SARs in environmental hazard assessment for P-screening

Aim:
- Compare newly generated experimental data (REACH) with QSAR prediction.

Motivation:
- (Q)SAR is one of the REACH Annex XI adaptation methods to fulfil the REACH standard information requirements.
- Can be useful to assess properties of substances/constituents (including profiling UVCB/multi for PBT profiling) if no experimental data is available.

1. Are hazards assessed differently when using QSARs compared to experimental studies?
2. What is the impact for regulatory decision-making?
Experimental data (REACH generated new studies)*

- Ready Biodegradation (OECD TG 301)
- Bioaccumulation (OECD TG 305)
- Chronic toxicity to fish (OECD TG 210)

VS

QSAR predictions (mono-constituents)

- EpiSuite™
- VEGA QSAR
- CATALOGIC
- iSafeRat

*Experimental data generated via REACH Evaluation processes and formally assessed ‘as accepted’
## Assessment of (Q)SARs: Principles

Three-staged flagging for substances out of the applicability domain and/or need extra care

<table>
<thead>
<tr>
<th>Flag A (model)</th>
<th>Flag B (user guide)</th>
<th>Flag C (ECHA additional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAT - SaturateSolubility (Effect level exceeds WS by factor 10)</td>
<td>MET - inorganics, inorganic salts and metals including organometals</td>
<td>R2 - of ECOSAR class is &lt; 0.6</td>
</tr>
<tr>
<td>ACR - AcuteToChronicRatios (empirically derived class-specific ratio)</td>
<td>HYD - hydrolytically unstable or highly reactive chemicals</td>
<td>N - (number) of substances used in the training set of the class is &lt; 5</td>
</tr>
<tr>
<td>KOW1 - LogKowCutOff (endpoint-specific)</td>
<td>SALT - complex) salts - SMILES is changed to neutral species automatically</td>
<td>ION - ionizable substances; &gt; 90 % pH range 4 - 9 (percepta output)</td>
</tr>
<tr>
<td>MW - DomainOfApplicability (MW &gt; 1000)</td>
<td>Kow or MW or FRAG (fragment) or FLU (perfluorinated substance) or CNC (imidazole ring, quaternary nitrogen, nitrogen heterocycles other than pyridine) out of domain</td>
<td>SURF 1 - Surfactans (&lt; 45 mN/m)</td>
</tr>
<tr>
<td></td>
<td>ION - ionized at pH 4-9</td>
<td>SURF 2 - Surfactans (45-60 mN/m)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KOW input - fragment not present in KOWWIN training set</td>
</tr>
</tbody>
</table>
Prediction of environmental fate and hazard properties by QSARs – comparison to experimental data

Chronic fish toxicity (OECD TG 210)
- 176 substances
  - 89 with experimental data (+23 not yet evaluated)
  - 49 organic mono-constituent substances

Bioaccumulation (OECD TG 305)
- 49 substances
  - 23 with experimental data (+ 10 under assessment)
  - 17 organic (organo-metallic) mono-constituent substances

Ready biodegradation (OECD TG 301 B/D/F)
- 40 substances
  - 23 with experimental data (+ 12 under assessment)
  - 11 organic mono-constituent substances

See ECHA poster: (1.11.P-Th070) How Well QSARs Predict Aquatic Toxicity of REACH Registered Substances?

QSAR analysis done with organic mono-constituents
### Ready biodegradability

Predictions in the Table below:
- **cell in green** – prediction match experimental degradation level (10-day window not considered);
- **cell in red** – prediction did not match experimental degradation level
- **value in yellow** - there is Flag (specified in Flags column).

<table>
<thead>
<tr>
<th>Substances</th>
<th>Experimental results</th>
<th>Predictions by specific model</th>
<th>Flags</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Experimental Degradation after 28 d, %</td>
<td>Pot. P/vP (R.11)</td>
</tr>
<tr>
<td>301 B</td>
<td>0-5</td>
<td>n/a</td>
<td>NO</td>
</tr>
<tr>
<td>301 D</td>
<td>0-5</td>
<td>no</td>
<td>NO</td>
</tr>
<tr>
<td>301 F</td>
<td>50-55</td>
<td>n/a</td>
<td>NO</td>
</tr>
<tr>
<td>301 D</td>
<td>60-65</td>
<td>no</td>
<td>NO</td>
</tr>
<tr>
<td>301 D</td>
<td>60-65</td>
<td>no</td>
<td>YES</td>
</tr>
<tr>
<td>Similar to 310</td>
<td>65-70</td>
<td>yes</td>
<td>NO</td>
</tr>
<tr>
<td>301 F</td>
<td>65-70</td>
<td>no</td>
<td>YES</td>
</tr>
<tr>
<td>301 F</td>
<td>90-95</td>
<td>yes</td>
<td>YES</td>
</tr>
<tr>
<td>301 B</td>
<td>90-95</td>
<td>yes</td>
<td>NO</td>
</tr>
<tr>
<td>310</td>
<td>90-95</td>
<td>yes</td>
<td>YES</td>
</tr>
<tr>
<td>301 F</td>
<td>95-100</td>
<td>yes</td>
<td>YES</td>
</tr>
</tbody>
</table>
Outcome of the project

→ Only category B flags were applicable for predictions for ‘Ready Biodegradability’:
  - MW is beyond ranges applicable;
  - structure fragments are out of domain of specific model.

→ Current analysis indicates
  o that summary conclusion from BIOWIN is conservative;
  o that as recommended in Guidance R.11: combination of BIOWIN models predicts potential P/vP substances relatively well;
  o that for non-RBD substances all 5 CATABOL/CATALOGIC models predicted low degradation.

→ Limited number of substances addressed – work ongoing.

→ There are some hundreds of RBD studies conducted after 2009 in REACH database - methodology developed will be used to extend analysis to substances with valid (curated) RBD studies.
Grouping and read across
ECHA grouping work for prioritisation of hazard and risk assessment

→ Preparatory work to support REACH and CLP processes ⇒ prioritise substances for future EU regulatory risk management (EU RRM).

→ Information (mainly) from REACH registration dossiers
   ⇒ ‘no priority for now’
   ⇒ more information needed
   ⇒ EU RRM needed

For P assessment:

→ Often only screening level information available.
→ Grouping approaches to find trends in degradation potential.

✓ Since 2019: over 6300 substances grouped in ~225 groups
✓ EU RRM* proposed for ~35% of substances

Examples:
• Flame retardants groups
• Hydrocarbyl siloxanes

Working with Groups - ECHA (europa.eu)
**PBT/vPvB and PMT/vPvM candidates**

(by end July 2023)

→ For PBT/PMT there is insufficient information for many substances/groups even on screening level

→ Clarification of hazard and consequently regulating PBT/PMT substances may therefore be a long process

→ Greater confidence in QSAR predictions would reduce the number of inconclusive cases

→ Reliable QSARs could be used to:
  
  ➔ Provide ‘screening’ level information

  ➔ Prioritise substances (or constituents) for which data generation is most needed

  ➔ To speed up action where it matters the most.

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*Since 2019, 225 groups were assessed*
Relevant guidance

→ REACH Guidance on IR&CSA updated!
  ✓ IR_CSA_R7b_v5.0_202312_en (europa.eu)
  ✓ IR_CSA_R11_v4.0_202312_en (europa.eu)

→ OECD (Q)SAR Assessment Framework: Guidance for the regulatory assessment of (Quantitative) Structure – Activity Relationship models, predictions, and results based on multiple predictions

CLP Guidance for new hazard classes under drafting!

See ECHA presentation: Wed 10:05

7.02.T-03 - The OECD (Q)SAR Assessment Framework for REACH Dossier Evaluation
Do you have any questions?

ECHA poster: (1.11.P-Th070) *How Well QSARs Predict Aquatic Toxicity of REACH Registered Substances?*
Thank you

The above represents the opinion of the authors and is not an official position of the European Chemicals Agency.

marta.sobanska@echa.europa.eu

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