How Well QSARs Predict Aquatic Toxicity of REACH Registered Substances?

Lale Carstensen 1, Tatiana Netzeva 2, Doris Hirmann 2, Romanas Cesnaitis 3, Anna-Maija Nyman 2
1 ECHA traineeship 1 Sept 2023 – 29 Feb 2024
2 European Chemicals Agency, FI-00121 Helsinki, FINLAND

Introduction

• All standard information requirements can be adapted by a reliable and relevant QSAR adaptation (Annex XI, Section 1.3)
• But do QSARs always produce same information on all the effects measured in a reliable OECD TG 210 study (hatching and survival, abnormal appearance, abnormal behaviour, weight, length)?
• Purpose of this study was to assess whether the use of QSARs would estimate hazards differently to standard experimental studies and whether any differences would affect regulatory decision-making.

Materials and methods

1. We collected newly conducted reliable long-term fish studies (OECD TG 210) resulting from ECHA evaluation decisions
   • 89 experimental studies received (>23 not yet evaluated), out of which 49 were for monoconstituent;
2. We predicted chronic fish toxicity (NOEC) by QSAR models ECOSAR v2.2, VEGA v1.2.0 (IRFMN v1.0.1) and iSafeRat® Desktop version 4.2 for the same (monoconstituent) substances;
3. We predicted NOEC values (most sensitive) were compared to the predictions;
4. We assessed whether any deviation between experimental data and prediction would affect regulatory risk management by exceeding the specific thresholds
   • Chronic 1 or 2 classification (assuming non-rapid degradation),
   • T criterion under PBT assessment.

Results

What effect endpoint drives the NOEC (substances sorted according to the lowest NOEC)?

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Short-term fish studies (OECD TG 210)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>Length</td>
</tr>
</tbody>
</table>

Conclusions

1) Further work is needed in model development for them to be used in regulatory hazard assessment instead of experimental long-term fish studies such as OECD TG 210:
   • Improvements needed to widen the applicability domain. The models we tested could produce predictions for:
     ➢ ECOSAR: 18/49 substances (no warning flags + ECWA warnings); ECOSAR: 8/49 (no warning flags);
     ➢ VEGA: 3/49 substances (high reliability);
     ➢ iSafeRat: 16/49 substances.
   • Different regulatory outcome with (Q)SAR
     ➢ ECOSAR: No flags but still 50% mismatch for regulatory outcome ("Esters", "Amides")
     ➢ ECOSAR: Flag C (ECHA) predictions had 82% mismatch. Flags based on N, R2, need to be considered (e.g. "Amides", "Carbonyl Ureas", "Aliphatic Amines", "Benzoizoxoles")
     ➢ iSafeRat provides a better match: 10/16 the same regulatory outcome and 0/16 nonconservative T.

2) The OECD TG 210 study may not capture the long-term effects properly for superhydrophobic substances (there are issues with maintaining the substance in the solutions etc)
   • ECOSAR and iSafeRat for such substances are often overconservative but are more correct.