Performance of the iSafeRat® Model in the Recent ECHA Evaluation of Chronic Fish Toxicity Predictions

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Introduction

Chronic fish toxicity is a mandatory endpoint for environmental hazard assessment under the **REACH regulation**, particularly for **Persistent, Bioaccumulative and Toxic (PBT)** substances. While the **Fish Early Life Stage test (FELS, OECD TG 210)** remains the gold standard, the **3Rs principle** and regulatory pressure to reduce vertebrate testing have made **QSAR models** essential alternative tools when experimental data are lacking. Several chronic aquatic toxicity models are available for regulatory purposes, **ECOSAR**, **VEGA**, and **iSafeRat®**, but their performance and domain of applicability differ substantially. Recently, **ECHA** published a comparative evaluation of these three tools against newly submitted REACH experimental datasets, providing a unique opportunity to **benchmark their accuracy under real regulatory conditions**. This poster focuses on results obtained with the **iSafeRat® model**, discusses the causes of the observed discrepancies, and highlights the lessons learned for future model improvement.

iSafeRat® Model & KREATiS Workflow

iSafeRat® FishEC10 is a QSAR model developed by **KREATiS** for the prediction of **chronic fish toxicity**, designed as a set of linear regressions between fish EC10 and water solubility values, that meet regulatory requirements for dossier submissions e.g., for **REACH**.

In standard use, iSafeRat® software operates within a **four-step cascade workflow**:

1. **MechoA** (Mechanism of Action) is predicted from molecular structure, determining which local model of iSafeRat® FishEC10 will be applied ;
2. **log K_{OW}** is predicted from molecular structure;
3. **Water solubility** is predicted from log K_{OW};
4. **Chronic fish toxicity** is predicted from water solubility by iSafeRat® FishEC10.

Nevertheless, regulatory documentation cannot be generated automatically by the software as this task is performed in-house by KREATiS experts. A prediction is produced **only** if the substance is **not outside the applicability domain (AD)**, ensuring that **every result delivered is reliable**. In the standard **KREATiS regulatory workflow**, experts review all available input parameters (experimental or predicted) to **choose the most reliable input** for the prediction[2].

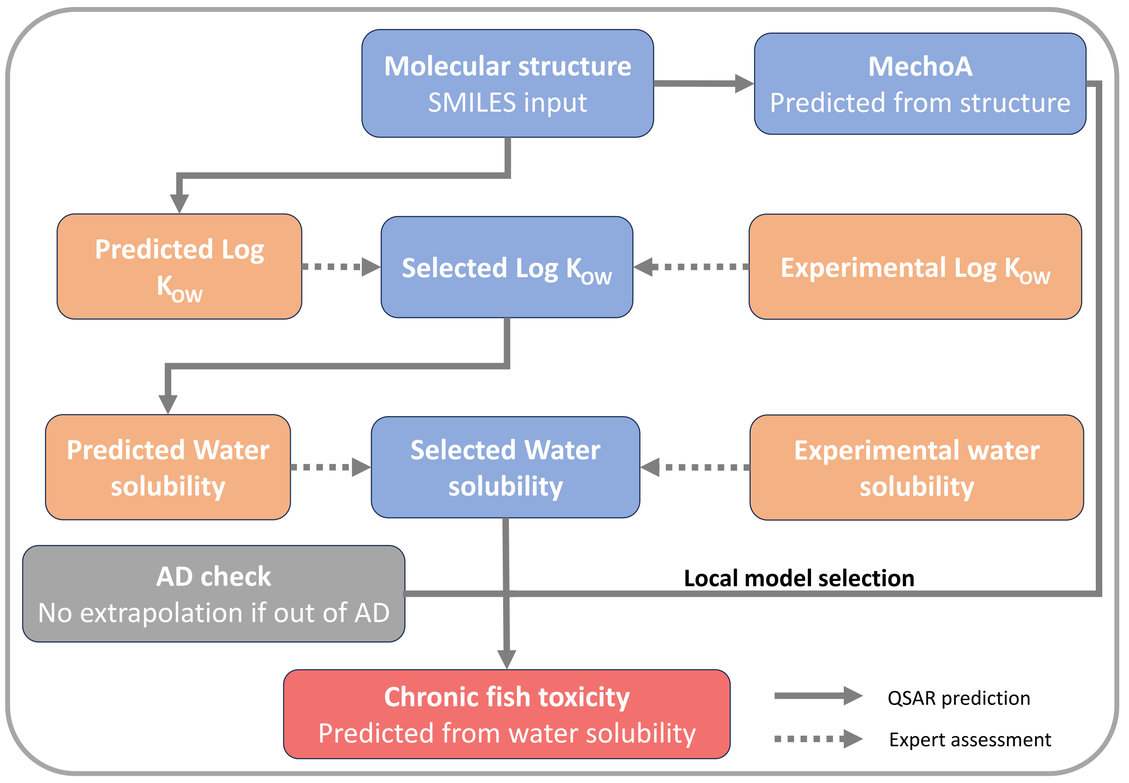

Figure 1. KREATiS regulatory workflow for chronic fish toxicity prediction using iSafeRat®

ECHA Evaluation Methods

- **Dataset:** 49 organic monoconstituent substances with GLP-compliant FELS studies (OECD TG 210) submitted under REACH, covering three fish species : *Pimephales promelas*, *Danio rerio* and *Oryzias latipes*[1]
- **Endpoint:** Lowest reported NOEC across all measured parameters (hatching, survival, weight, length)
- **Models evaluated:** ECOSAR v2.2 | VEGA v1.2.0 (IRFMN v1.0.1) | iSafeRat® Desktop v4.2.18
- **Prediction conditions:** All predictions generated directly from SMILES, with no expert correction of intermediate parameters *(worst-case scenario)*
- **Performance criterion:** A prediction is classified as well-predicted if it deviates from the experimental NOEC by **less than a factor of 10**, consistent with CLP and PBT classification thresholds

ECHA Evaluation Results

Out of the 49 substances in the ECHA dataset, **iSafeRat®** models produced predictions for **18 compounds** falling within its applicability domain. One substance was identified as an outlier, with toxicity underestimated by more than a factor of 10. Overall, **17 out of 18 predictions were well-predicted**, For **ECOSAR**, **25 out of 49 predictions** were produced without uncertainty flags. For **VEGA, only 2 predictions** out of 49 were considered highly reliable (ADI > 0.75), both within a factor of 10 of the experimental NOEC, though the dataset is too limited to draw any conclusions on model performance.

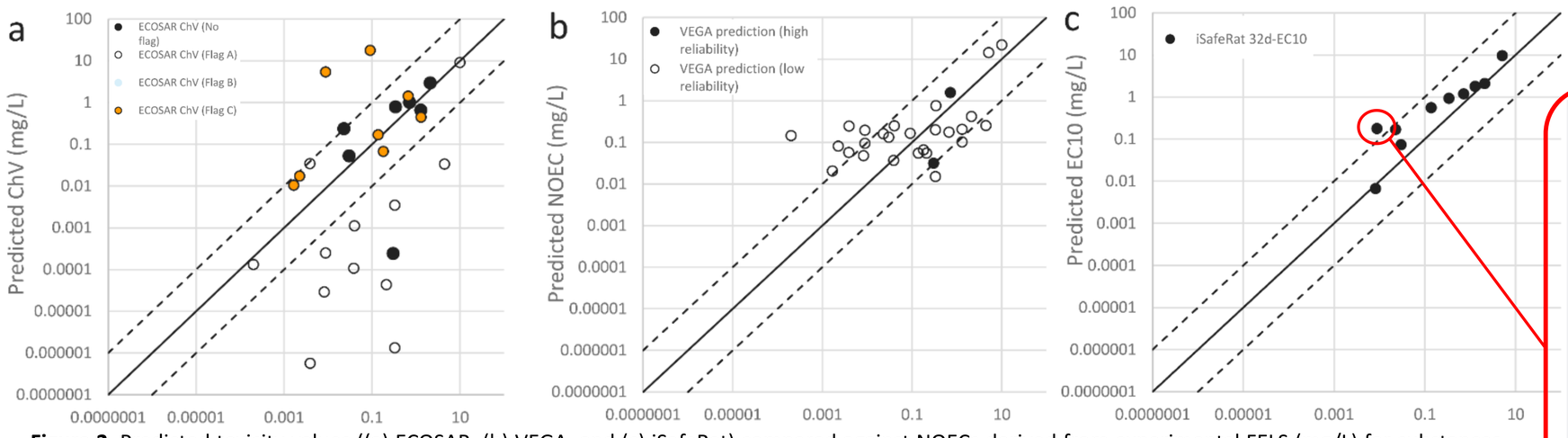

Figure 2. Predicted toxicity values ((a) ECOSAR, (b) VEGA, and (c) iSafeRat) compared against NOECs derived from experimental FELS (mg/L) for substances which induced effects in the study. Filled black circles are reliable predictions by the model. Empty circles are predictions where the model flags an uncertainty in the prediction (ECOSAR) or low reliability (VEGA). iSafeRat does not provide values that are considered unreliable by the model itself. Additionally, for ECOSAR we plotted in orange filled circles the predictions where some additional considerations on uncertainty were associated (such as the number of substances in the training set <5 or low Rs2). Figure from Nyman et al. (2025)[1].

Outlier

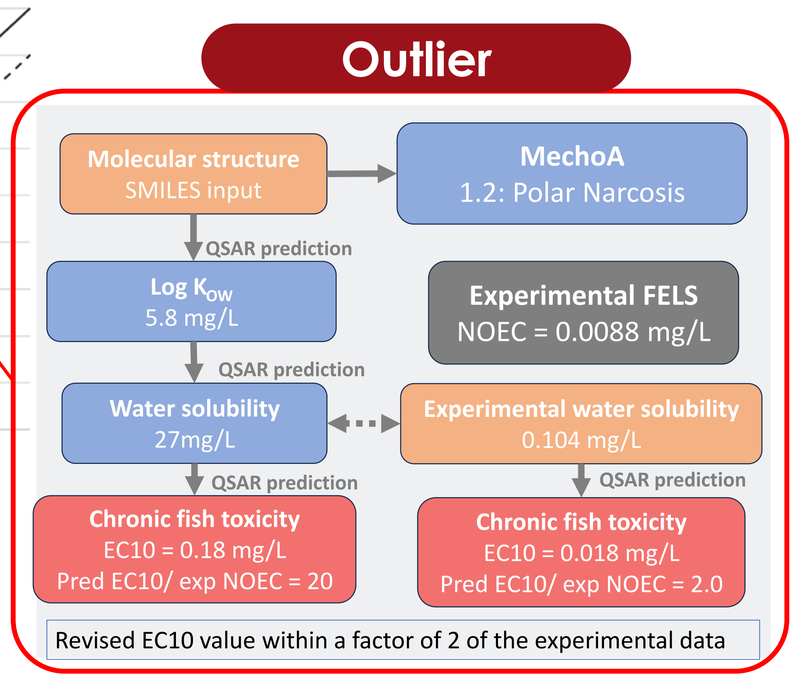

Figure 3. Impact of water solubility input on chronic fish toxicity prediction for the outlier substance (EC No. 253-039-2)

Lessons Learned & Perspectives

The main lesson drawn from this evaluation concerns the **critical role played by intermediate parameters** in the prediction cascade. As demonstrated by the single outlier case, an inaccurate **log K_{OW}** or **water solubility** value can propagate through the cascade and lead to a significantly erroneous final toxicity prediction.

Two key principles emerge from this analysis :

- 🔬 **Verify intermediate parameters:** Predicted log K_{OW} and water solubility should always be checked against reliable experimental data when possible, or considered by an expert chemist before running the final toxicity prediction.
- 👤 **Apply expert judgement**: An informed user who critically reviews each step of the cascade is a **key factor** in achieving the best possible prediction, both to assess the reliability of input parameters and to interpret the predicted output.

With ongoing model refinements and improvement of model's applicability domains, **KREATiS anticipates enhanced performance** in forthcoming evaluations, exceeding the results observed under the stringent conditions of the present ECHA publication.

Conclusion

This poster presents and discusses the performance of the **iSafeRat® chronic fish toxicity model** as evaluated by ECHA (Nyman et al. (2025)[1]. With **17 out of 18** in-domain predictions classified as **well-predicted**, the results are overall highly satisfactory, especially considering that the evaluation was conducted under **worst-case conditions** with no expert correction of intermediate parameters.

The analysis of the single outlier clearly illustrates that predictive accuracy is not solely dependent on the model itself, but also on the **quality of the input parameters** used in the cascade. When reliable experimental data are available and integrated at each step, the performance of iSafeRat® is expected to **exceed** what was observed in this evaluation.

These findings confirm the value of **iSafeRat®** as a reliable QSAR tool for chronic fish toxicity prediction in a regulatory context, while reinforcing the **importance of expert judgement**. KREATiS remains committed to the **continuous improvement** of its models and anticipates **enhanced performance** in future versions of our models.

Reference

[1]Nyman, A.-M., Carstensen, L., Cesnaitis, R., Netzeva, T., & Hirmann, D. (2025). Replacing Fish Early Life Stage Toxicity Test: Performance of Three QSAR Tools for Recently Submitted REACH Data. *Environmental Science & Technology*. https://doi.org/10.1021/acs.est.5c08163

[2]Paul Thomas, Pascal Bicherel, Franklin Bauer (2018).How in silico approaches can increase confidence in environmental hazard and risk assessment. Integrated Environmental Assessment and Management 15, 1, 40–50

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