U.S. EPA Fragrance Technical Expert Meeting
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Evaluating Chronic Aquatic Toxicity of Fragrances

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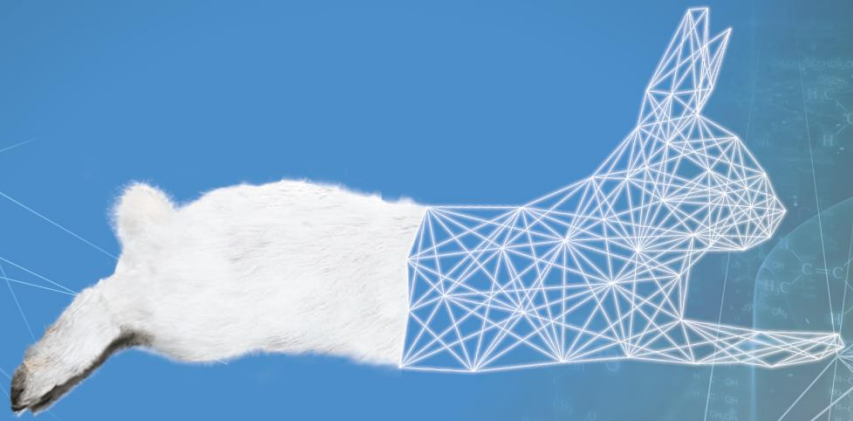

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Overview

Goal: High level of environmental protection through the use of advanced scientific methods whilst reducing animal testing for the assessment of fragrances

Stepwise approach to assessing chronic fish toxicity:

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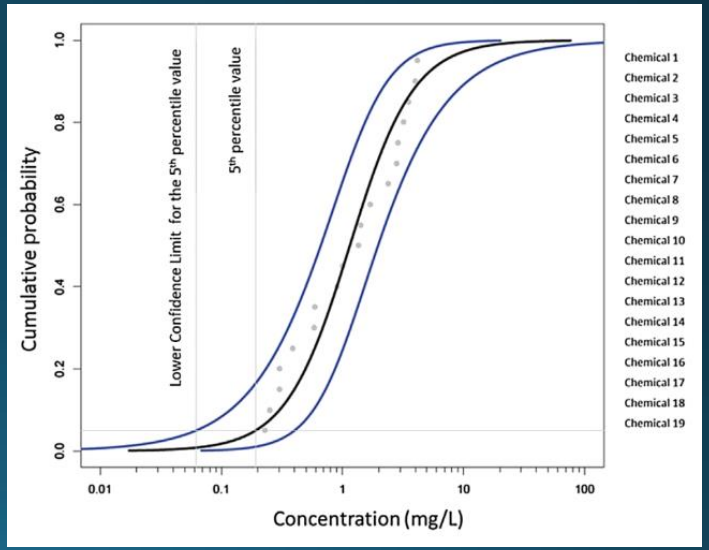
Waiving chronic testing

- Based on limited exposure and rapid biodegradation

Stepwise approach to assessing chronic fish toxicity

Using predictive tools before considering testing

- Species Sensitivity Distributions (SSDs)
- Ecological Threshold of Toxicological Concern (eco-TTC)



Belanger S. et al. It is time to develop ecological thresholds of toxicological concern to assist environmental hazard assessment. *Environ Toxicol Chem*. 2015;34(12):2864-2869. doi:10.1002/etc.3132

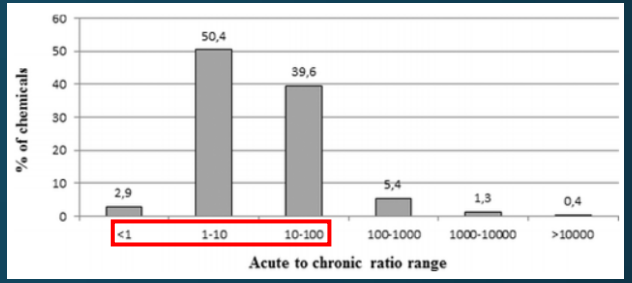
Stepwise approach to assessing chronic fish toxicity

Read-across

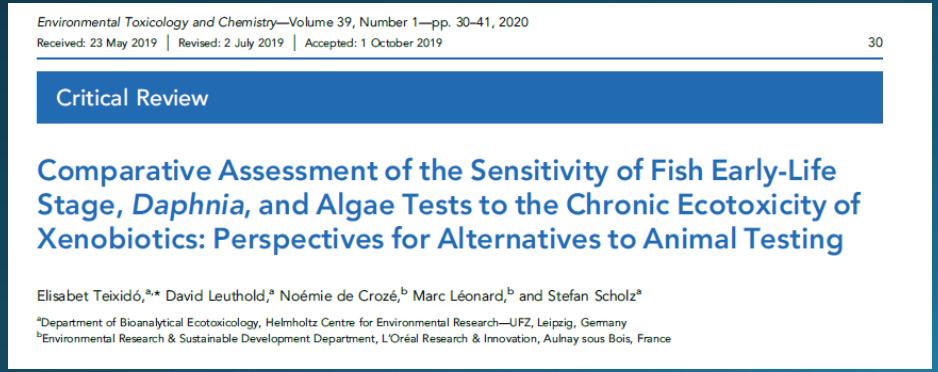
- Category or analogue approach
- Difficult for data-poor chemicals

Weight-of-evidence approach / IATA

- Integrated approaches rather than 1:1 replacements
- **Acute-to-chronic toxicity ratios** of >100 protective for narcotics (Kienzler et al., 2017).
- Daphnia and algae data similar to FELS data for narcotics (Teixido et al., 2019).
- **Fish embryo acute toxicity test** (FET, OECD TG 236): Baseline toxicity at similar concentrations in FET and FELS (Scholz et al., 2018).



Kienzler A. et al. Waiving chronic fish tests: possible use of acute-to-chronic relationships and interspecies correlations. *Toxicol Environ Chem.* 2017;99(7-8):1129-1151.



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Critical Review

Comparative Assessment of the Sensitivity of Fish Early-Life Stage, *Daphnia*, and Algae Tests to the Chronic Ecotoxicity of Xenobiotics: Perspectives for Alternatives to Animal Testing

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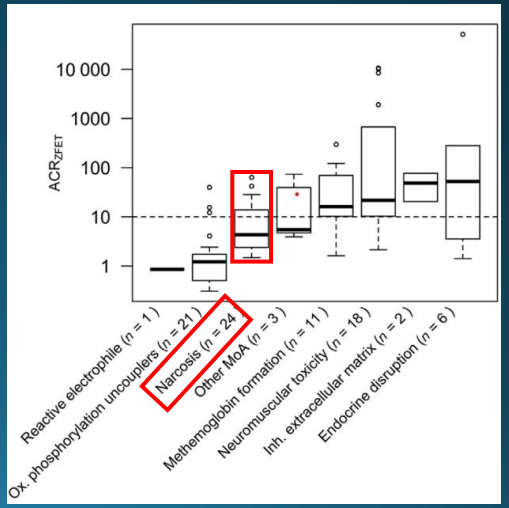
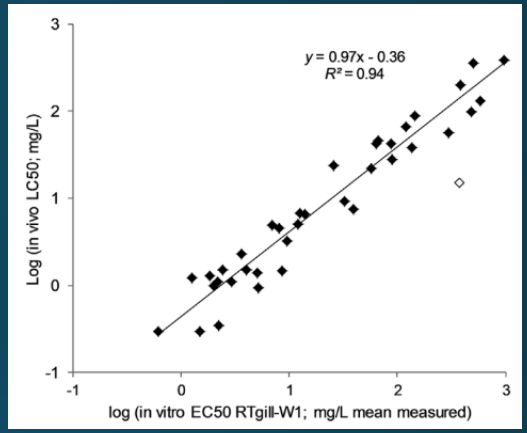


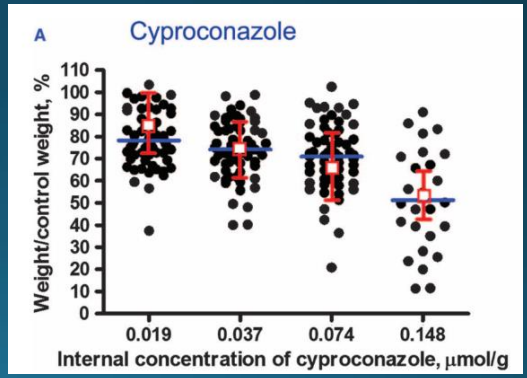
Scholz S. et al. Meta-analysis of fish early life stage tests-Association of toxic ratios and acute-to-chronic ratios with modes of action. *Environ Toxicol Chem*. 2018;37(4):955-969.

Weight-of-evidence approach / IATA

- **RTgill-W1 cytotoxicity test** (OECD TG 249): Good predictivity of acute toxicity of 38 fragrances (Natsch et al., 2018).
- Cell proliferation to predict fish growth (Stadnicka-Michalak et al., 2015).
- Take into account applicability domains of methods
- Non-vertebrate data sufficient, e.g., chronic daphnid testing?
- Future goal: AOP networks to predict chronic apical endpoints



Natsch A. et al. Accurate prediction of acute fish toxicity of fragrance chemicals with the RTgill-W1 cell assay. *Environ Toxicol Chem*. 2018;37(3):931-941.



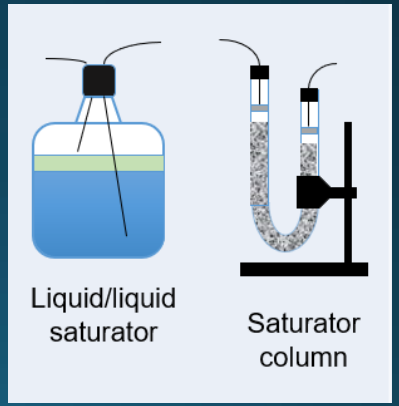
Stadnicka-Michalak J. et al. Toxicology across scales: Cell population growth in vitro predicts reduced fish growth. *Sci Adv*. 2015;1(7):e1500302. doi:10.1126/sciadv.1500302

Chronic fish testing as a last resort

a. Determine concentration range for chronic tests using **baseline toxicity models** (e.g., QSARs for Kow)

b. Careful application of **OECD GD 23** on Aqueous-Phase Aquatic Toxicity Testing of Difficult Test Chemicals

- Poorly water-soluble chemicals
- Highly volatile chemicals
- Avoid the use of solvents through direct addition, generator systems, passive dosing, flow-through exposure systems



Outlook

- Consider applying stepwise approach for assessment of fragrances
- Is there scope for conducting a joint analysis of fragrance data with stakeholders to explore how confidence in advanced methodology can be increased and grouping and read-across for fragrances can be supported while ensuring a high level of environmental protection?

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