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THINKING AHEAD IN TOXICOLOGY

CHALLENGES ENCOUNTERED DURING THE INITIAL STAGES OF EXPOSURE ASSESSMENT IN REACH REGISTRATIONS

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Introduction

Two decades have gone by since the implementation of the EU REACH regulation, and registrants are still facing numerous challenges at every step of exposure assessment, such as collection of key input parameters, description of the lifecycle tree, definition of a strategy, and/or exposure estimation itself.

A scientifically sound rationale is required for the selection of the key input parameters affecting the human health and environmental exposure assessment, including physico-chemical (PC) and environmental fate (E-fate) properties, an especially daunting task in the case of complex substances such as UVCBs.

ECHA Guidance Chapter R.12 on building life cycle trees must be understood and followed. Organized and logic lists of uses are key to ease the communication down the supply chain, and some watchouts on tonnage and spERCs selection should be considered to avoid over-estimation of exposure.

This poster presents several case studies with UVCB substances where an iterative process was adopted to refine the exposure estimates within the framework of current European Chemical Agency (ECHA) guidance.

Prior to starting an assessment, critical review of the substance's properties and intended uses helped the assessors define the scope. Not only the values for key endpoints but also how the data was generated and the logic behind the selection of these values and their consistent application were part of this exercise and guided the overall strategy for exposure assessment.

Overall, the case studies reflect a tiered approach that should be applied to identify where additional resources need to be targeted for the refinement of assessment approaches, further data generation or gathering, or the consideration of risk management activities.

Considerations prior to starting an assessment

Minimal list of key input parameters needed for an assessment

Input parameter	Workers	Consumers	Environment
Physical state	x		
Molecular weight (MW)	x	x	x
Melting point (MP)	x		x
Vapour pressure (VP)	x	x	x
Partition coefficient: log Kow			x
Water solubility (WS)			x
Biodegradation in water			x
Bioaccumulation: BCF (aquatic)			x
Adsorption/desorption: log Koc			x

Determination of substance properties (and logic behind selection)

- Estimated (QSAR) vs. Experimental vs. Read Across.
- Maximum value vs. Average value vs. Weighted average value vs. Most representative constituent value.

Some watch-outs

- Water solubility – watch out for poorly soluble substances (<1 mg/L), review for consistency against ecotoxicity testing values.
- Vapour pressure - watch out for negligible VP (below 0.01 Pa) for liquids (SVC)
- Log Kow /Log Koc – watch out for poorly soluble substances as partitioning could be overstimated.
- Log Kow /Log Koc – review if Equilibrium Partitioning Method (EPM) was implemented for soil and sediment during the PNEC calculations (implication on the adsorptive factor of 10).

Challenges related to life cycle tree creation

Guidance on life cycle tree creation

- Follow ECHA Guidance Chapter R12 on life cycle tree rules (and correct the uses with irrelevant ERCs/PROCs/PCs/ACs which are incompatible with the nature of the uses (e.g., ERC 1 for a formulation)).
- Organize the life cycle tree and bring clarity and logic to the flow.

Some watch-outs

- Watch out for mandatory service life uses based on specific Environmental Release Categories used (ERC 8c/8f/5).
- Watch out for inconsistent reporting of tonnage information between uses which leads to an overestimated assessment (e.g., PEC regional).

Review of input parameters within a life cycle tree

- Vapour pressure
  - Process °C vs. Experimental °C.
  - Selection of spERCs.
- Melting point
  - Process °C vs Melting point °C (assessment conducted as liquid).

Overcoming challenges

Additional resources

- Use of Tier 2 tools.
- Use of biomonitoring data.

Data generation

- *In vitro* dermal absorption assay.
- Kinetics data.
- Soil and/or sediment degradation.

Additional conditions of use

- On-site treatment plant.
- Specialized RMMs.

Selection of key vapour pressure value

Background: Complex UVCB substance (liquid) with 6 constituents; each representing 10-25% of the composition. Vapour pressure determination conducted via experimental study OECD 104 (VP at < 1.1 x 10^{-8} Pa) considered unreliable due to high temperature at which the substance decomposed (based on flash point data).

Definition of worst-case:
Human Health: A high value VP maximises inhalation exposure.

Approach: (Q)SAR modelling - EPISuite v4.11 - for individual constituents, yielding a wide range of predicted values (from 9.8 x 10^{-14} to 4.2 Pa, with a weighted average of 1.4 Pa at 25°C).
Life cycle tree mentioned processes requiring VP at higher temperatures. Weighted average of 880 Pa at 95°C and 4150 Pa at 120°C were implemented in the exposure assessment.

Outcome: Following a conservative approach; 4.2 Pa at 25°C was selected for exposure assessment of scenarios at room temperature. VP values at higher temperatures only used for relevant exposure scenarios with higher operating temperatures. The test substance was considered as having low volatility at room temperature.

Approach	Experimental value 1.1 x 10-8 Pa	Lowest predicted value 9.8 x 10-14 Pa	Highest predicted value 4.2 Pa	Weighted average value 1.4 Pa
HH: RCR inhalation (Ind. PROC 8b operating T °C = 40°C)	2.09E-3	2.09E-3	0.104	0.104

Impact of change in WS and log Kow values

Background: Complex UVCB with >10 constituents; 3 main constituents representing 54% of the composition. Initially (Tier 1 testing), log Kow determined by HPLC peaks of these constituents and not in line with the water solubility value (initially determined via the shake-flask method).

Approach: The log Kow was re-calculated as a ratio of water solubility (re-determined through CMC method since the substance was surface active) and n-octanol solubility as part of Tier 2 testing.

Outcome: The resulting WS and Log Kow values were in line and found to be significantly different from the initial values. This resulted in significant difference in exposure estimates for some of the environmental compartments (snapshot from the Chesar 3.9 tool below).

Tier 1 result:
Log Kow/WS: 0.2/1.8E5 mg/L

Environmental exposure es		
Fresh water	6.67E-5 mg/L	0.454
Sediment (freshwater)	6.67E4 mg/kg dw	0.454
Marine water	6.67E-6 mg/L	0.454
Sediment (marine water)	6.67E3 mg/kg dw	0.454
Sewage Treatment Plant	10.00 mg/L	3.279
Agricultural soil	0.457 mg/kg dw	1.55E-5

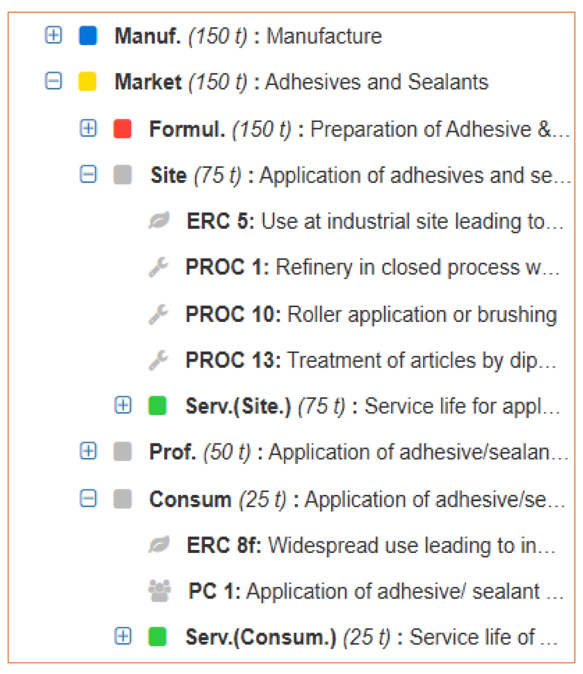
Tier 2 result:
Log Kow/WS: 4.85/10 mg/L

Environmental exposure estimat		
Fresh water	1.6E-5 mg/L	0.109
Sediment (freshwater)	1.6E4 mg/kg dw	0.109
Marine water	1.6E-6 mg/L	0.109
Sediment (marine water)	1.6E3 mg/kg dw	0.109
Sewage Treatment Plant	2.4 mg/L	0.787
Agricultural soil	0.146 mg/kg dw	4.98E-6

Building of Life Cycle tree

Background: Substance requiring numerous uses and/or contributing activity types.

Approach: Build the life cycle tree with as many markets as required, including in each market the relevant uses, starting with Formulation, down to Consumer uses, and integrating service life requirements when needed (market knowledge and/or ERC 5/8c/8f mandatory).



In ideal assessments, the sum of Site, Professional, and Consumer use tonnage information should correspond to the Formulation tonnage information (the market tonnage information).

Outcome: A life cycle tree needs to be properly structured, to easily understand the path taken by the substance throughout its use life.

Conclusions

- Hazard and exposure teams should work hand-in-hand during the input parameter selection to clarify the different considerations required prior to starting an assessment.
- Define the input parameters, life cycle tree, and strategy that make the most sense for a proper exposure assessment.
- Challenges may be overcome with additional resources, data generation and/or additional conditions of use.