Persistence assessment in the regulatory assessment and management of chemicals

Setac Europe 34th Annual Meeting

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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

Potentially persistent (REACH)

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

Thresholds in Persistence assessment		REACH/CLP
Screening	**Mineralisation (%)**	
	Readily biodegradable	Not P/vP
	Inherently biodegradable fulfilling spesific criteria	Not P/vP
Assessment	**Half-life (days)**	
Water fresh/estuarine	> 40 (marine > 60) > 60	P vP
Sediment fresh/estuarine	> 120 (marine > 180) > 180	P vP
Soil	> 120 > 180	P vP

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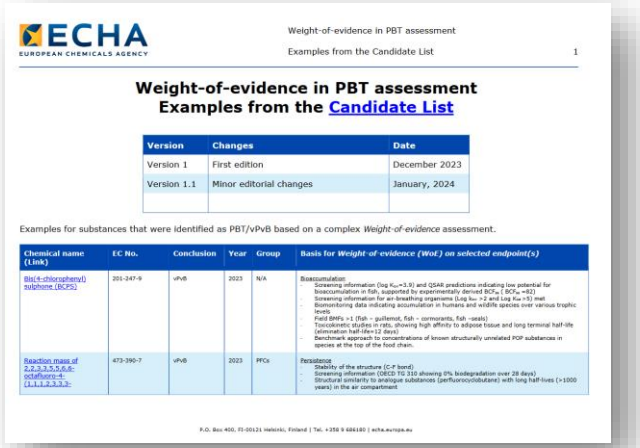
Use of (Q)SARs in persistence assessment

(Q)SARs as part of Weight-of-Evidence in P-asssessment

- (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 constituens of a UVCB substances,
  - ✓ predicting formation of degradation products.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Weight-of-evidence in PBT assessment
Examples from the Candidate List 1

Weight-of-evidence in PBT assessment
Examples from the Candidate List

Version	Changes	Date
Version 1	First edition	December 2023
Version 1.1	Minor editorial changes	January, 2024

Examples for substances that were identified as PBT/vPvB based on a complex *Weight-of-evidence* assessment.

Chemical name (Link)	EC No.	Conclusion	Year	Group	Basis for *Weight-of-evidence (WoE) on selected endpoint(s)*
Bis(4-chlorophenyl) sulphone (BCPS)	201-247-9	vPvB	2023	N/A	Bioaccumulation - Screening information (log K_{ow}=3.9) and QSAR predictions indicating low potential for bioaccumulation in fish, supported by experimentally derived BCF_K (BCF_K =82) - Screening information for air-breathing organisms (Log k_M >2 and Log K_M >5) met - Biomonitoring data indicating accumulation in humans and wildlife species over various trophic levels - Field BMFs >1 (fish – guillemot, fish – cormorants, fish –seals) - Toxicokinetic studies in rats, showing high affinity to adipose tissue and long terminal half-life (elimination half-life=12 days) - Benchmark approach to concentrations of known structurally unrelated POP substances in species at the top of the food chain.
Reaction mass of 2,2,3,3,5,5,6,6-octafluoro-4-(1,1,2,3,3,3-hexafluoropropoxy)-1-butanesulfonic acid and 2,2,3,3,4,4,5,5-octafluoro-5-(1,1,2,3,3,3-hexafluoropropoxy)-1-pentanesulfonic acid	473-390-7	vPvB	2023	PFCs	Persistence - Stability of the structure (C-F bond) - Screening information (OECD TG 310 showing 0% biodegradation over 28 days) - Structural similarity to analogue substances (perfluorocyclobutane) with long half-lives (>1000 years) in the air compartment

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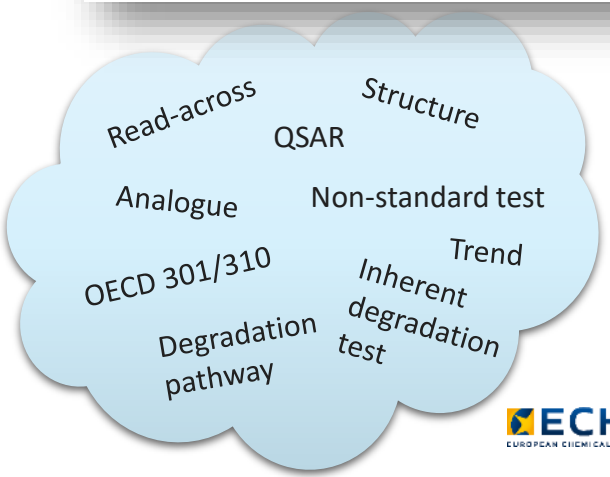

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Use of (Q)SARs in environmental hazard assessment for P-screening

Aim:

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

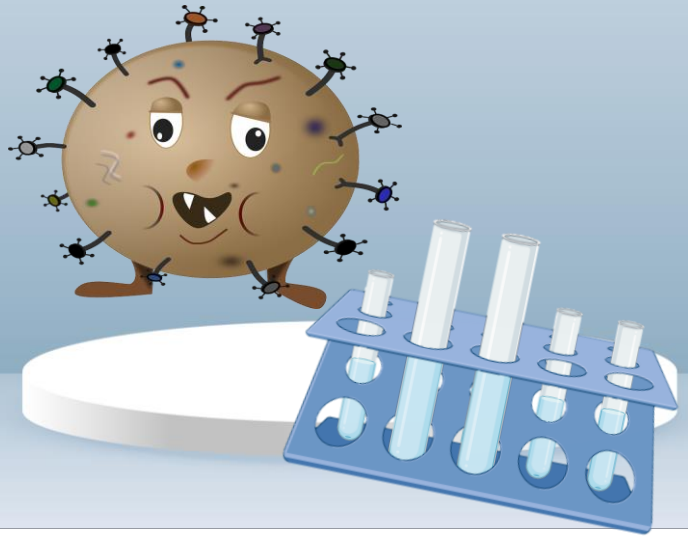
Motivation:

- (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)



V/S

QSAR predictions (mono-constituents)

EpiSuite™
VEGA QSAR
CATALOGIC
iSafeRat

Source: starline on freepik (background image), Lovibond.com (respiratoric bottle), biorender.com (other)

*Experimental data generated via REACH Evaluation processes and formally assessed 'as accepted'

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Assessment of (Q)SARs: Principles

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

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

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**

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

QSAR analysis done with organic mono-constituents

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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).

Substances	Experimental results		Predictions by specific model										
Experimental TG OECD 301/310	Degradation after 28 d, %	10-day window met	BIOWIN	BIOWIN 2	BIOWIN 3	BIOWIN 6	Pot. P/vP (R.11)	CATALOGIC Kinetic 301F v.13.16 (%, BOD 28d)	CATABOL 301C v.02.08 (%, BOD 28d)	CATALOGIC 301C v.11.15 (%, BOD 28d)	CATABOL 301B v.02.07 (%, ThCO2 28d)	CATALOGIC Kinetic 301B v.02.09 (%, ThCO2 28d)	Flags
301 B	0-5	n/a	NO	0.0	1.86	0	YES	21	0	1	0	1.12	Cata. models - 36.36-90.91% of correct fragments.
301 D	0-5	no	NO	0.0	1.85	0	YES	0	0	1	0	1.14	Cata. models - 22.22-77.78% of correct fragments.
301 F	50-55	n/a	NO	0.60	2.79	0.09	NO	0	4	6	1.23	0	BIOWINs - FRAG, CNC. Cata. models - 0% of correct fragments.
301 D	60-65	no	NO	0.58	2.79	0.52	NO	0	77	67	71.8	0	BIOWINs 2/3 - FRAG, CNC; BIOWIN 6 - CNC. Cata. model - 71.43% of correct fragments.
301 D	60-65	no	YES	1.0	3.38	0.78	NO	54	74	76	84.2	30.5	Cata. models - 73.08-92.31% of correct fragments.
Similar to 310	65-70	yes	NO	0.14	2.96	0.49	NO	6	38	11	34	38.1	BIOWINs - FRAG. Cata. models - 42.86-85.71% of correct fragments.
301 F	65-70	no	YES	0.9	2.81	0.64	NO	59	76	70	99.9	81	BIOWINs - FRAG. Cata. models - 0-66.67% of correct fragments.
301 F	90-95	yes	YES	0.9	2.81	0.64	NO	48	76	70	99.9	58.4	BIOWINs - FRAG. Cata. models - 0-66.67% of correct fragments.
301 B	90-95	yes	NO	0.57	2.62	0.42	NO	85	4	5	1.76	100	Cata. models - 71.43% of correct fraction.
310	90-95	yes	YES	1.0	2.90	0.73	NO	81	39	68	39.4	91.9	BIOWINs - FRAG.
301 F	95-100	yes	YES	0.9	2.81	0.64	NO	59	76	75	99.9	82	BIOWINs - FRAG. Cata. models - 0-66.67% of correct fragments.

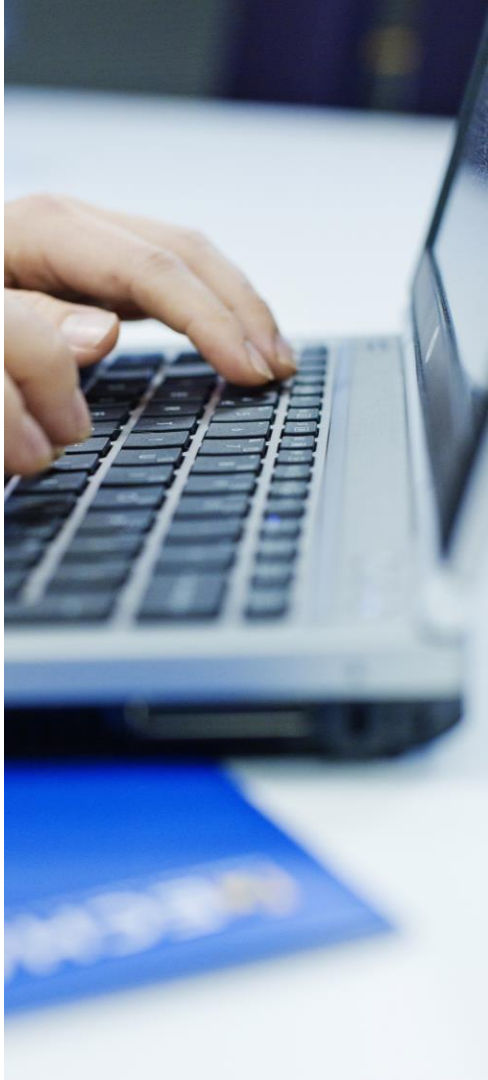
Outcome of the project

→ 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
- that summary conclusion from BIOWIN is conservative;
- that as recommended in Guidance R.11: combination of BIOWIN models predicts potential P/vP substances relatively well;
- 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)

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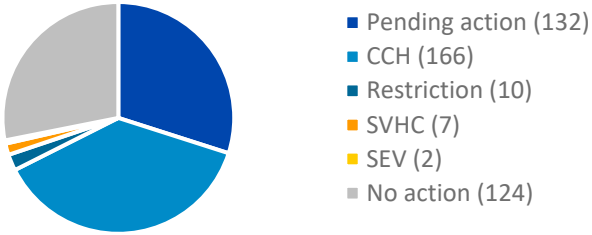
PBT/vPvB and PMT/vPvM candidates

(by end July 2023)

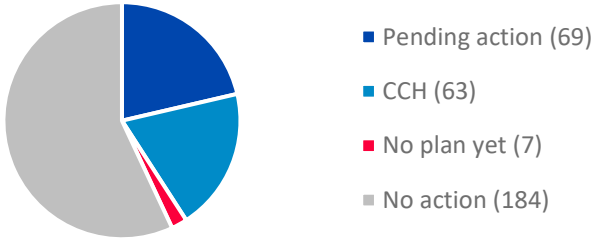
- → For PBT/PMT there is insufficient information for many substances/groups even on screening level
- → Clarification of hazard and consequently regulating PBT/PMT substances may therefore be a long process
- → Greater confidence in QSAR predictions would reduce the number of inconclusive cases
- → 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.

In **62 groups* potential PBT/vPvB** substances (441)



(Inconclusive: 865 substances from 100 groups)

In **23 groups* potential PMT/vPvM** substances (323)



(Inconclusive: 25 substances from 5 groups)

** Since 2019, 225 groups were assessed*

Relevant guidance

→ REACH Guidance on IR&CSA updated!

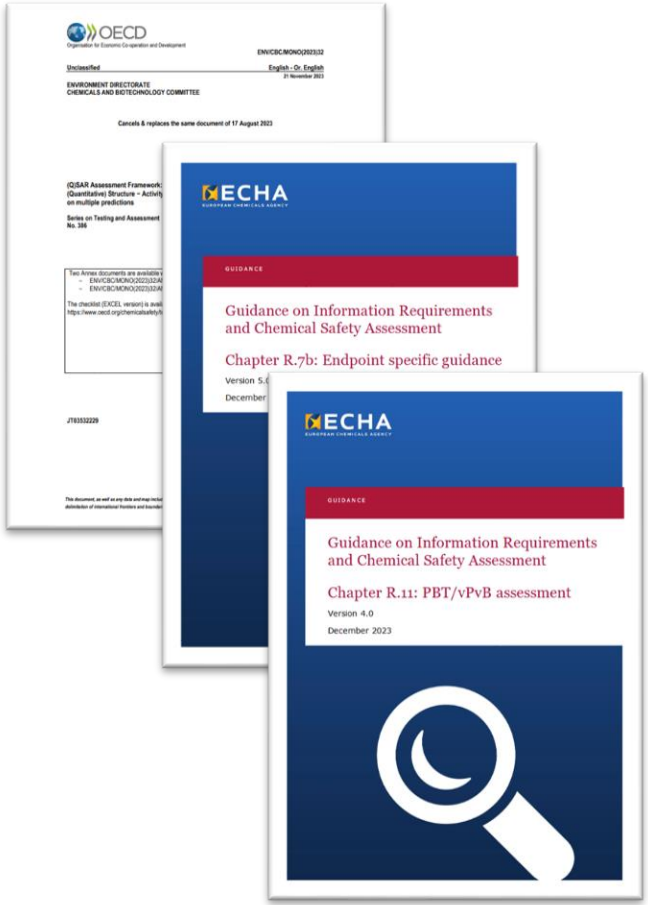
- ✓ *IR_CSA_R7b_v5.0_202312_en (europa.eu)*
- ✓ *IR_CSA_R11_v4.0_202312_en (europa.eu)*

CLP Guidance for new hazard classes under drafting!

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

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

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