CHEMICAL SIMILARITY

Structuring Risk and Hazard Assessment

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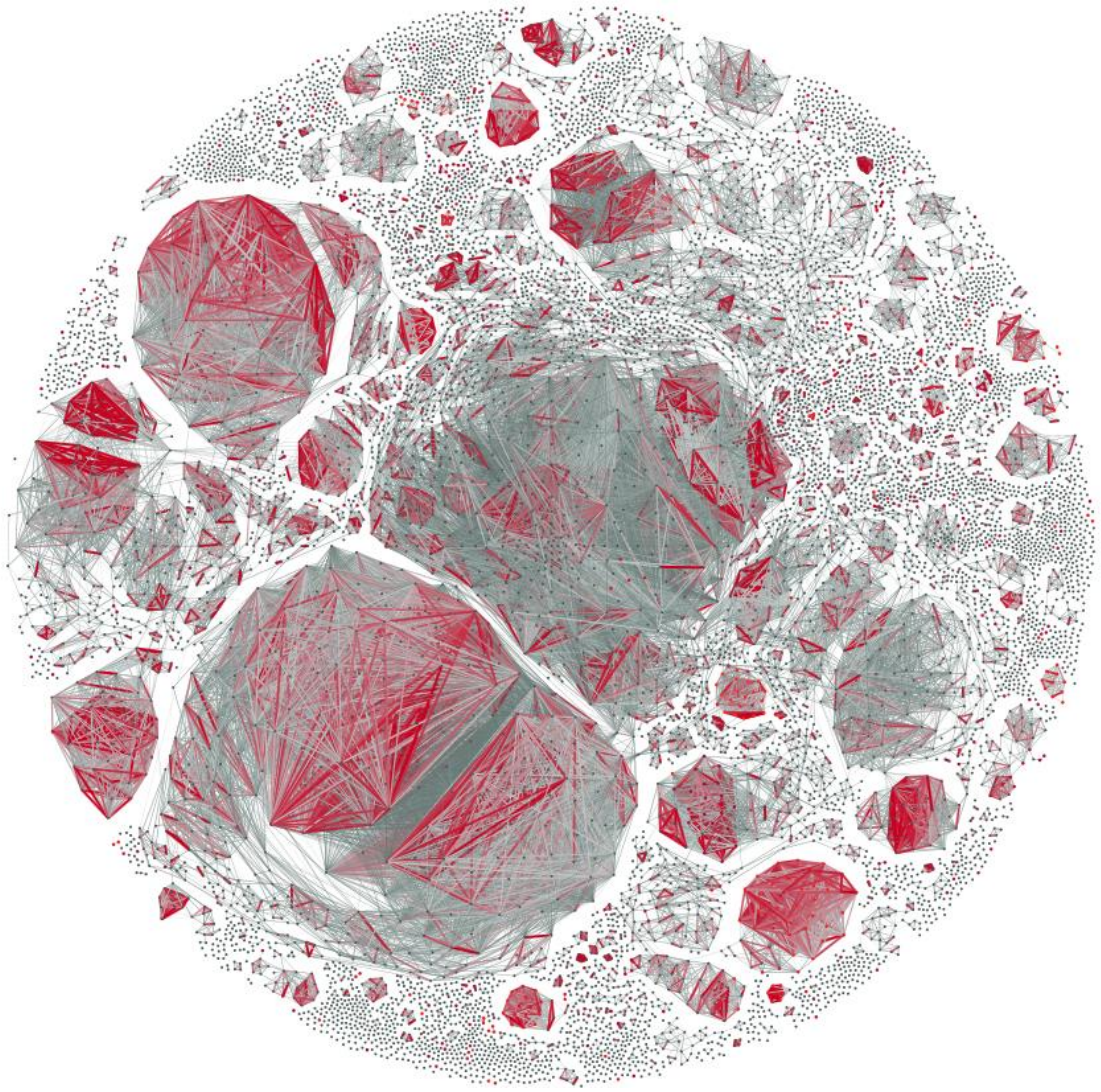
Chemical universe

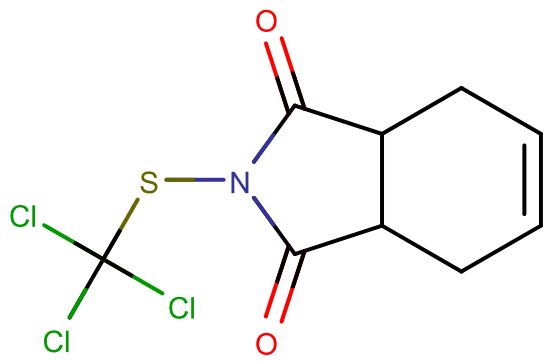
- >350,000 chemicals and chemical mixtures
- Goal: ensure safe use
- Challenges:
  - Lack of (reliable) data
  - Time-consuming processes

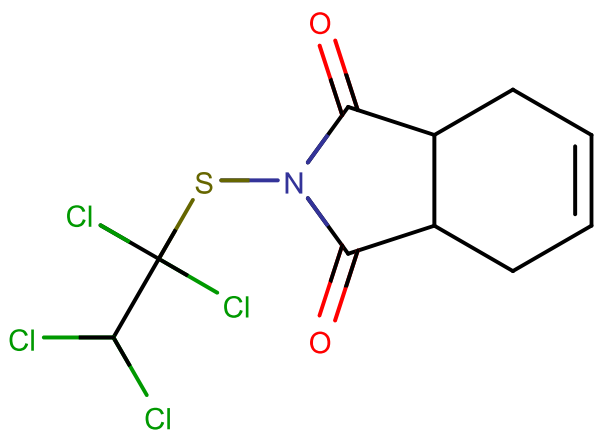


Optimize risk and hazard assessment

- Make more efficient use of available data and knowledge

- Role for chemical similarity:
  - Similar property principle:
    Structural similar chemicals are likely to have similar properties

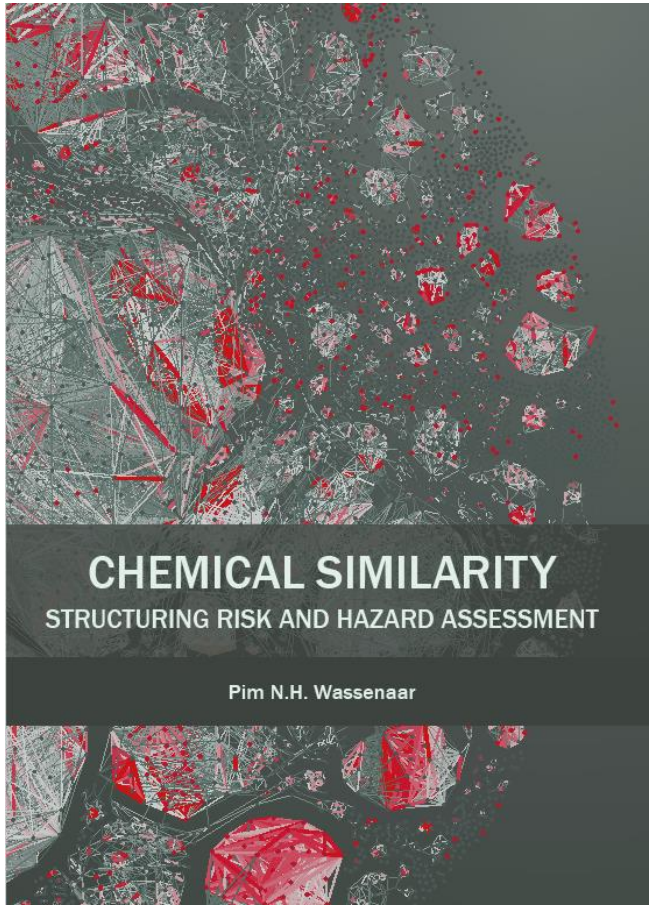




Aim of thesis

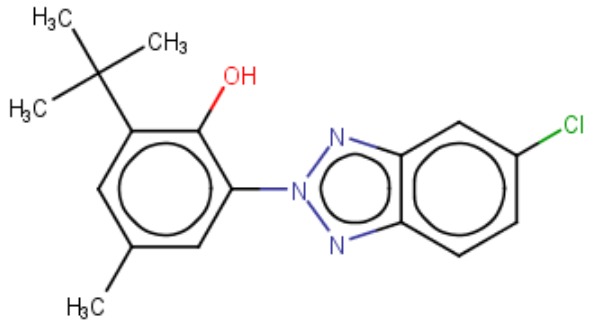
- Investigate how the use of **chemical similarity** could optimize the:
  1. Screening and prioritization; and
  2. Evaluation of chemicals

- Primary focus on SVHCs
  - C, M, R, PBT/vPvB and ED

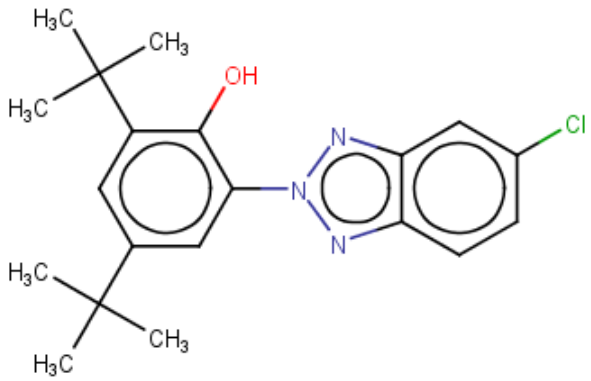


1. Early and effective signaling of concerns

- Signal potential concerns as early as possible:
  - Before widespread exposure
  - Based on limited available data
  - Alternative to resource-intensive expert judgements



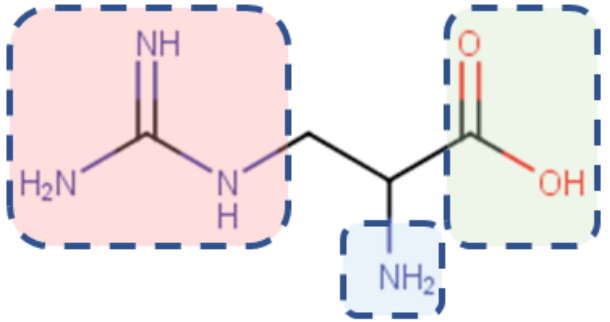
- Similarity-based screening models
  - Identify potential substances of concern based on structural similarity to known SVHCs

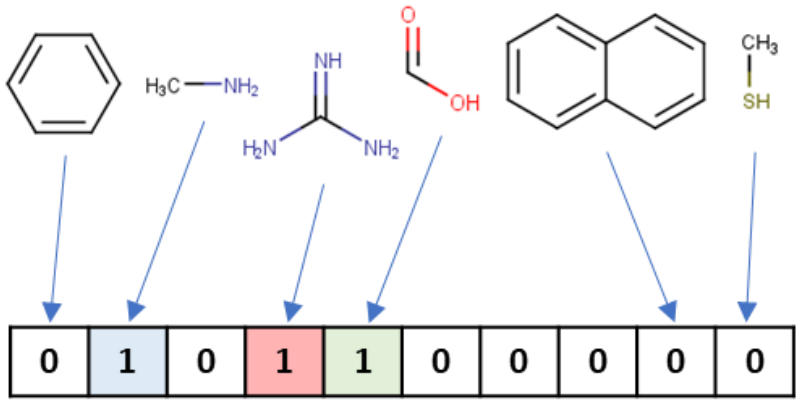


Similarity-based screening models

- General methodology
  - *Fingerprints*
  - *Similarity coefficients*
  - *Threshold values*

Step 1: Define structure





Similarity-based screening models

- General methodology
  - *Fingerprints*
  - *Similarity coefficients*
  - *Threshold values*

- Model optimization and validation
  - *Tested > 500 model combinations*
  - *Using list of SVHC and non-SVHC substances*
  - ➢ *5 sub-models for various SVHC endpoints*

Step 2: Calculate similarity

Substance A →	0	1	0	1	1	0	0	0	0	0
Substance B →	0	1	1	0	1	0	0	0	1	0
	D	C	B	A	C	D	D	D	B	D

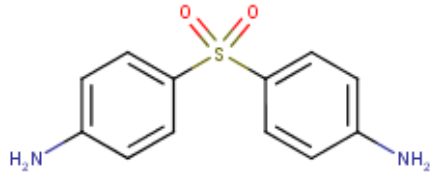
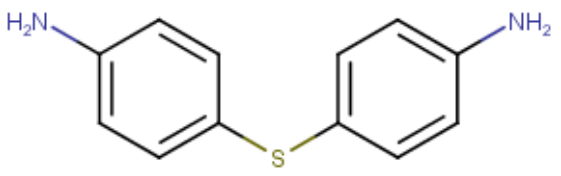
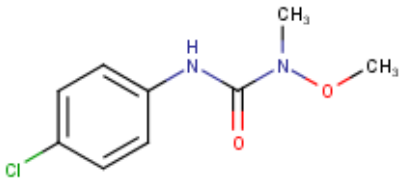
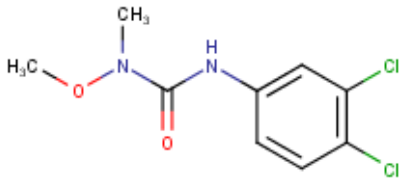
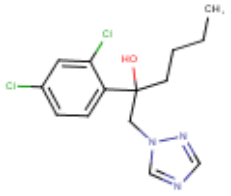
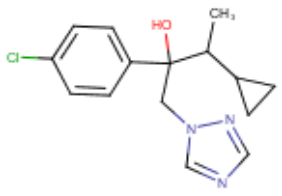
$$Sab = \frac{N_C}{N_a + N_B + N_C}$$

Step 3: Comparison to threshold

Value between 0 and 1

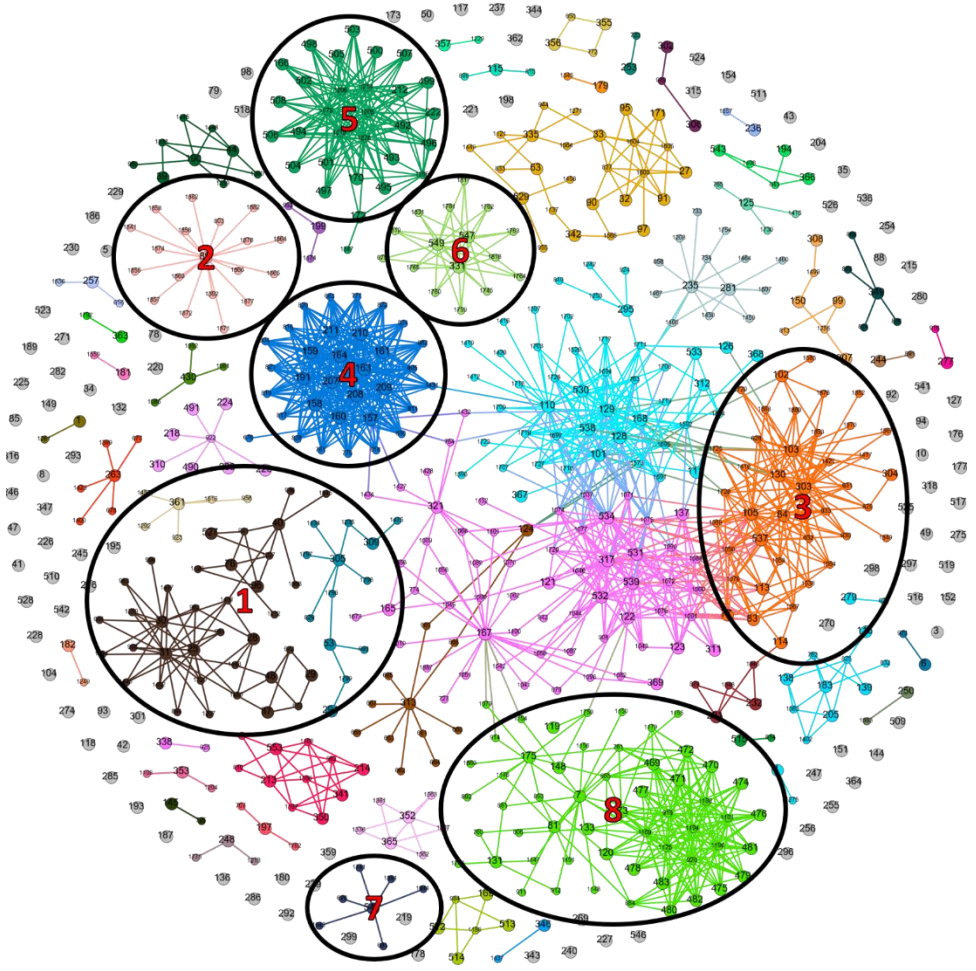
Results

- Individual substances with a high similarity to an SVHC

Unknown concern	*SVHC*
	
	
	

Results

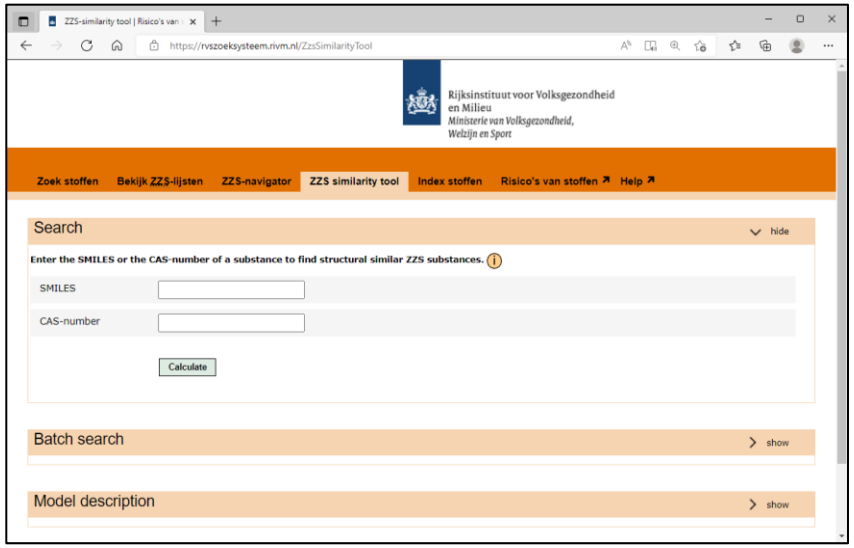
- Individual substances with a high similarity to an SVHC
- Groups of substances
  - Effective use of available data
  - Reduce (animal) testing
  - Accelerate the Risk Assessment
  - Prevent ‘regrettable substitution’
- Trigger for further evaluation:
  - Similar biological properties/effects?



Application – screening tool

ZZS similarity tool

- Freely accessible web-based tool
  - Ease of use and interpretation
  - Provide clear follow-up
  - ≈ 6000 unique visitors!



Risk assessment

- Identify and prioritize potential substances of concern for further evaluation
  - REACH-registered substances
  - Monitoring data
  - Support licensing authorities

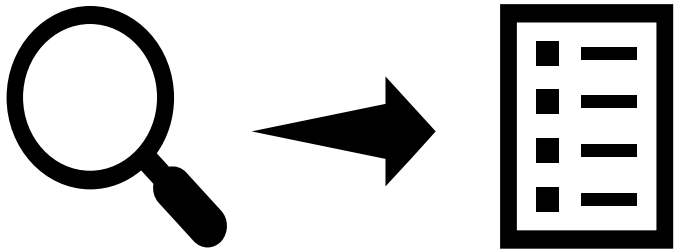
Safe-by-design (R&D)

- Identify potential adverse effects
- Guiding the identification of suitable candidates/alternatives

- *Wassenaar et al. (2019). https://doi.org/10.1016/j.comtox.2019.100110*
- *Wassenaar et al. (2021). https://doi.org/10.1016/j.yrtph.2020.104834*
- *Wassenaar et al. (2022). https://doi.org/10.1002/jcc.26859*
- *https://rvszoeksysteem.rivm.nl/ZzsSimilarityTool*

2. From screening to evaluation

- Does chemical similarity also translate into biological similarity?
  - Influence of variability
  - Chemical similarity for evaluation



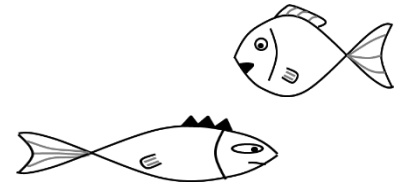
Variability and uncertainty

- To conclude on biological similarity, we need to know the variation in biological activity

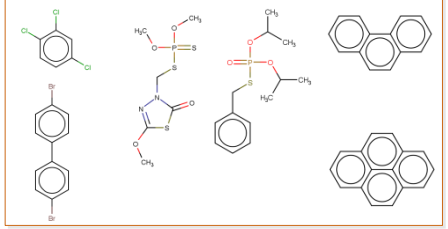
- Case study on BCFs
  - Collected a list of high quality BCFs tested for single chemicals
  - Identified factors contributing to variability
  - Quantified unexplained variability
    - Laboratory practices
    - Biological variation (intra-species differences)

- Results suggest:
  - For B-assessment: use multiple experiments to capture variability
  - For similarity assessment: difficult to conclude on biological similarity based on single study outcomes.

Species



Mixture exposure

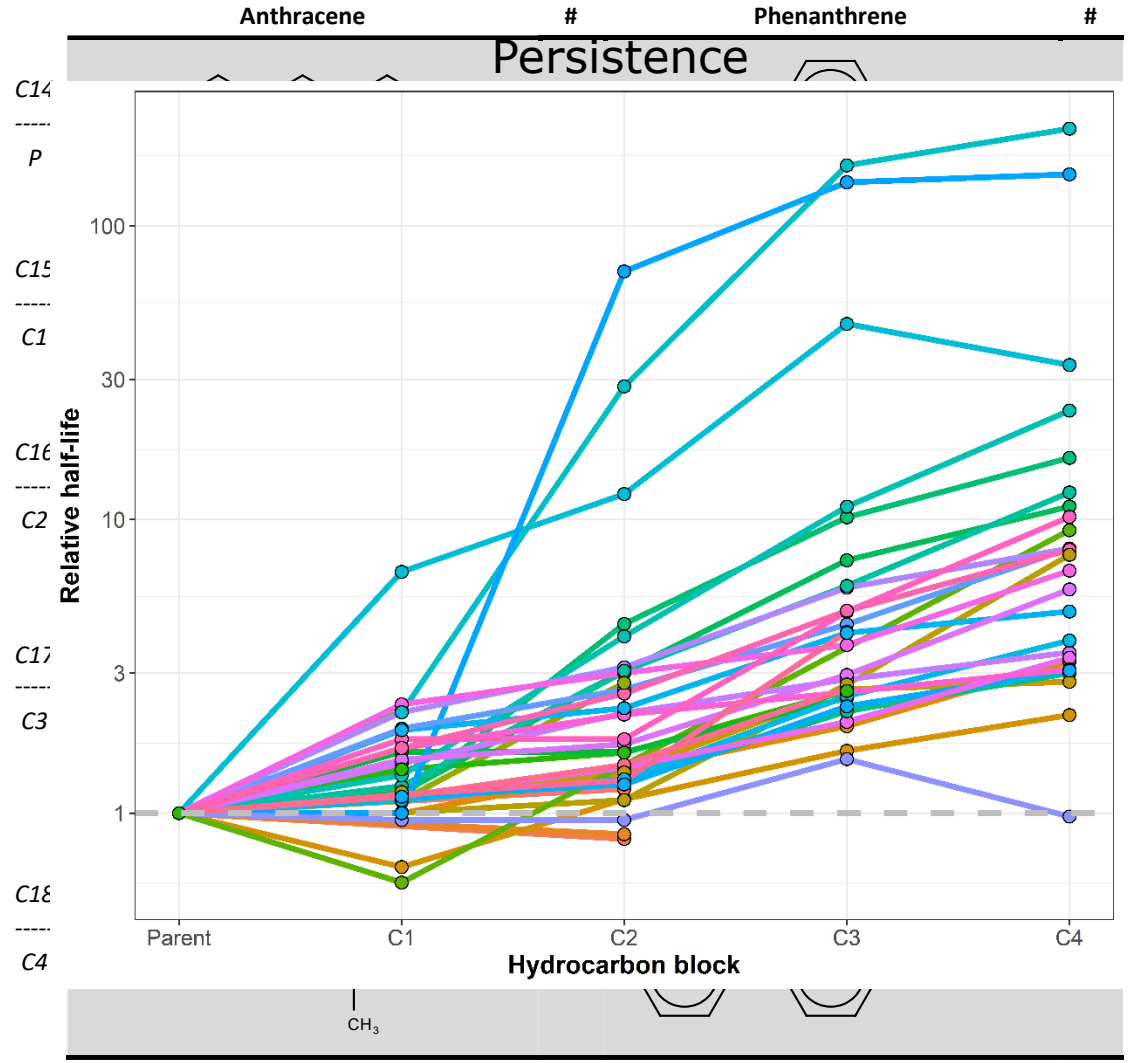


BCF	Range ± 2xSD
100	38–262
500	191–1312
2000	762–5249
5000	1905–13122
10000	3810–26244

• Wassenaar et al. (2020). https://doi.org/10.1016/j.chemosphere.2019.124731

PBT evaluation

- Evaluation of PBT/vPvB properties of a group of structurally similar chemicals:
  - Alkylated three-ring PAHs = 884 constituents
  - Experimental and QSAR data
- Used WoE approach and trend analyses
  - Lack of 'reliable/relevant' experimental data
- Conclusion: alkylated three-ring PAHs are more or equally P, B and T compared to parent three-ring PAHs
- Confirms the validity of chemical similarity as screening feature



• Wassenaar et al. (2021). https://doi.org/10.1016/j.chemosphere.2021.130113

Thesis conclusions

Challenges in chemical regulation:

- Lack of (reliable) data
- Time-consuming processes

General conclusions

More extensive use of chemical similarity can contribute to:

- Effective and efficient use available data and knowledge
- Speed-up risk assessment (groups)

Impact

Acting at the science-policy interface (Leiden University & RIVM):

- Results are directly incorporated and applied in practice
- Provides direct opportunities to:
  - Develop safe(r) chemical alternatives (SbD)
  - Stimulate the transition towards a 'toxic-free' environment

Outlook

Explore the use of Artificial Intelligence / Machine Learning to optimize risk assessment

Thanks for your attention

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