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Mathematisch-naturwissenschaftliche Fakultät

Early-stage hazard assessment – What do we have and what should we aim for?

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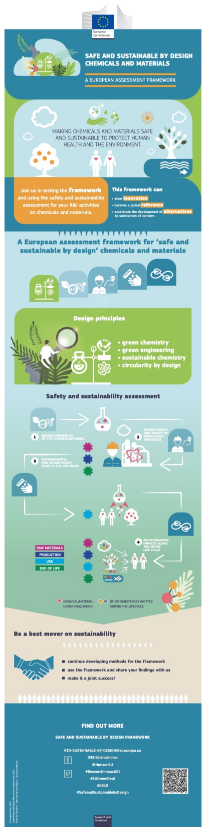
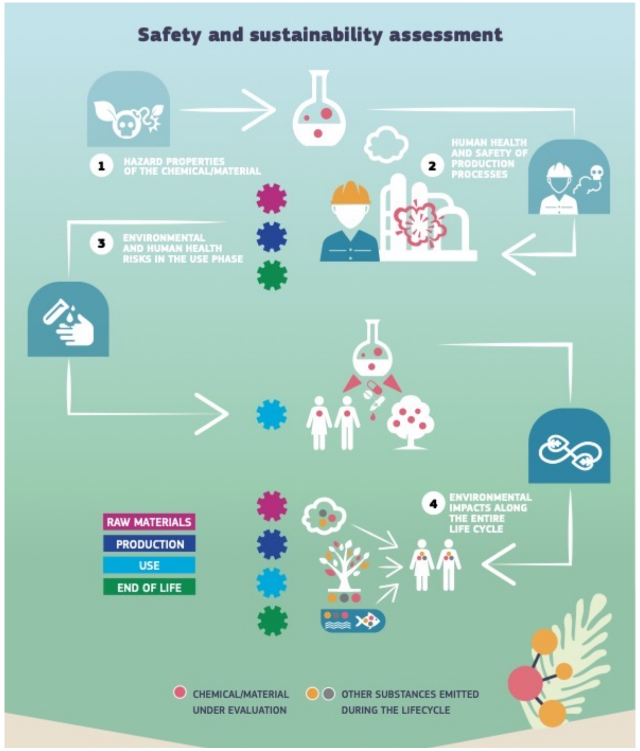
EC framework on "Safe-and-sustainable-by-design" (SSbD) (*EC, 2022*)





Infographic: https://op.europa.eu/en/publication-detail/-/publication/11cd64f5-76a8-11ed-9887-01aa75ed71a1/language-en

Hierarchical safety and sustainability assessment:

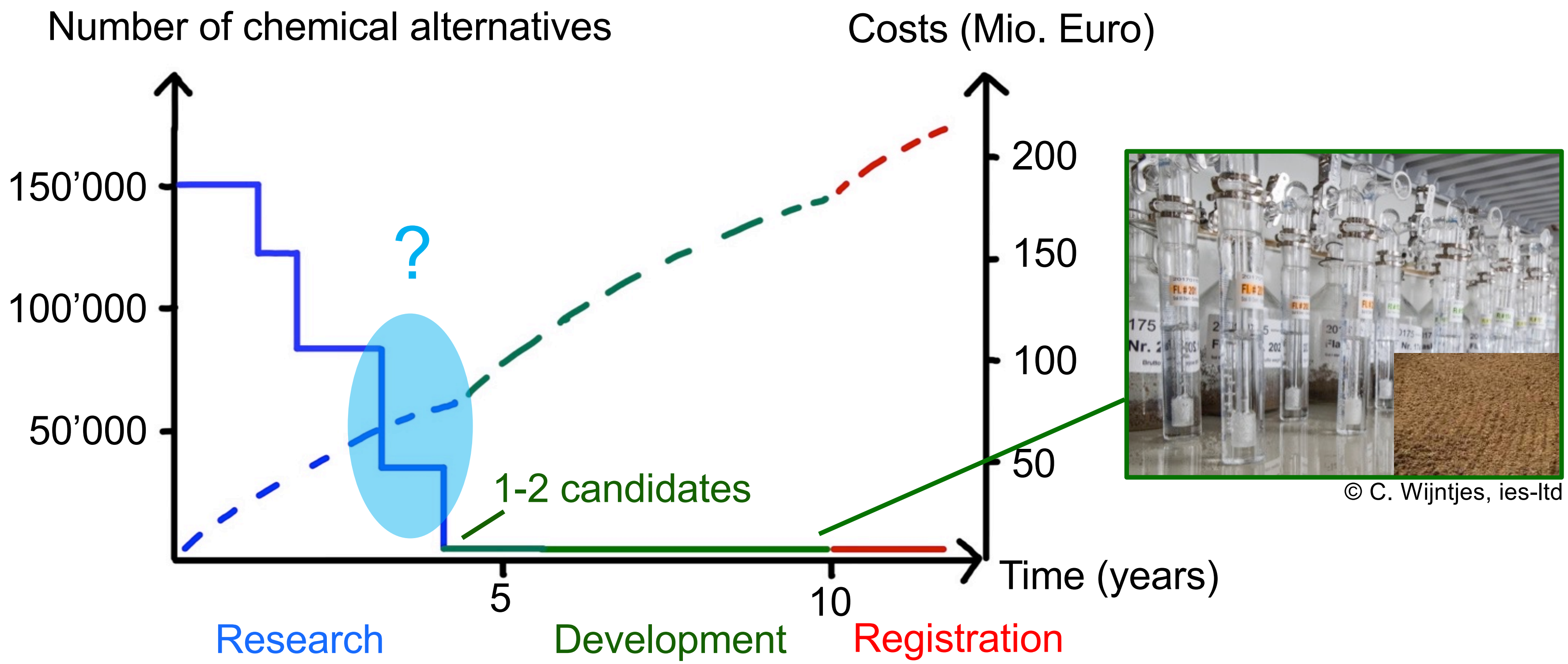
1. **Hazard assessment of chemical or material**
2. Human health & safety of production process
3. Hazards and risk of final application of chemical or material
4. Environmental impact throughout life-cycle of chemical or material

Regulatory hazard criteria

- Cause-effect relationships difficult to establish for chemicals:
  - Complex relationships between presence of chemical and effects on human health and environment
  - Cause and effect can be far apart in space and time
- Need for application of Precautionary Principle:

  “Full scientific certainty that a chemical (or chemical product) causes harm cannot be required to take action to prevent such harm” (*UNGA, 1992*), see also ”Late lessons learned from early warning” (*EEA, 2013*) for chemical-related case studies
- Regulatory hazard criteria implement precautionary principle:
  - **PBT**: **P**ersistent, **b**ioaccumulative, **t**oxic; **vPvB**: **V**ery **p**ersistent and **v**ery **b**ioaccumulative
  - **T** includes **c**arcinogenic, **m**utagenic, toxic to **r**eproduction (**CMR**), and endocrine disrupting chemicals (**EDC**) (*EC, 2023*)
  - **M**: **M**obility, new hazard category under CLP (*EC, 2023*) → **PMT** and **vPvM**

Overview of R&D process for pesticides



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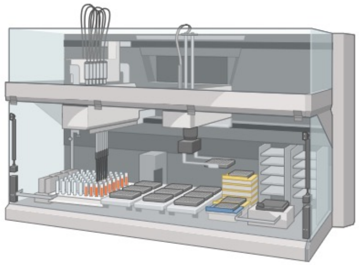
Agrochemical Research & Development, Phillips McDougall, March 2016

New approach methodologies (NAMs)

- Alternatives assessment and SSbD require new methods
  - High-throughput (fast, resource-efficient)
  - Animal-free
  - Applicable to many chemicals (“scalable”)
  - Robustly predictive of behavior in the environment (“standardizable”, “mechanistic”)

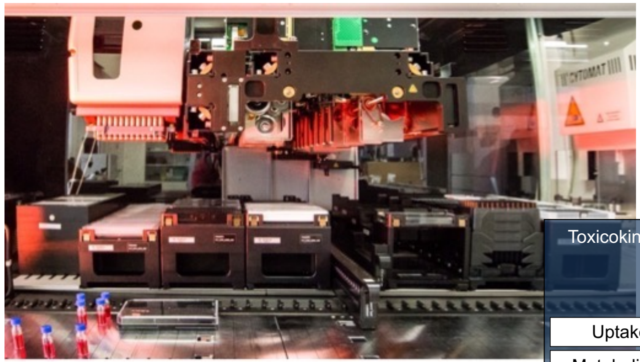


High-throughput assays (*in vitro*)

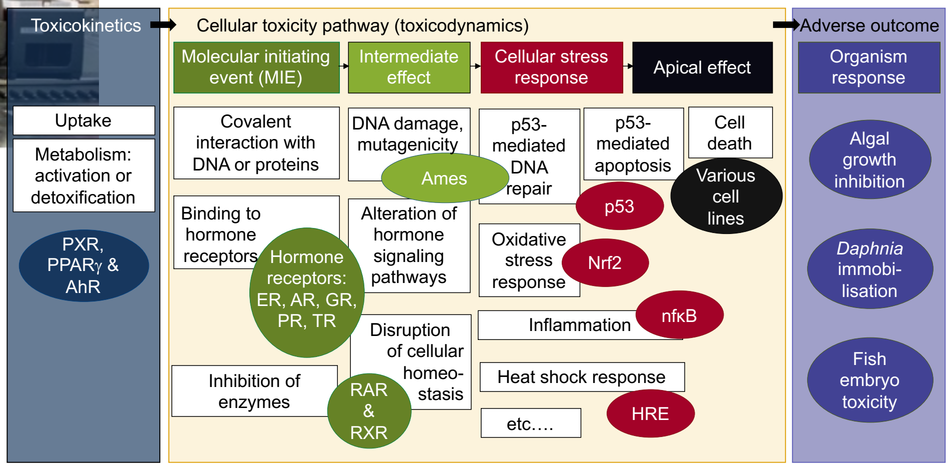
Computational, structure-based predictions (*in silico*)

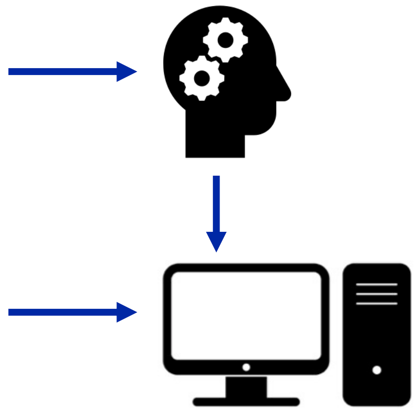
High-throughput testing in (eco-)toxicology (T)

Tox21 and ToxCast (U.S. EPA, NIH, FDA, NIEHS): > 10k substances tested on > 50 bioassays



High-throughput assays (*in vitro*)



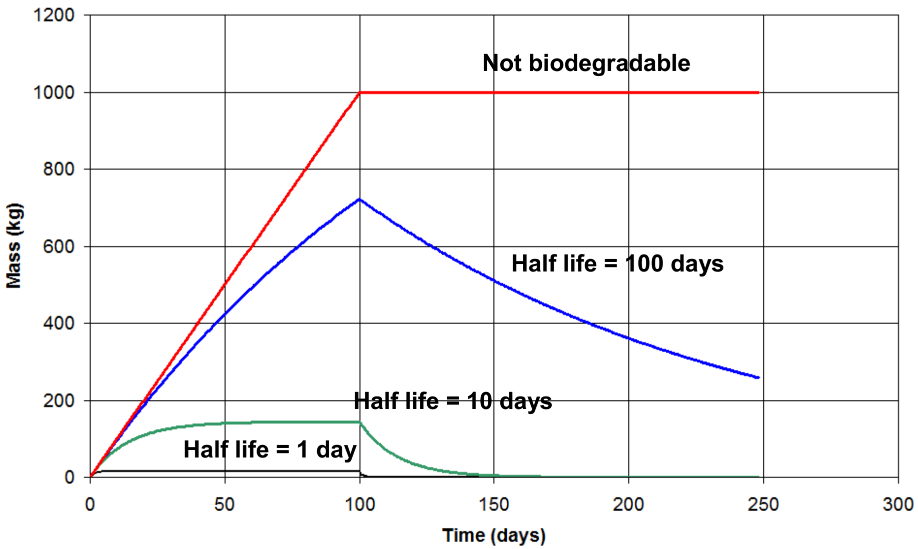


Computational, structure-based predictions (*in silico*)

Escher, Neale, Leusch, 2021: *Bioanalytical Tools in Water Quality Assessment*

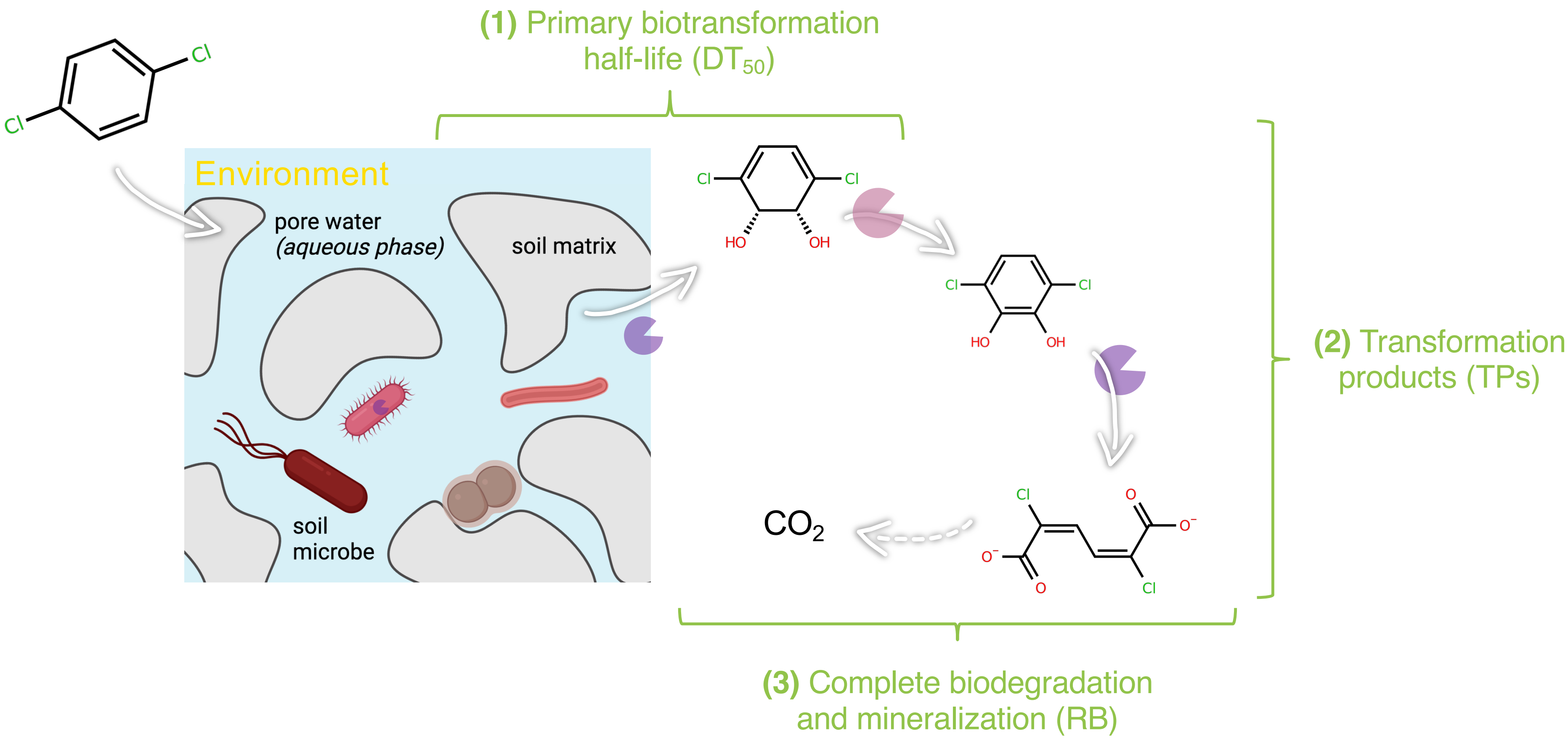
Persistence (P)

– Persistence: “Propensity for a chemical to remain in the environment before being transformed by chemical and/or biological processes in a particular environment” (*Boethling et al., 2009*)



– P-sufficient approach (*Cousins et al., 2019*): High persistence alone should be established as a sufficient basis for regulation of a chemical

Different flavours of P

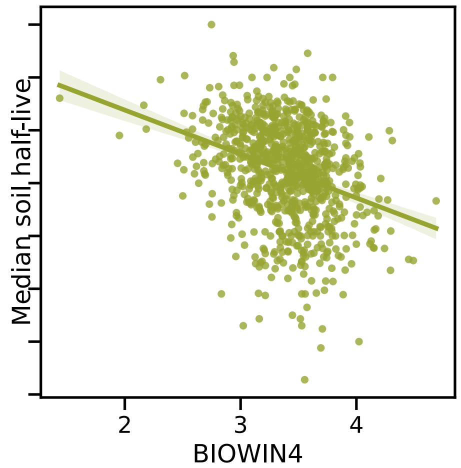


In silico ready biodegradabiliy prediction

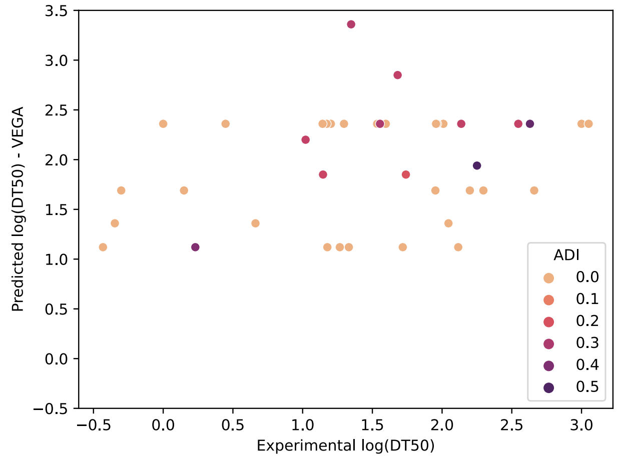
- Many freely available and commercial software tools available
- Mostly classification models
- Typical accuracy: approx. 80+%
- Largest training data set currently used: >6000 chemicals, >12000 data points (*Huang and Zhang, 2022*)
- Take home:
  - Ready biodegradability reasonably well predictable
  - Models applicable to wide range of chemicals (e.g., reasonable predictions for >98% of > 850,000 environmentally relevant chemicals in the DSST database (*Huang and Zhang, 2022*))

In silico half-life predictions

- Very few models predict half-lives, e.g.,
  - OPERA from US EPA (only for hydrocarbons)
  - BIOWIN, using extrapolation factors
  - VEGA (*Lombardo et al., 2022*)
    - Semi-quantitative models trained on data for soil, sediment, water (approx. 180 chemicals for each endpoint) (data mostly from Gouin et al. (2004))
    - R2: 0.75 - 0.82 on validation sets (20%); RMSE (log t1/2): 0.34 - 0.36
- Take home:
  - Half-life prediction very challenging
  - Data sets currently too small



BIOWIN predictions of OECD 307 DT50 values
n=895 (pesticides)



VEGA predictions of OECD 309 DT50 values
n=39 (APIs)
R2: -0.35
RMSE: 1.07

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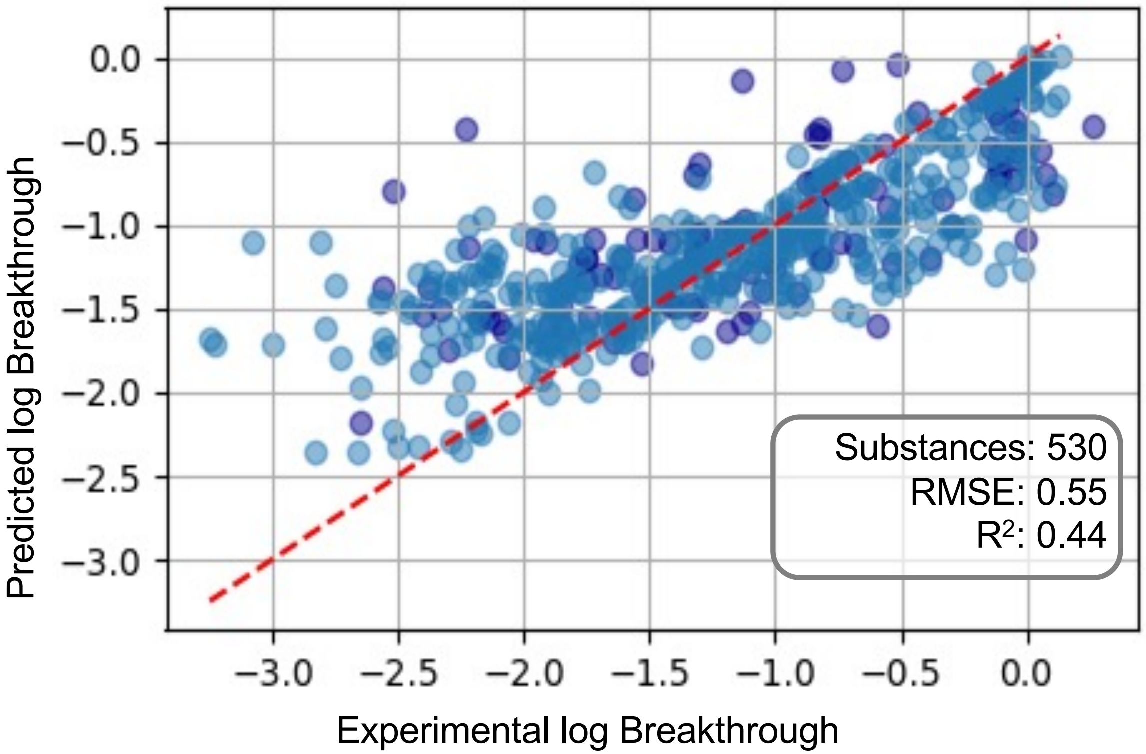
Recent own *in silico* work – Predicting biodegradation in WWTPs



Machine learning model: Random Forest regressor and MACCS fingerprints

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Bundesamt für Umwelt BAFU

Cordero, Hafner, Fenner, *manuscript in preparation*

High-throughput assays for ready biodegradability

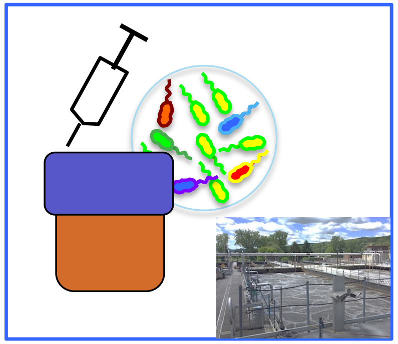
- *Martin et al., ES&T, 2017*:
  - 96 well-plates, filled with activated sludge, 28 days
  - Colorimetric read-out through reaction of phenol-containing compounds with diazonium salts
  - Probability of biodegradation across dilution series

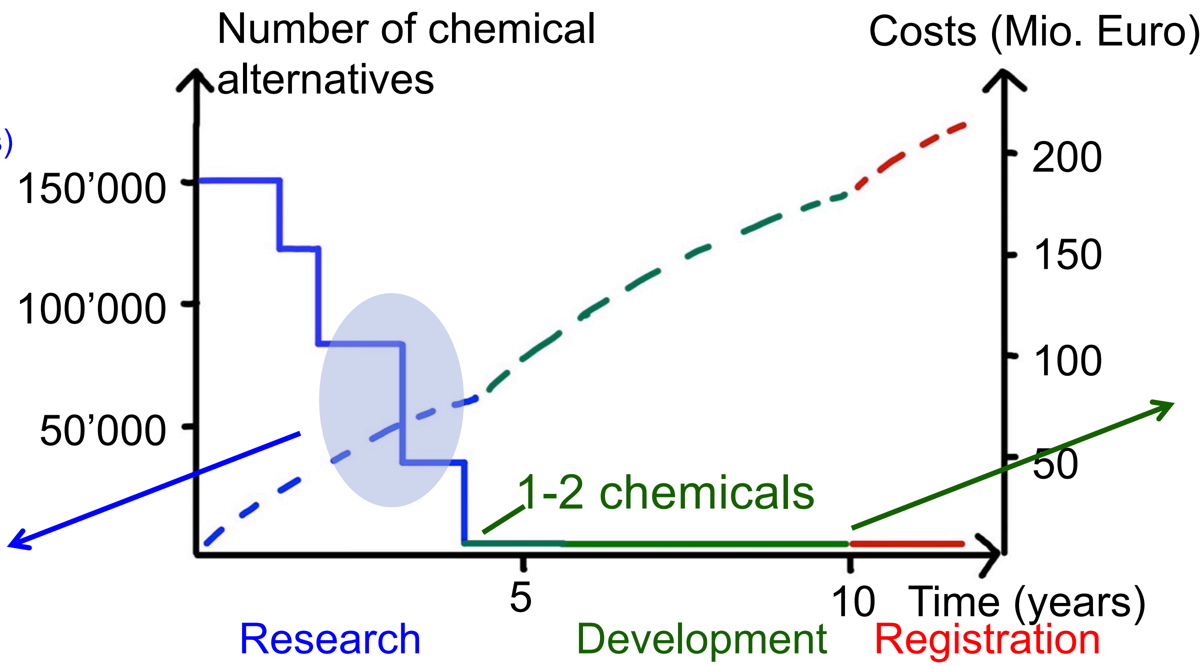
- *Brillet et al., ESPR, 2016*:
  - 24 well-plates monitored with non-invasive O_2 probe filled with activated sludge, 28 days
  - Inocula with fresh/sea water, soils, activated sludge; different T & cell density
  - Probability of degradation across >800 conditions/inocula
  - Under further development with different read-out (personal communication)

Activated sludge as in vitro assay for P screening? – Read-across approach

Activated sludge studies:

- Short duration (2-3 days)
- Mix of multiple substances





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Soil simulation studies according to OECD 307:

- Long duration (> 60 days)
- Radioactively labelled chemicals

Activated sludge as in vitro assay for P screening? – Read-across approach


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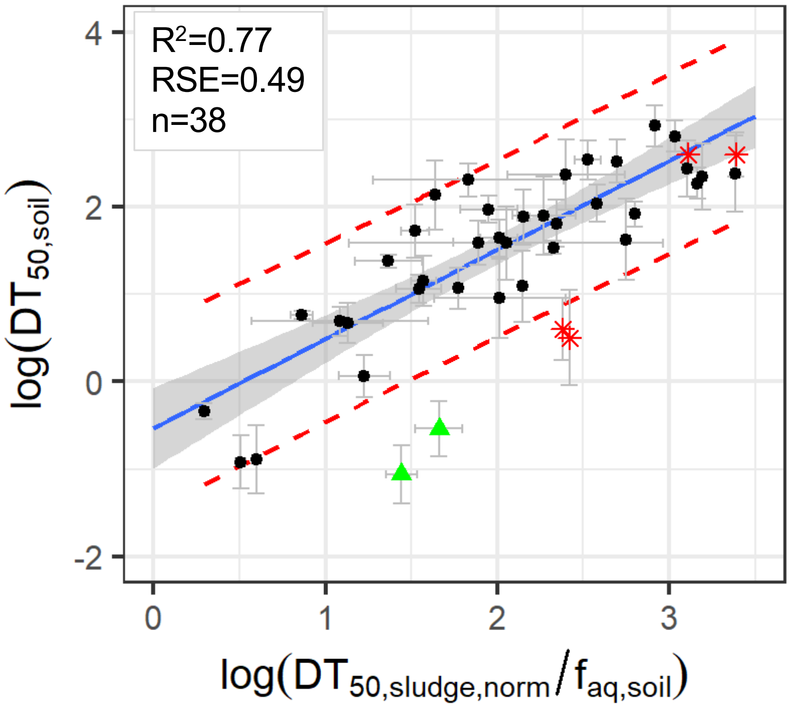
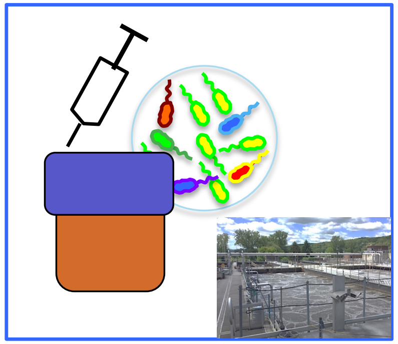
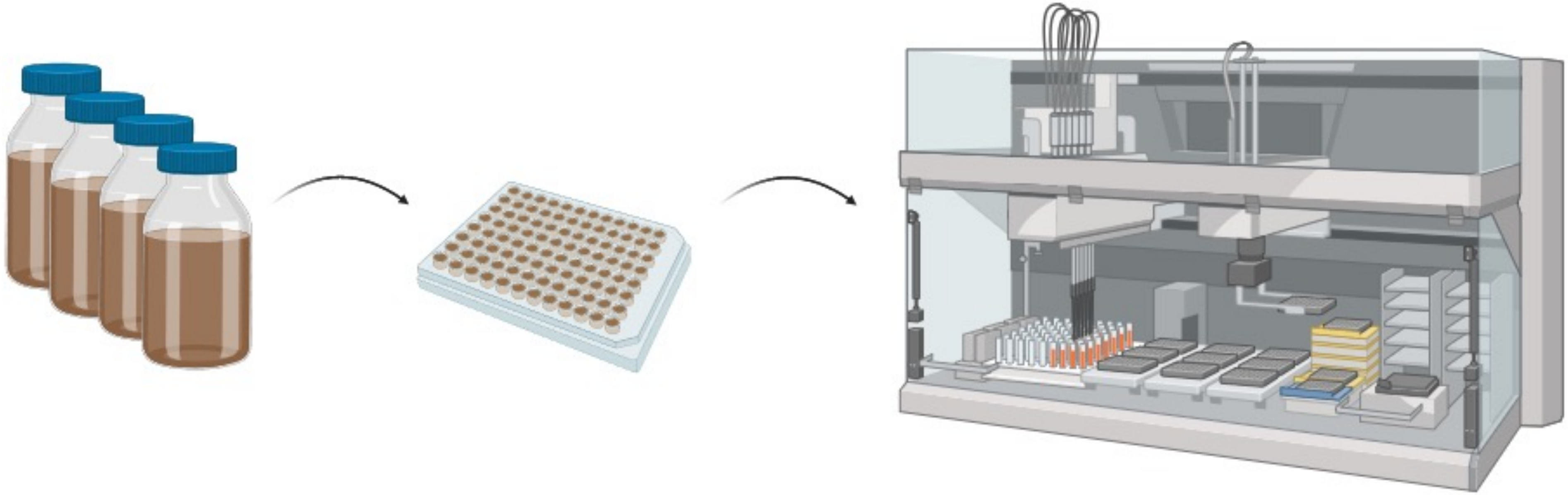




Fenner et al. (2020) *Environ. Sci. Technol.*, **54**, 3148

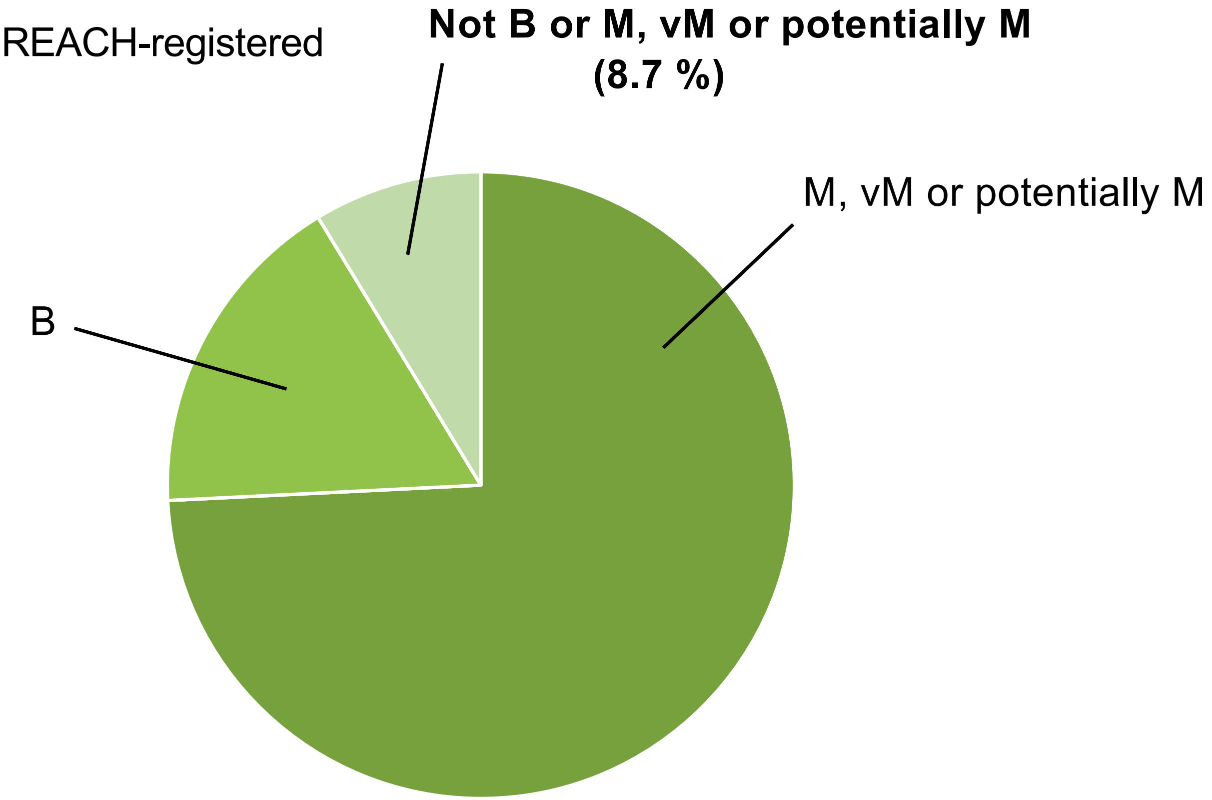
Towards automating P screening

Sarah Partanen
UZH, Eawag



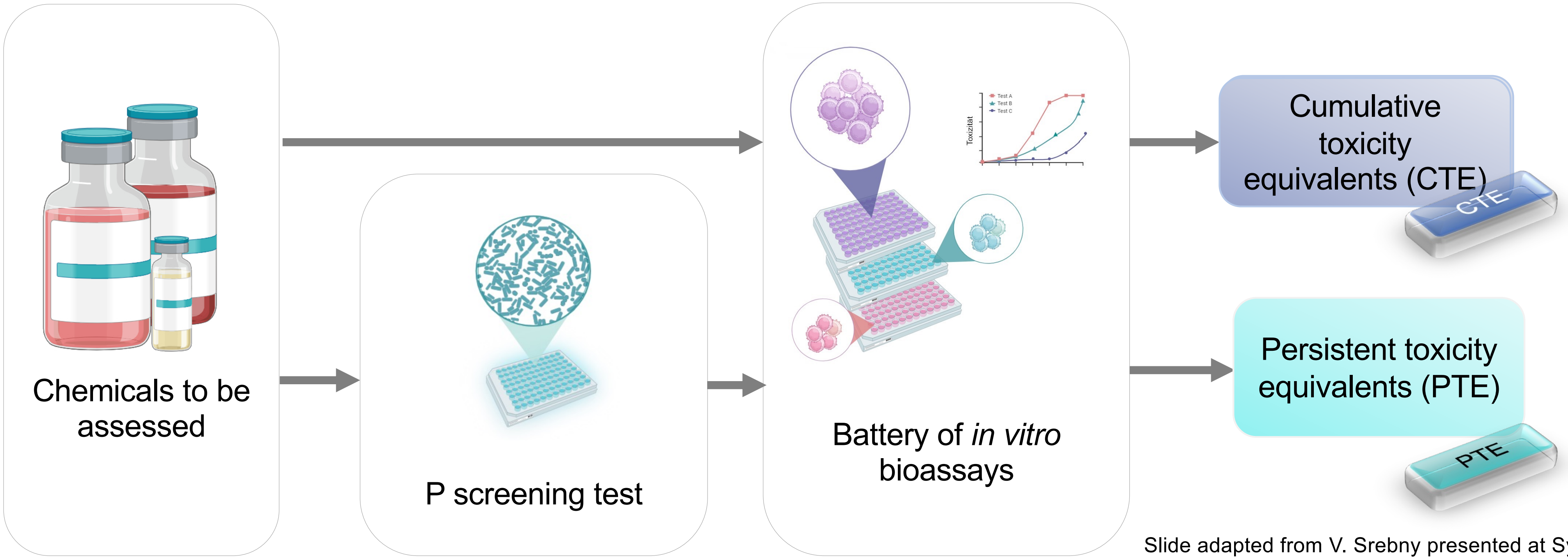
What about B and M?

– E.g., 13,405 unique REACH-registered



Arp and Hale (2022) *ACS Environ. Au*, 6, 482
Escher et al. (2023) *Environ. Sci. Technol.*, **54**, 3148

The CTE/PTE concept for hazard assessment



Slide adapted from V. Srebny presented at SynCom Workshop "Zwei Neue Indikatoren für die Gefahren–bewertung in der EU-Chemikalien Politik" (Dec 2023)

Escher et al. (2023) *Environ. Sci. Technol.*, **54**, 3148

Early-stage hazard assessment – What do we have and what should we aim for?

- Efficient (new) methods for alternatives assessment and “benign-by-design” dearly needed
- Automation of *in vitro* assays currently most promising
  - More data also basis for developing better models
- Suggestion to reduce hazard assessment to key hazards: P and T (CTE/PTE concept)
  - Method development ongoing
  - Amongst others: PARC case study on BPA replacements (Escher, UFZ)
- Applicability of methods to materials??

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Umwelt Bundesamt

cefic

LRI
The Long-range Research initiative

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