Probabilistic Points of Departure: A Tiered Approach for Life Cycle Impact Assessment

Workshop: Advancing Quantitative Analysis in Human Health Assessments through Probabilistic Methods

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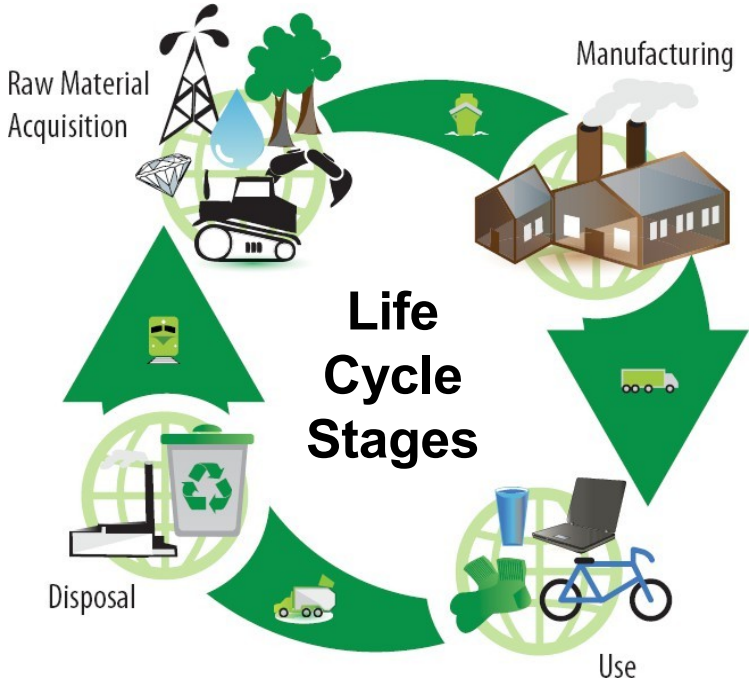
What is the Life Cycle?

"the major activities in the course of the product's life-span from its manufacture, use, and maintenance, to its final disposal, including the raw material acquisition required to manufacture the product." -EPA 2006 (Life Cycle Assessment: Principles and Practice)



Often iterative in nature

Goal and Scope Definition

Life Cycle Inventory

Life Cycle Impact Assessment

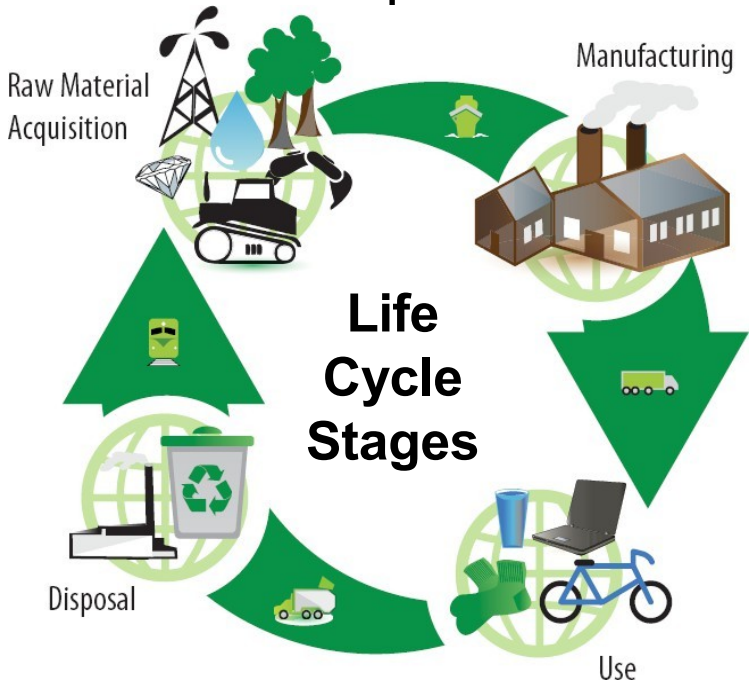
Interpretation

Impacts on Health and Environment

Inputs

- Raw materials
- Energy

Etc.



Outputs

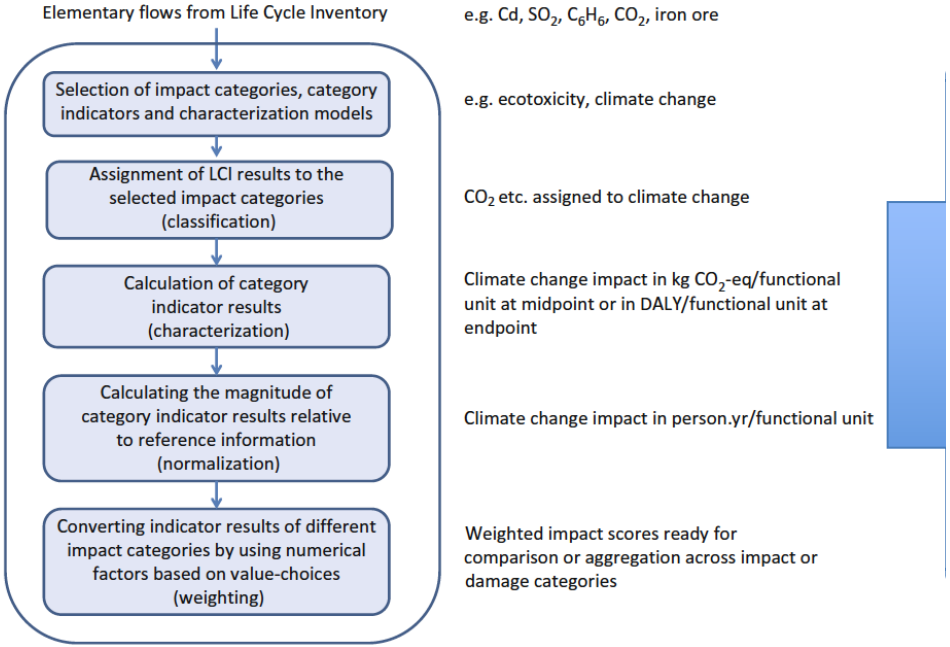
- Atmospheric emissions
- Waterborne wastes
- Solid wastes
- Co-products

Etc.

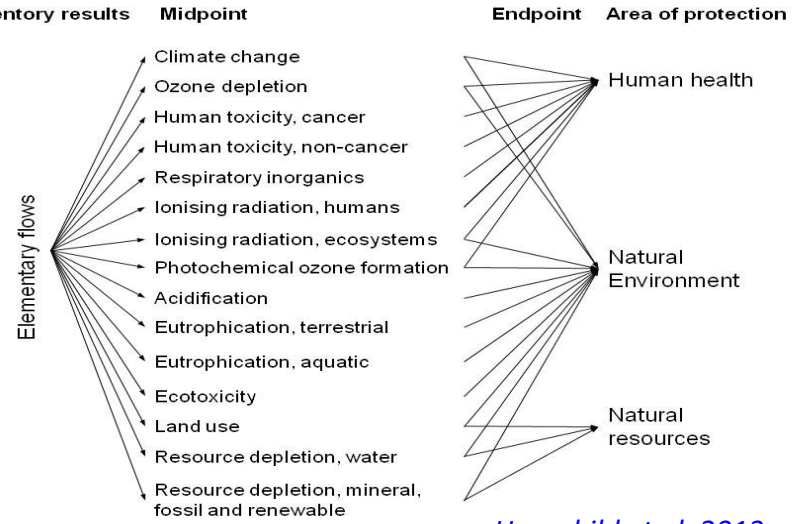
Impacts on Health and Environment

What does this have to do with Toxicology?

Five Steps of LCIA



Framework for Impact Categories



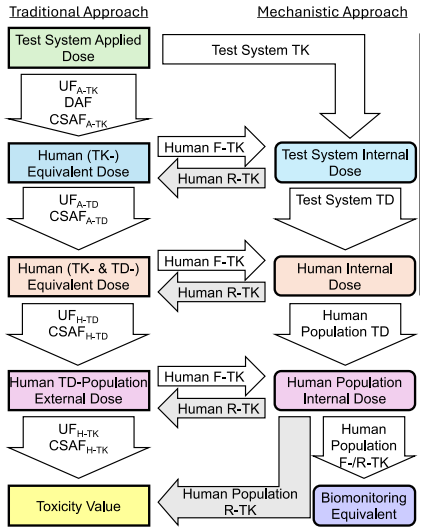
[Hauschild et al. 2013]

ISO 14040 standard, adapted by Hauschild and Huijbregts (2015) *Life Cycle Impact Assessment*, Ch 1

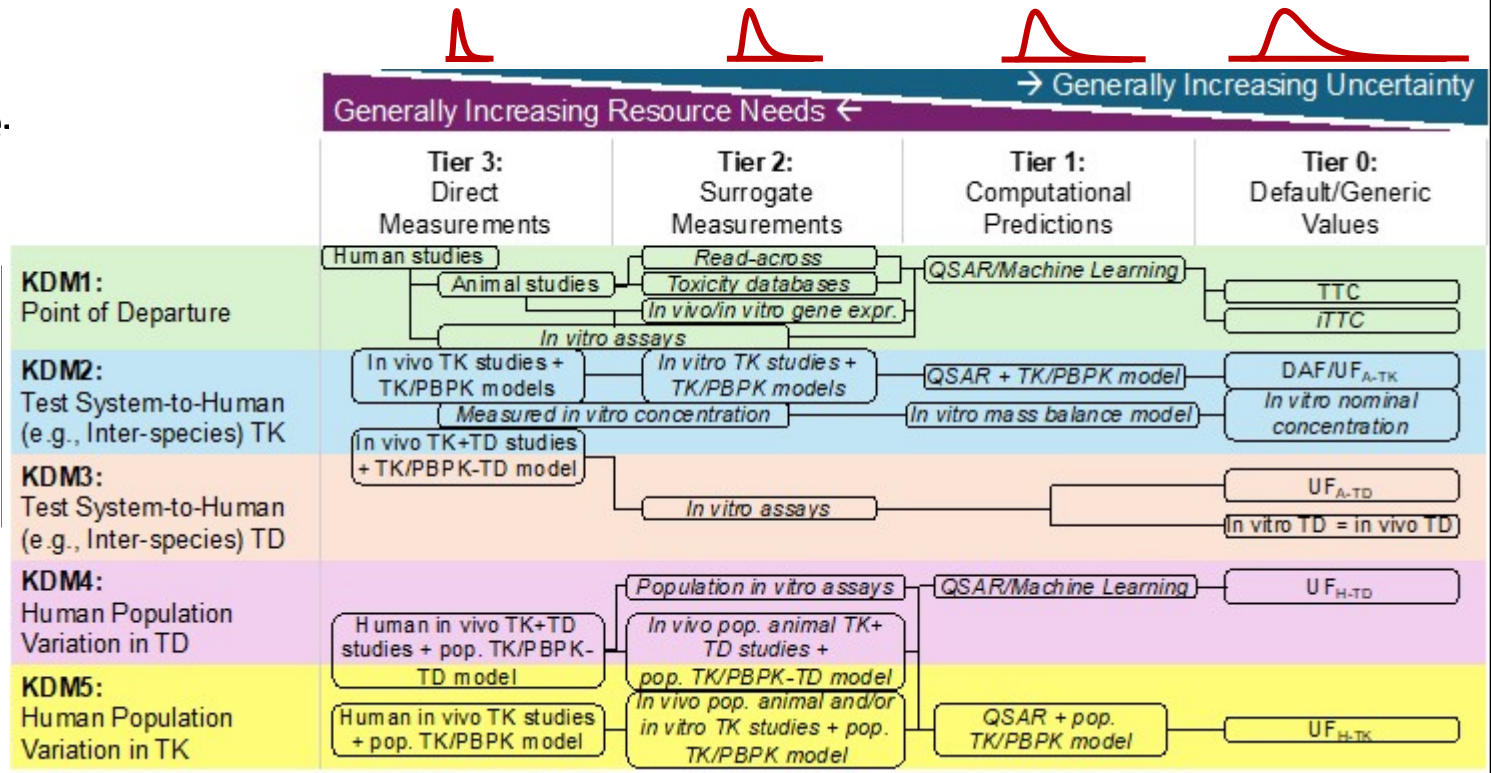
Context for this work

- 30,000−100,000 unique chemical substances are commonly used worldwide in various products, processes, or services
- LCIA is a comparative assessment approach that includes characterizing toxicological impacts on human health from all possible chemical exposures associated with the life cycles of those products, processes, or services
- Points of Departure (PODs) are are essential part of characterizing toxicity-related human health impacts in LCA
- Regulatory/authoritative PODs cover a very limited set of chemicals
- Treating “no number” chemicals as non-toxic underestimates impacts, which can bias decision-making

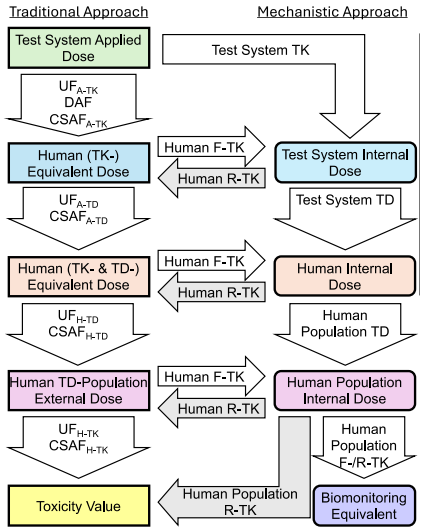
Unified Probabilistic Framework for Dose-Assessment



Lu et al. (in press, JTEH-B)



Focus on KDM 1: Point of Departure Determination



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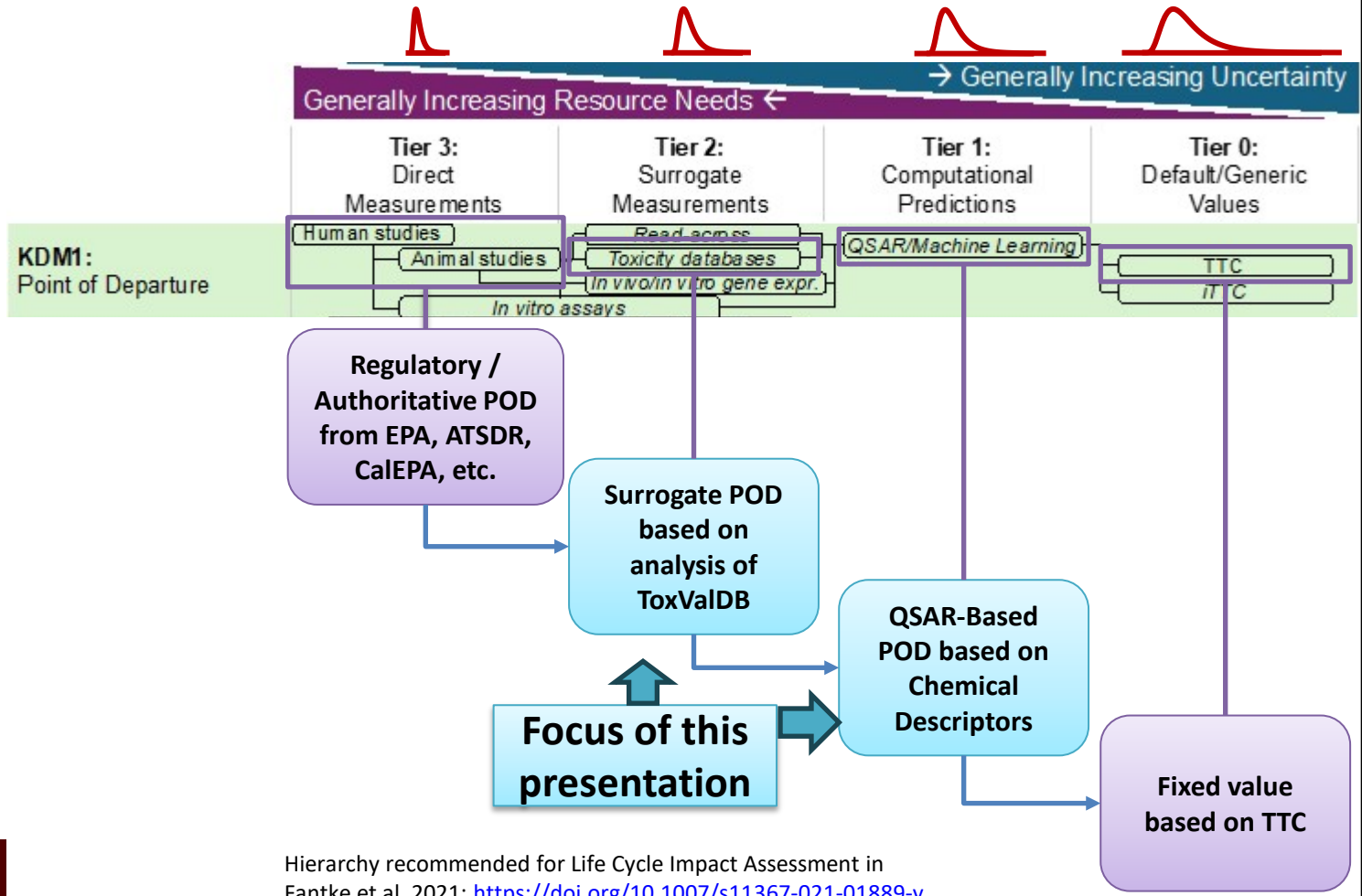


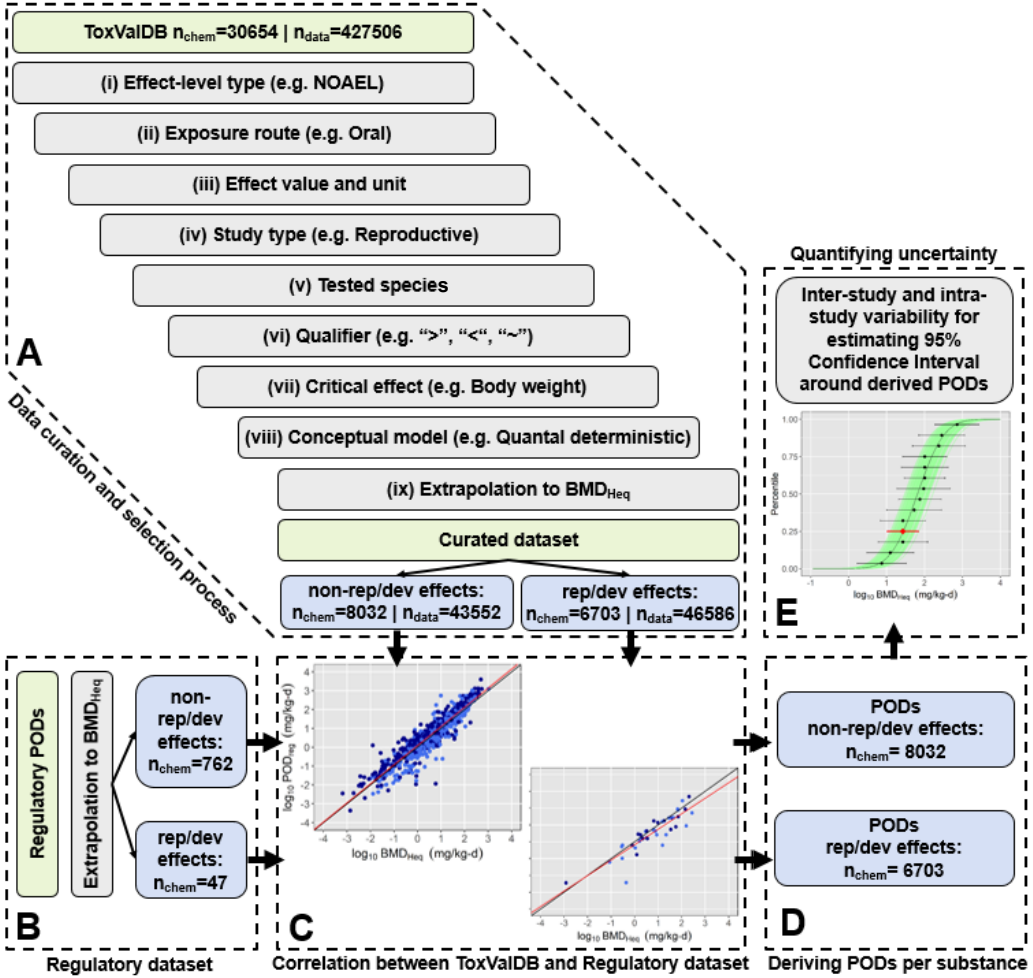
Hierarchy recommended for Life Cycle Impact Assessment in Fantke et al. 2021: https://doi.org/10.1007/s11367-021-01889-y

Surrogate POD based on analysis of ToxValDB

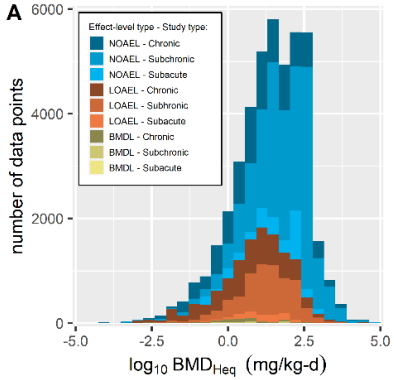
Develop a workflow for deriving PODs <u>with quantified uncertainty</u> for chemical substances <u>with</u> animal toxicology data but <u>without</u> regulatory/authoritative assessments.

A: Data curation and selection
B-C: Calibration to overlapping regulatory PODs from authoritative sources
D: Application to dataset from **A**
E: Uncertainty analysis

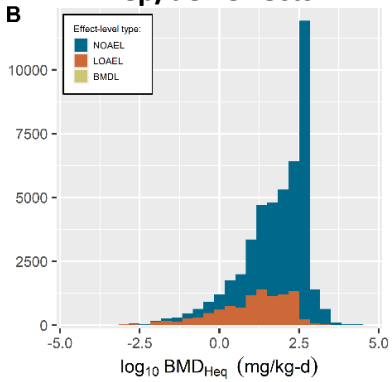
Oral PODs: Aurisano et al. 2023
Inhalation PODs: Aurisano et al. 2024

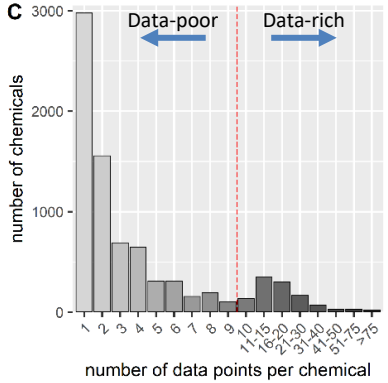


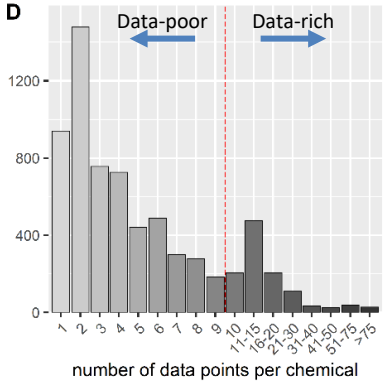
General non-cancer effects

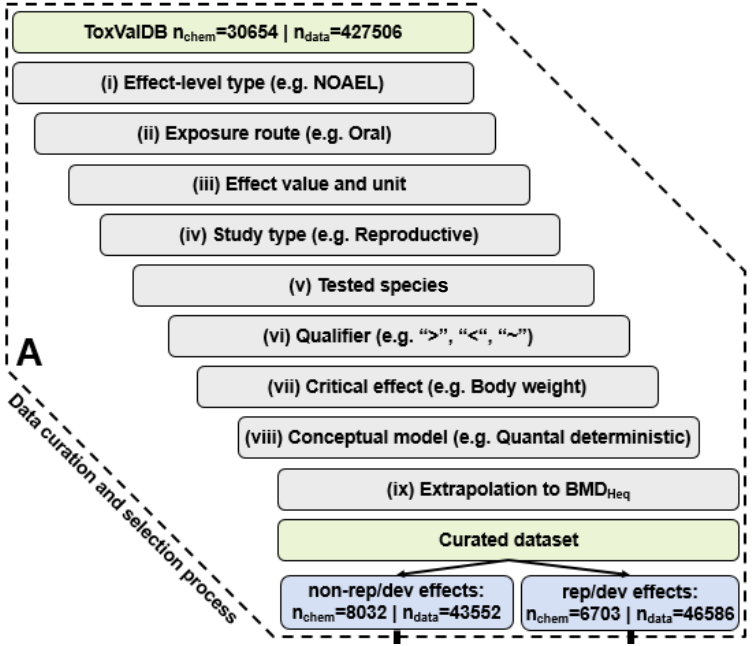


Rep/dev effects

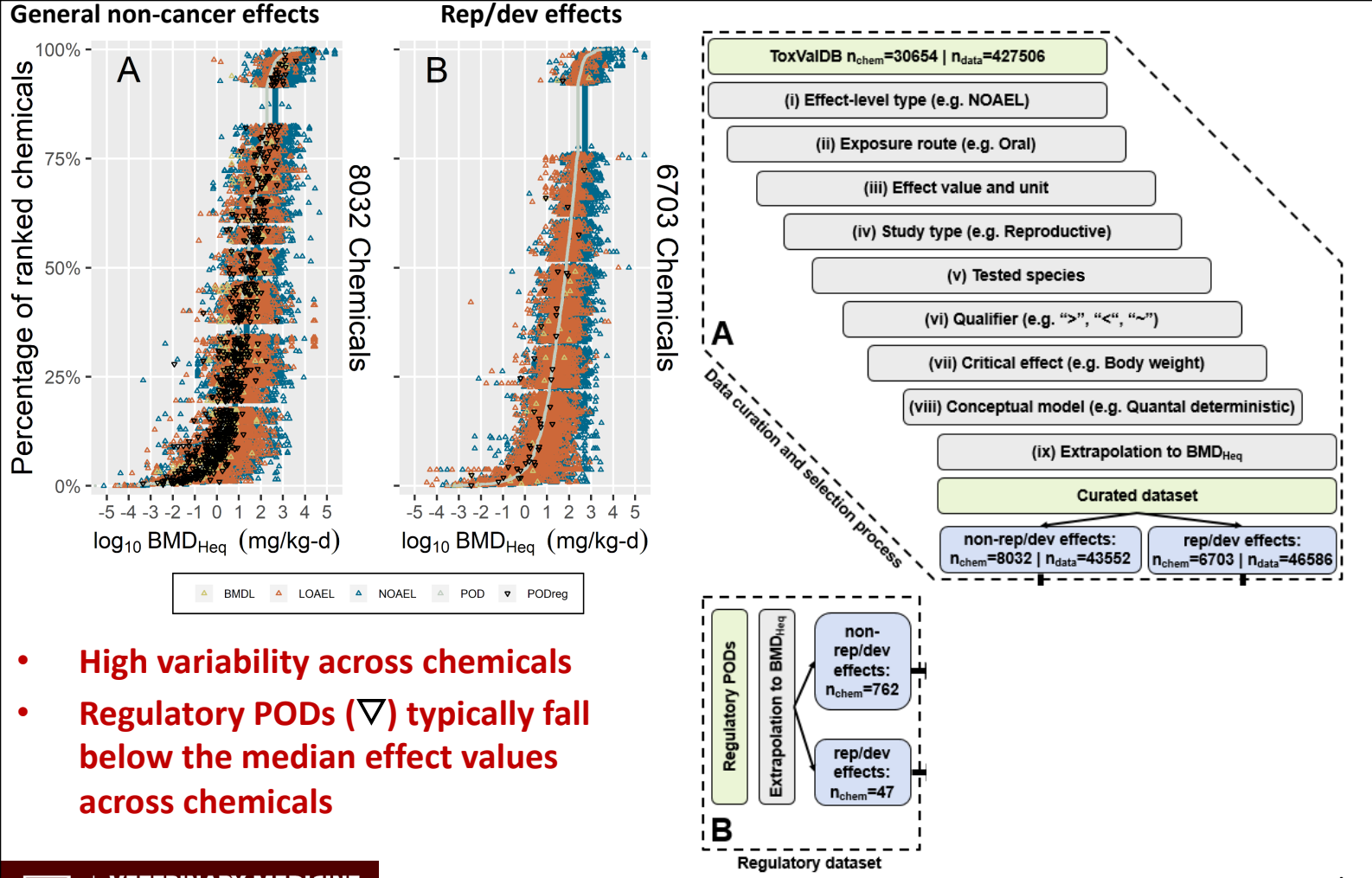








Aurisano et al. 2023, 2024



- **High variability across chemicals**
- **Regulatory PODs (▽) typically fall below the median effect values across chemicals**

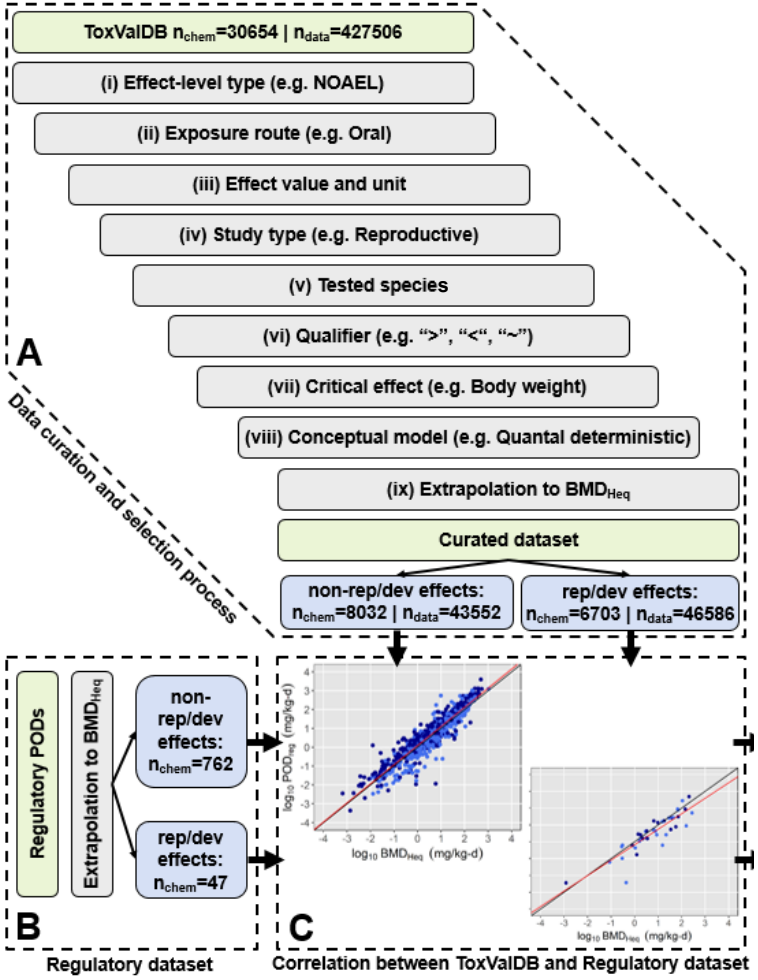
Aurisano et al. [2023](), [2024]()

Simple hypothesis: Regulatory PODs can be "modeled" as a "conservative" %ile of the (curated) ToxValDB data for each chemical.

- **Data-rich:** %ile from fitted on a log-normal distribution
- **Data-poor:** %ile from a fixed log-normal distribution ("avg" data-rich chemical)

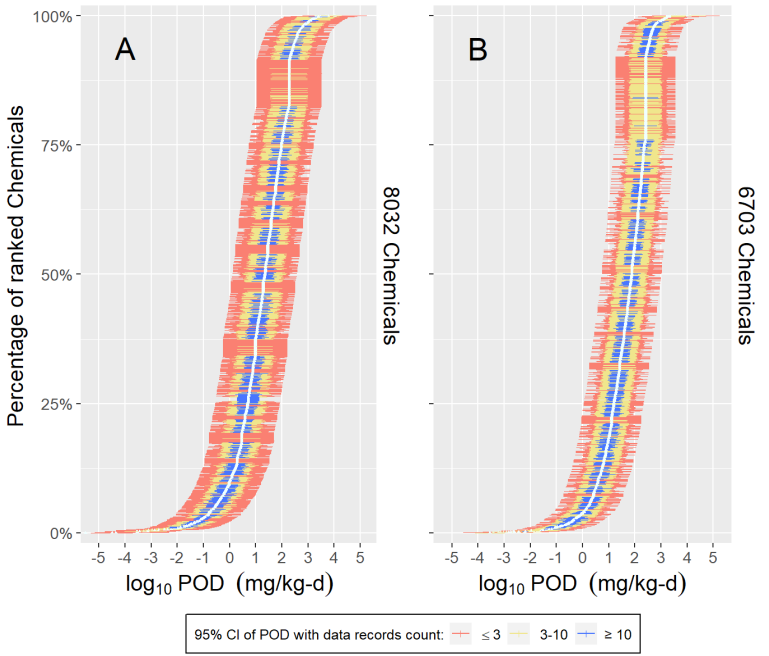
Results using 25th %-ile

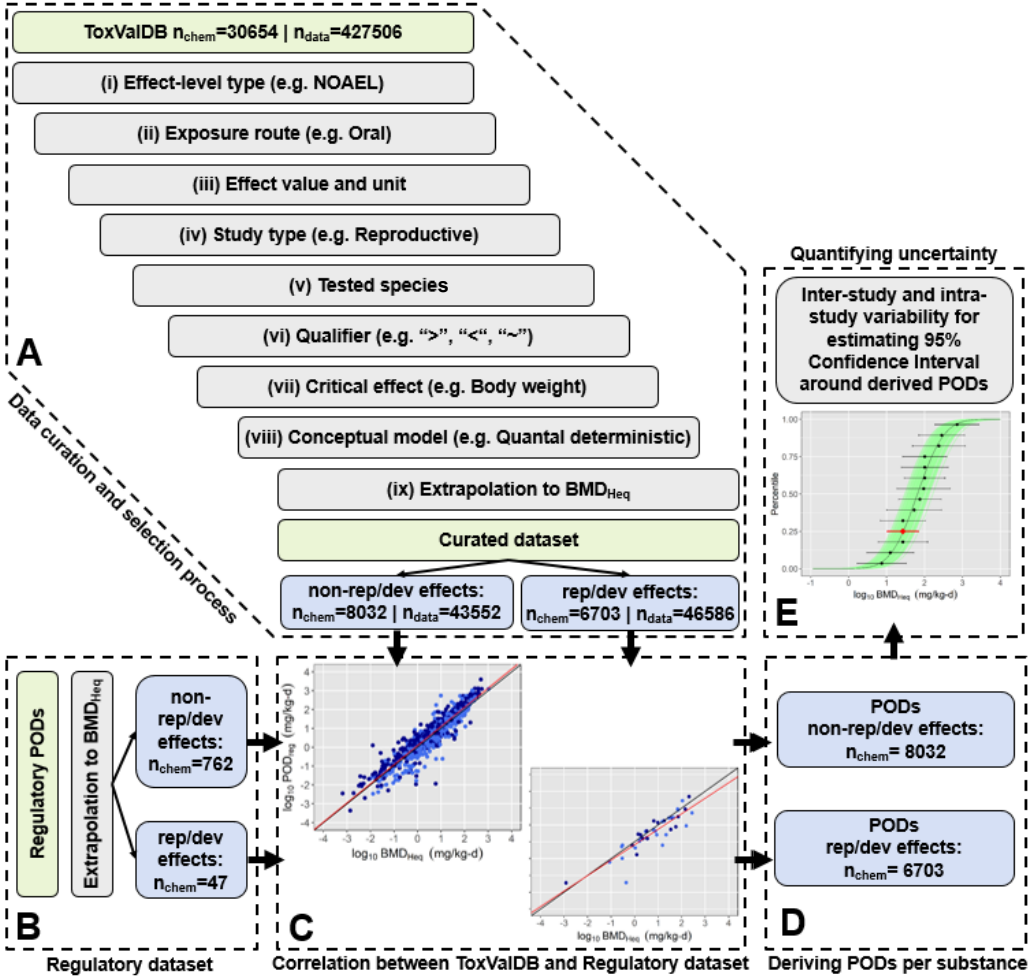
- Oral General non-cancer (n=744):
  R^2=0.85 RSE = 0.46 (log10 units)
- Oral Rep/dev (n=41):
  R^2=0.78 RSE = 0.53 (log10 units)
- Inhalation General & Rep/dev (n=174):
  R^2=0.76 RSE = 0.82 (log10 units)



Aurisano et al. 2023, 2024

Tiered uncertainty characterization based on number of (curated) ToxValDB data points, inter-, and intra-study variability





Aurisano et al. 2023, 2024

Surrogate POD based on analysis of ToxValDB

Approach: Expand coverage of chemicals with (non-cancer) toxicity values by

- Created a consistent and curated data set of *in vivo* chronic dose-response toxicity data from EPA ToxValDB
- Developed a statistical approach for calibrating toxicity data against regulatory values
- Quantified uncertainty from inter- and intra-study variability

Results: Surrogate PODs can be derived using the 25th %ile from ToxValDB

- Oral PODs expanded by ***n* > 10,000**
- Inhalation PODs expanded by ***n* > 2,000**

Limitations

- Tens of thousands of chemicals have no or inadequate data in ToxValDB
- *In vivo* testing data on these chemicals unlikely to expand substantially in the near future

Machine Learning to the Rescue?

Aurisano et al. 2023, 2024

QSAR-Based POD based on Chemical Descriptors

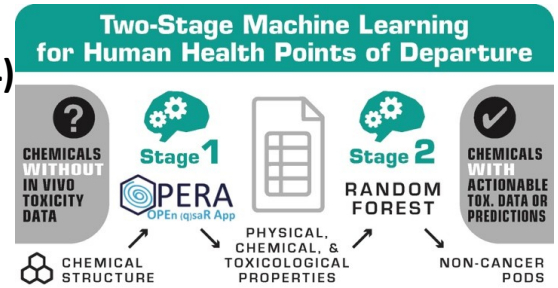
Conditional Toxicity Value (CTV) Predictor (2018)

- QSAR built on regulatory toxicity values
- Predicts oral and inhalation (experimental) NOAELs

Two-Stage Machine Learning Model (2024)

- QSAR for PODs building on surrogate oral PODs from Aurisano et al. (2023)
- Model for inhalation PODs in development

Both approaches perform better than ToxCast/in vitro NAMs for predicting regulatory PODs



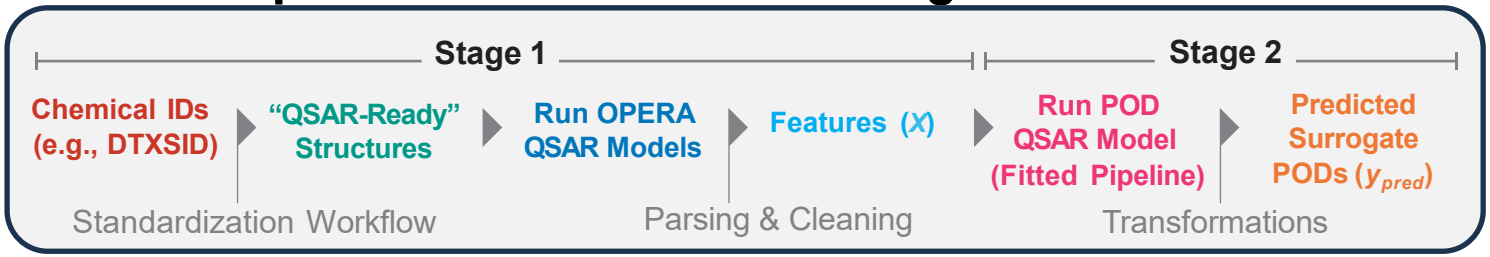
https://wchiu.shinyapps.io/Two-Stage-ML-Results-Browser/

Approach	RMSE	MedAE	R^2
CTV	N.R.	0.70	0.45
Two-Stage ML (general non-cancer)	0.69	0.40	0.48
Two-Stage ML (repro/dev)	0.58	0.31	0.49
ToxCast+httk (general non-cancer)	1.87	1.22	<0
ToxCast+httk (repro/dev)	1.52	0.84	<0

RMSE: Root-mean-squared-error (log10 units)
MedAE: Median absolute error (log10 units)
R^2: Coefficient of determination (<0 means worse that naïve constant model)

Wignall et al. 2018; Kvasnicka et al. 2024

Conceptual Framework: Two-Stage QSAR Model

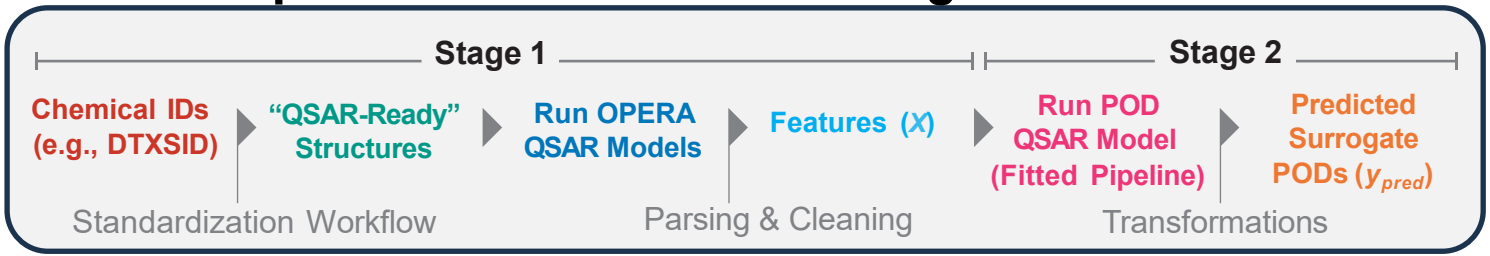


Why a two-stage model?

- Most chemical descriptors can be hard to interpret by a toxicologist or risk assessor (as opposed to a chemo-informaticist)
- Existing OPERA models provide open-source predictions for ***interpretable*** physical-chemical-toxicological parameters
- Analogous to a "supervised" neural network with a single intermediate layer composed of interpretable features.

Kvasnicka et al. 2024

Conceptual Framework: Two-Stage QSAR Model



Training Data Collection, & Preprocessing

g: general noncancer
rd: reproductive/developmental

Data Collection
Surrogate PODs from Aurisano et al. 2023 (y_{obs})

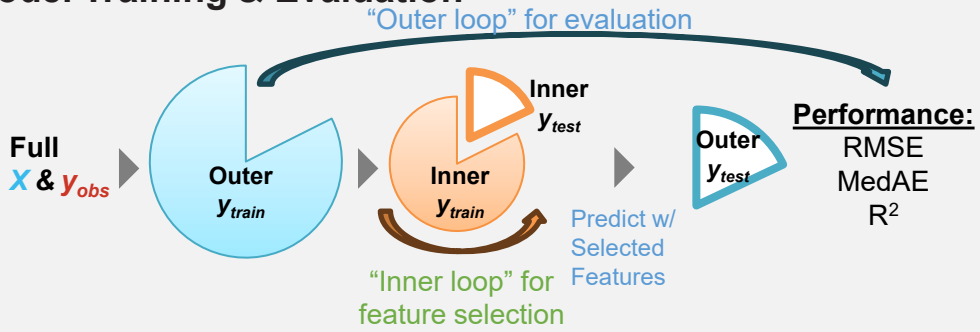
n_g = 5,209
n_{rd} = 4,938

Data Filtering
> 3 *in vivo* studies in ToxValDB & "QSAR-Ready"

n_g = 1,791
n_{rd} = 2,228

Feature Preparation
Run OPERA to generate features (X)

Model Training & Evaluation



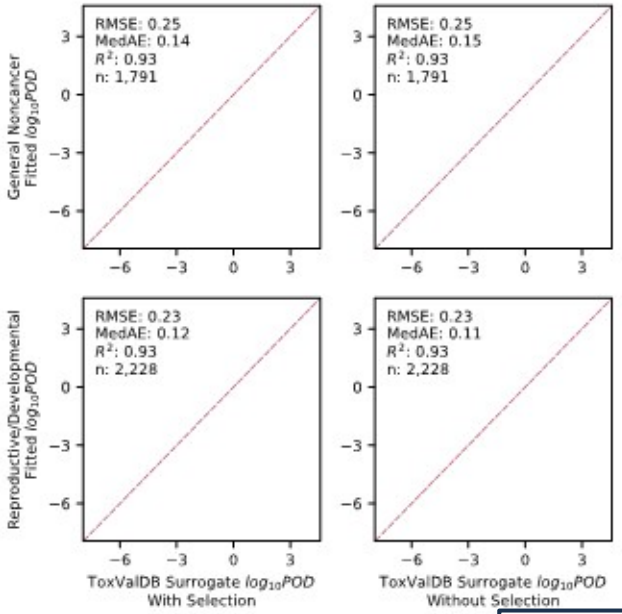
Performance:
RMSE
MedAE
R^2

Model Pipeline for Each Replicate
1. Feature Preprocessing
2. Random Forest Regression

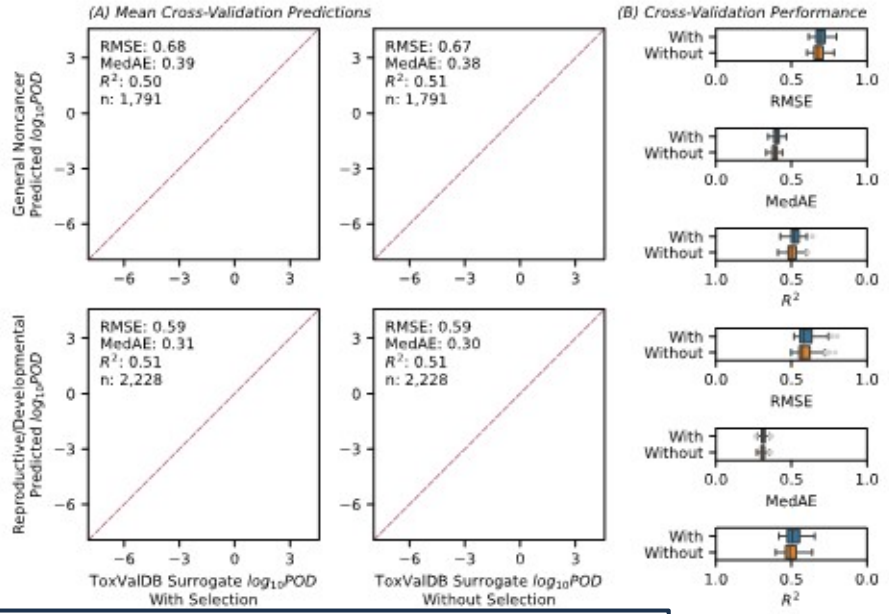
Kvasnicka et al. 2024

Model Evaluation

In-Sample Model Fitting



Out-of-Sample (Cross-Validation) Performance



Expected performance based on cross-validation results:

- Average Error (RMSE): **factor of 4~5**
- Typical Error (MedAE): **factor of 2~2.5**
- Explained Variance: ~**50%**

QSAR-Based POD based on Chemical Descriptors

https://wchiu.shinyapps.io/Two-Stage-ML-Results-Browser/

Applied to 800K+ chemicals from EPA CompTox Dashboard

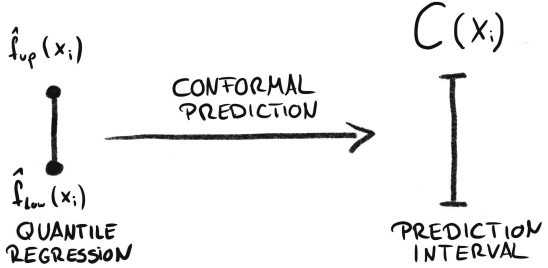
Limitations

- Same uncertainty estimate for every prediction
- Certain classes of chemicals excluded based on OPERA QSAR standardization workflow

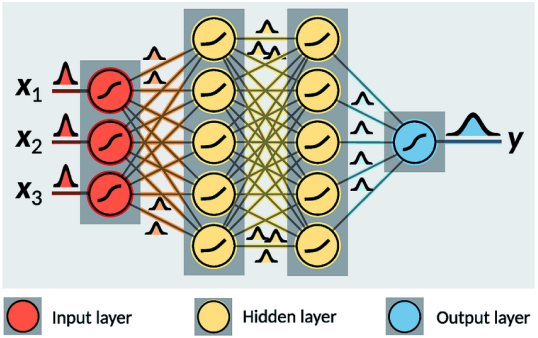
QSAR-Based POD based on Chemical Descriptors

Explore use of "Uncertainty-Aware" ML methods

- **Conformal prediction (CP)**



- **Bayesian neural network (BNN)**



- Addresses aleatoric *and* epistemic uncertainty
- Applied to >130K marketed chemicals

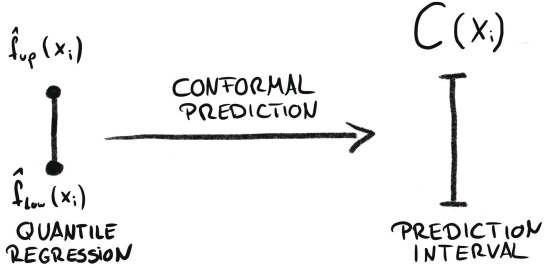
Preliminary Results

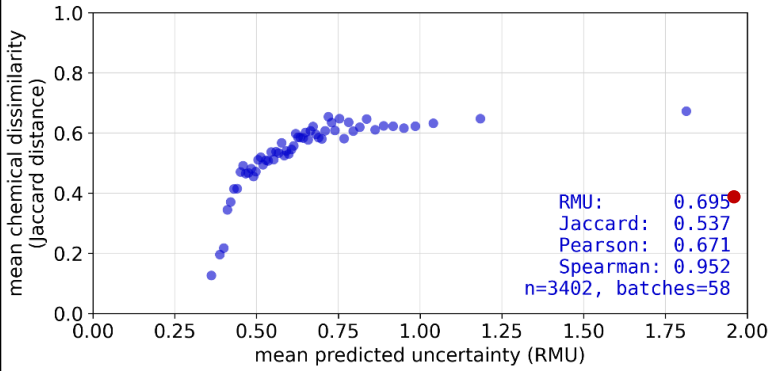
von Borries et al. in preparation

QSAR-Based POD based on Chemical Descriptors

Explore use of "Uncertainty-Aware" ML methods

- **Conformal prediction (CP)**





CP models performed better than BNN

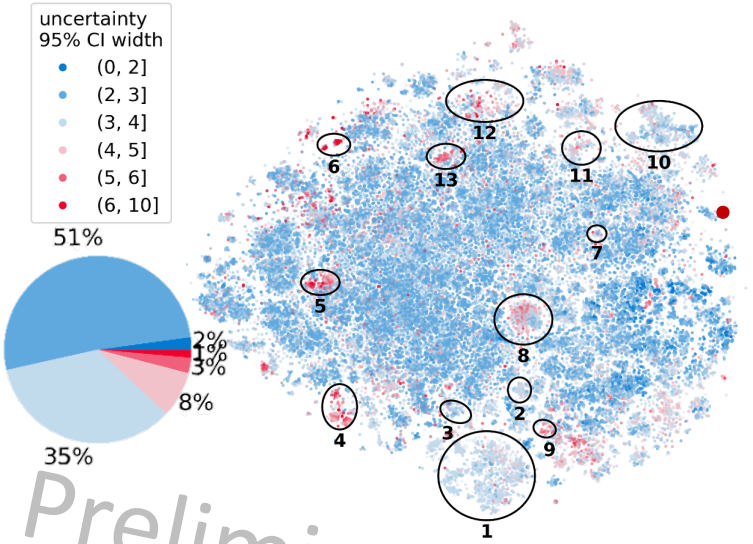
- Good coverage & well-calibrated confidence intervals
- Capture overall heteroscedasticity in prediction errors
- Higher uncertainty for new chemicals that are unlike training set chemicals

Preliminary Results

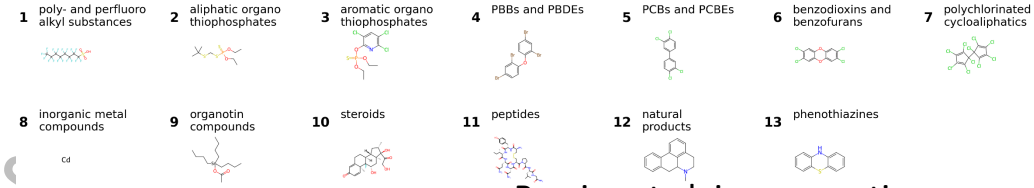
von Borries et al. in preparation

QSAR-Based POD based on Chemical Descriptors

Explore use of "Uncertainty-Aware" ML methods



- **Uncertainty hotspots**
  - polychlorinated and polybrominated compounds
  - metals and organometallics
  - alkaloids and phenothiazines
  - Peptides
- **Drivers of uncertainty**
  - low representation in the training data
  - low applicability of molecular descriptor developed for small organic molecules
  - (highly toxic) outliers



Preliminary Results

von Borries et al. in preparation

Summary: A Tiered Hierarchy of Probabilistic PODs

- LCIA requires PODs for tens-hundreds of thousands of chemicals for characterizing human health impacts of product, process, or service life cycles
- Regulatory/authoritative PODs cover a very limited set of chemicals
- Two classes approaches can fill these data gaps while also quantifying their uncertainty with varying degrees of sophistication
- **Key limitation:** Calibrated to existing regulatory PODs, which are largely based on experimental animal studies.
- **Counterfactual:** If we were to have new regulatory/authoritative assessments based on animal studies in the absence of any human data, we would make decisions based on them!