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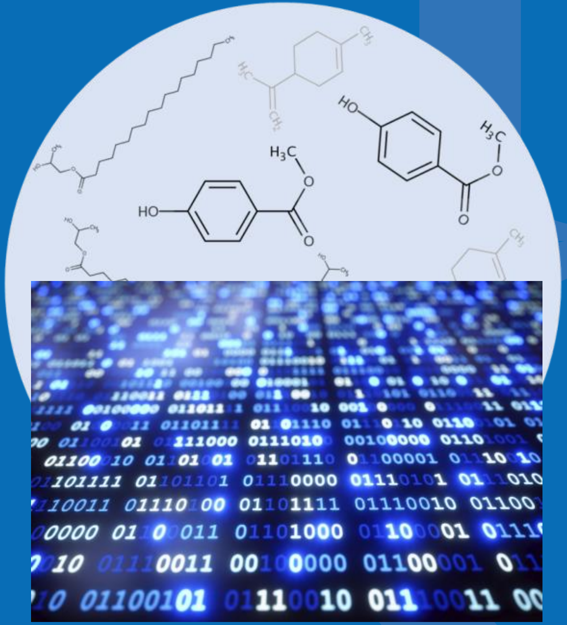
Filling Gaps in Exposure Data from Chemical Descriptors with Machine Learning

Kristin Isaacs
Center for Computational Toxicology and Exposure
United States Environmental Protection Agency

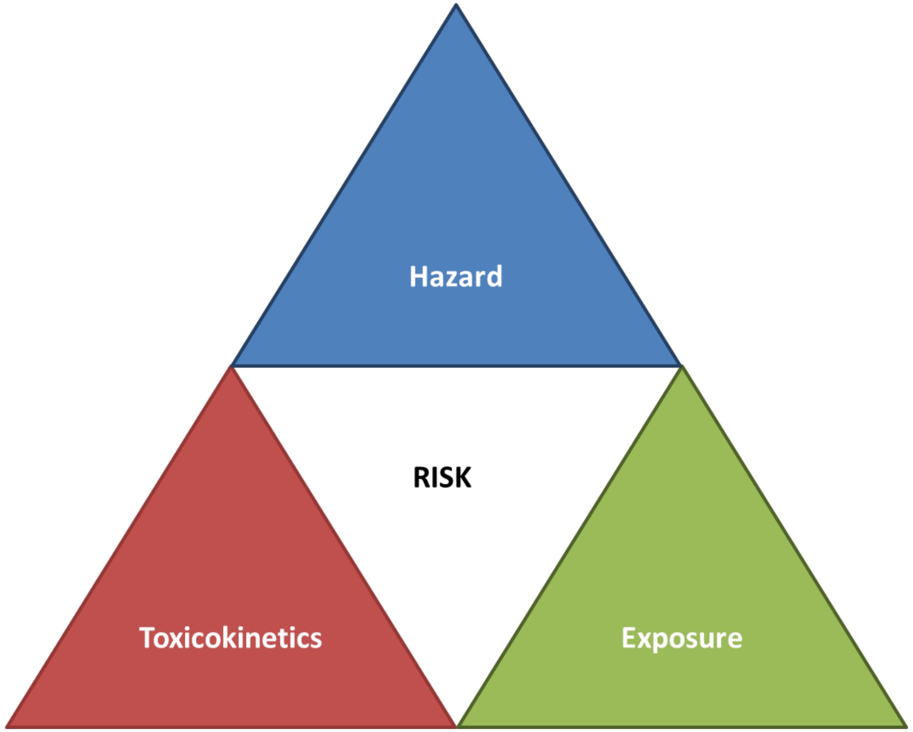


New Approach Methodologies for Exposure: Advancing Chemical Risk Assessment
Society of Toxicology Annual Meeting
March 16, 2021

Disclaimer

The views expressed in this presentation are those of the authors and do not necessarily reflect the views or policies of the U.S. EPA

The Exposure Forecasting (ExpoCast) Project



- Evaluating chemicals for risk to humans or the environment requires information on hazard and exposure potential

- Exposure potential quantifies the degree of contact between a chemical and a receptor

- Toxicokinetic information is required to bridge hazard and exposure (what real-world exposure is required to produce an internal concentration consistent with a potential hazard?)

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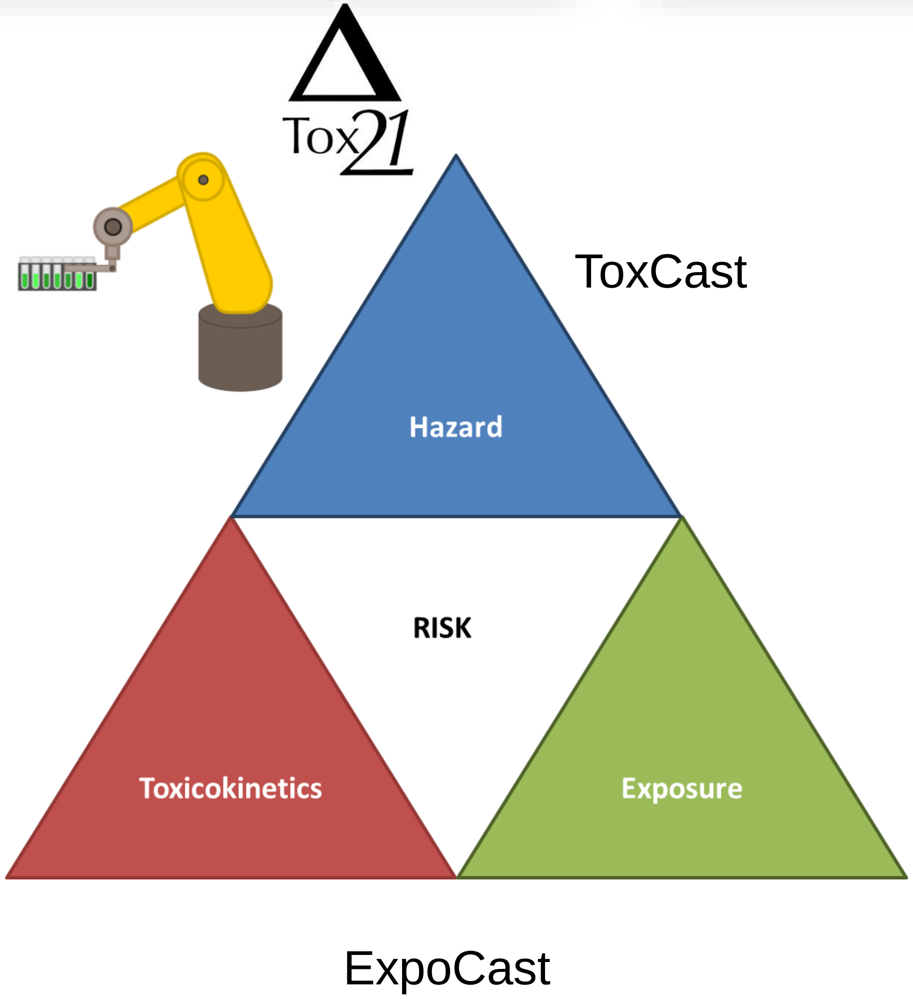

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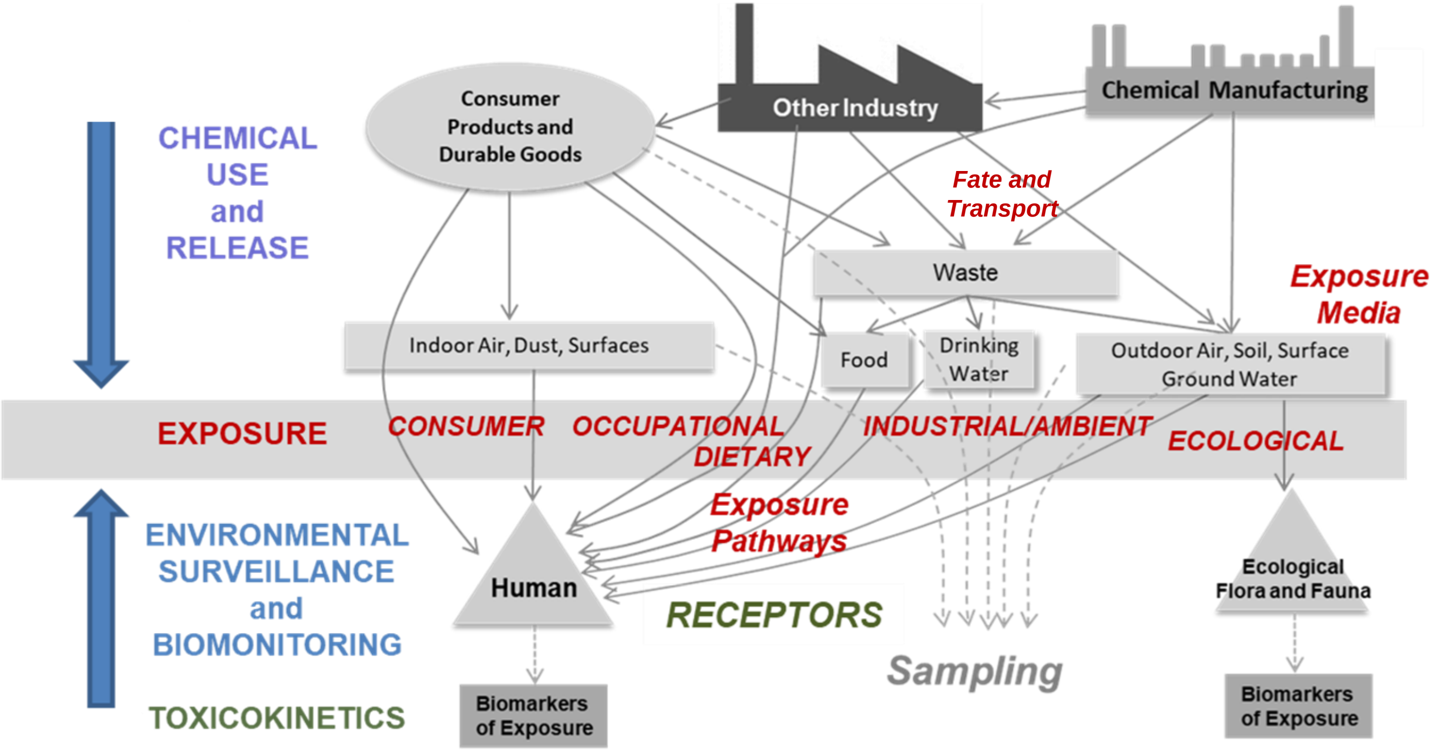
- Exposure potential quantifies the degree of contact between a chemical and a receptor
- Toxicokinetic information is required to bridge hazard and exposure (what real-world exposure is required to produce an internal concentration consistent with a potential hazard?)

The Exposure Data Universe

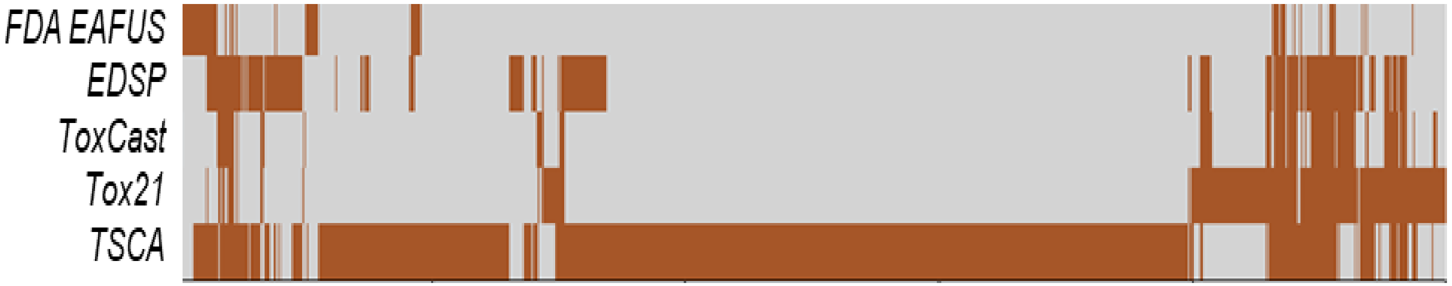
Forward Models
Use/Release → Exposure
Often pathway-specific



Reverse Models
Biomarker Concentrations→ Exposure
Useful for generating evaluation data

Traditional use, release, monitoring, and toxicokinetic data are still unavailable for 1000s of chemicals in commerce.

How Have ML Models Improved the Exposure-Relevant Data Landscape?



38,344 Inventory Chemicals

- Examined coverage of chemical inventories
- Regulatory lists
  - EPA Toxic Substance Control Act Non-Confidential Active Inventory
  - EPA Endocrine Disruptor Screening Program
  - FDA Everything Added to Food in the US (EAFUS)
- Chemicals tested in high-throughput screening
  - ToxCast
  - Tox21

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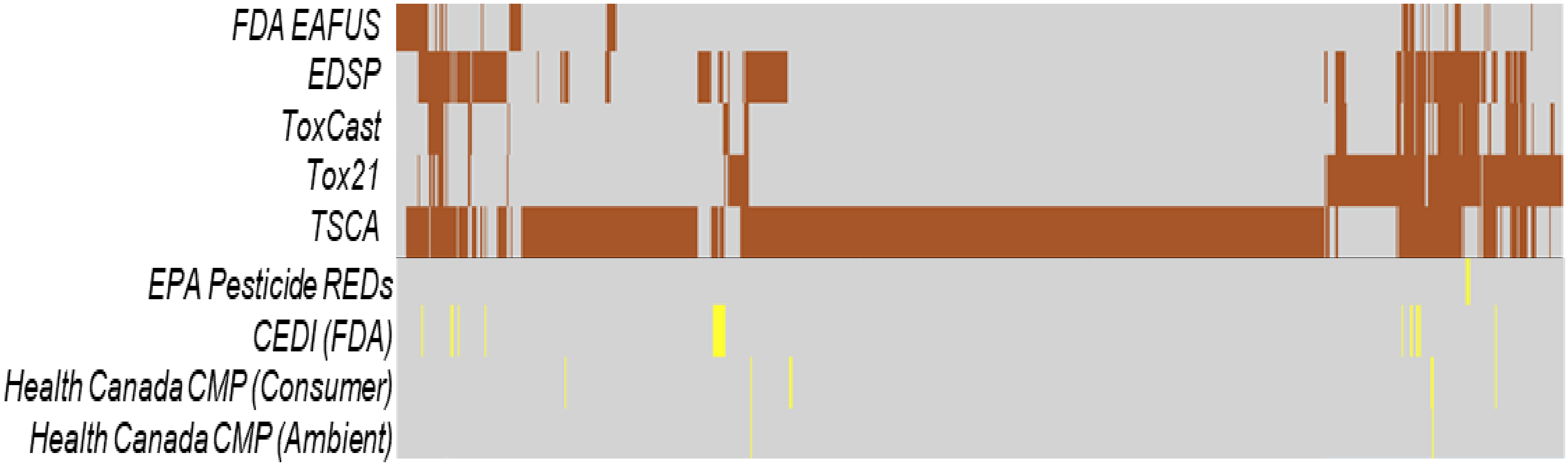

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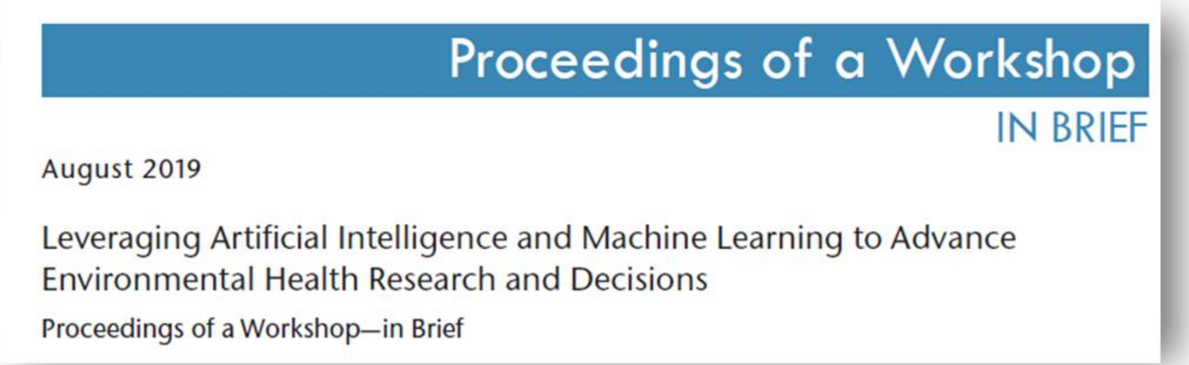
Machine Learning in Environmental Decision-Making

National Academies Workshop, June 2019



Proceedings of a Workshop

IN BRIEF

August 2019

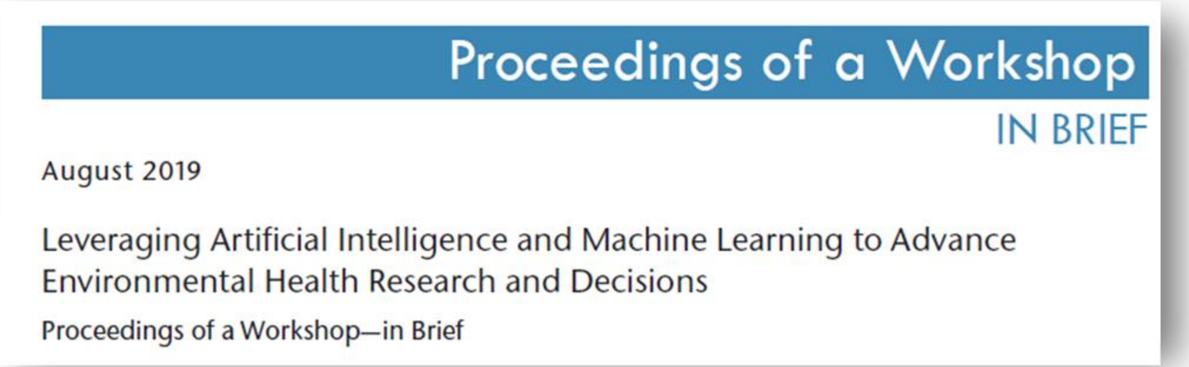
Leveraging Artificial Intelligence and Machine Learning to Advance Environmental Health Research and Decisions

Proceedings of a Workshop—in Brief

- “***Machine learning algorithms can analyze large volumes of complex data to find patterns and make predictions, often exceeding the accuracy and efficiency of people who are attempting the same task.***”
- Highlighted several areas of environmental health for which AI and machine learning could play an integral role in research, including
  - Predicting the toxicology of chemicals
  - Characterizing the exposome

Machine Learning in Environmental Decision-Making

National Academies Workshop, June 2019



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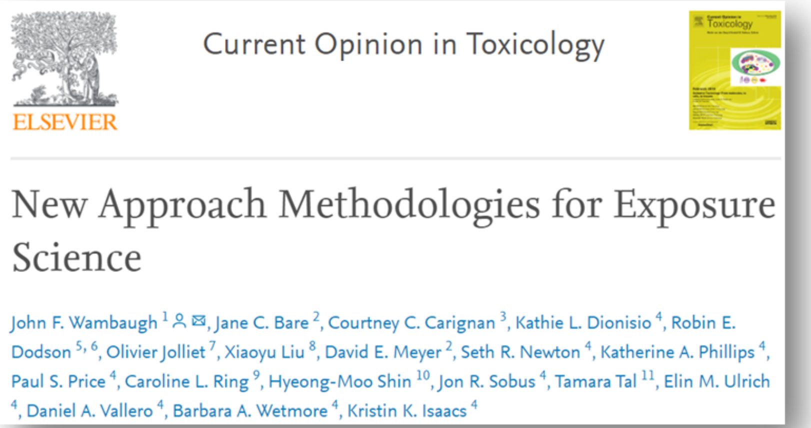


ELSEVIER

Current Opinion in Toxicology

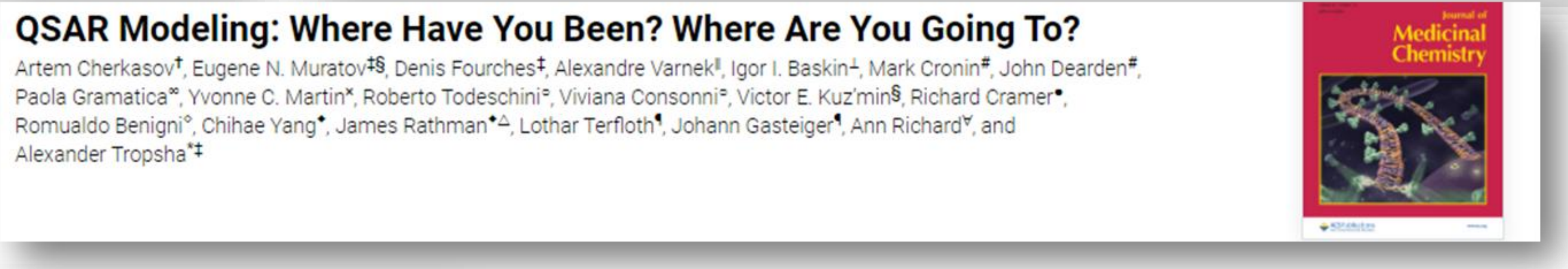
New Approach Methodologies for Exposure Science

John F. Wambaugh [1], Jane C. Bare [2], Courtney C. Carignan [3], Kathie L. Dionisio [4], Robin E. Dodson [5, 6], Olivier Jolliet [7], Xiaoyu Liu [8], David E. Meyer [2], Seth R. Newton [4], Katherine A. Phillips [4], Paul S. Price [4], Caroline L. Ring [9], Hyeong-Moo Shin [10], Jon R. Sobus [4], Tamara Tal [11], Elin M. Ulrich [4], Daniel A. Vallero [4], Barbara A. Wetmore [4], Kristin K. Isaacs [4]

- ***"Machine learning algorithms can analyze large volumes of complex data to find patterns and make predictions, often exceeding the accuracy and efficiency of people who are attempting the same task."***
- Highlighted several areas of environmental health for which AI and machine learning could play an integral role in research, including
  - Predicting the toxicology of chemicals
  - Characterizing the exposome

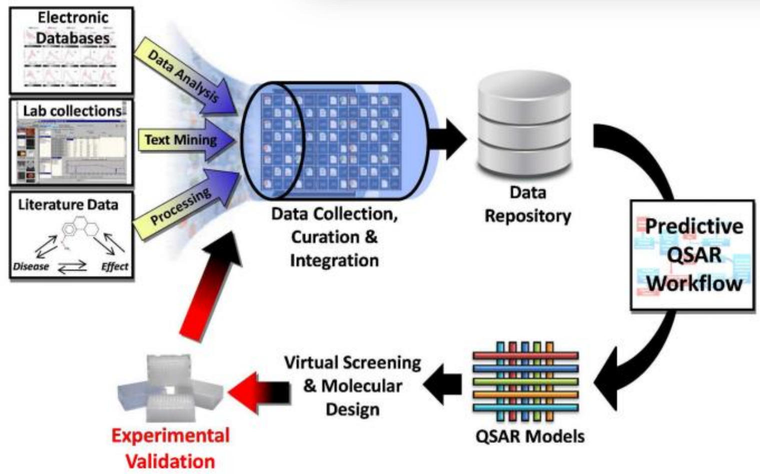
- Defined eight classes of NAMs for exposure, including
  - ***Chemical descriptors*** that provide information on chemicals in an exposure context (e.g., how chemicals are used)
  - ***Machine-learning approaches*** that use these descriptors to fill gaps in existing data

Learning from Physical Chemistry, Drug Discovery, & Toxicology

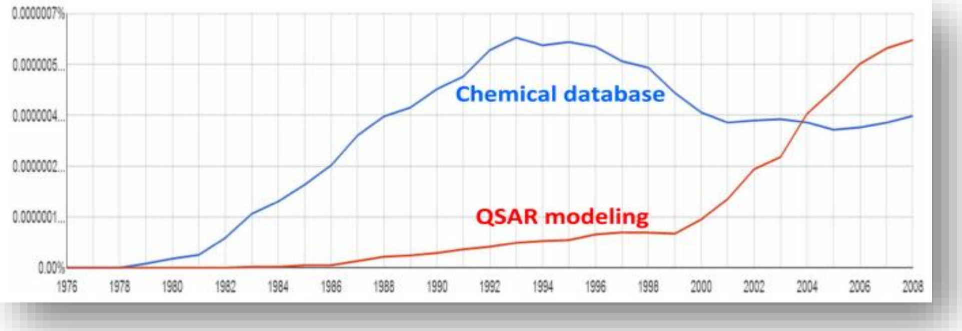


QSAR Modeling: Where Have You Been? Where Are You Going To?

Artem Cherkasov[†], Eugene N. Muratov[‡§], Denis Fourches[‡], Alexandre Varnek[‖], Igor I. Baskin[⊥], Mark Cronin[#], John Dearden[#], Paola Gramatica[∞], Yvonne C. Martin[×], Roberto Todeschini[=], Viviana Consonni[=], Victor E. Kuz'min[§], Richard Cramer[•], Romualdo Benigni[○], Chihae Yang[◆], James Rathman[◆△], Lothar Terfloth[¶], Johann Gasteiger[¶], Ann Richard[∀], and Alexander Tropsha[*‡]



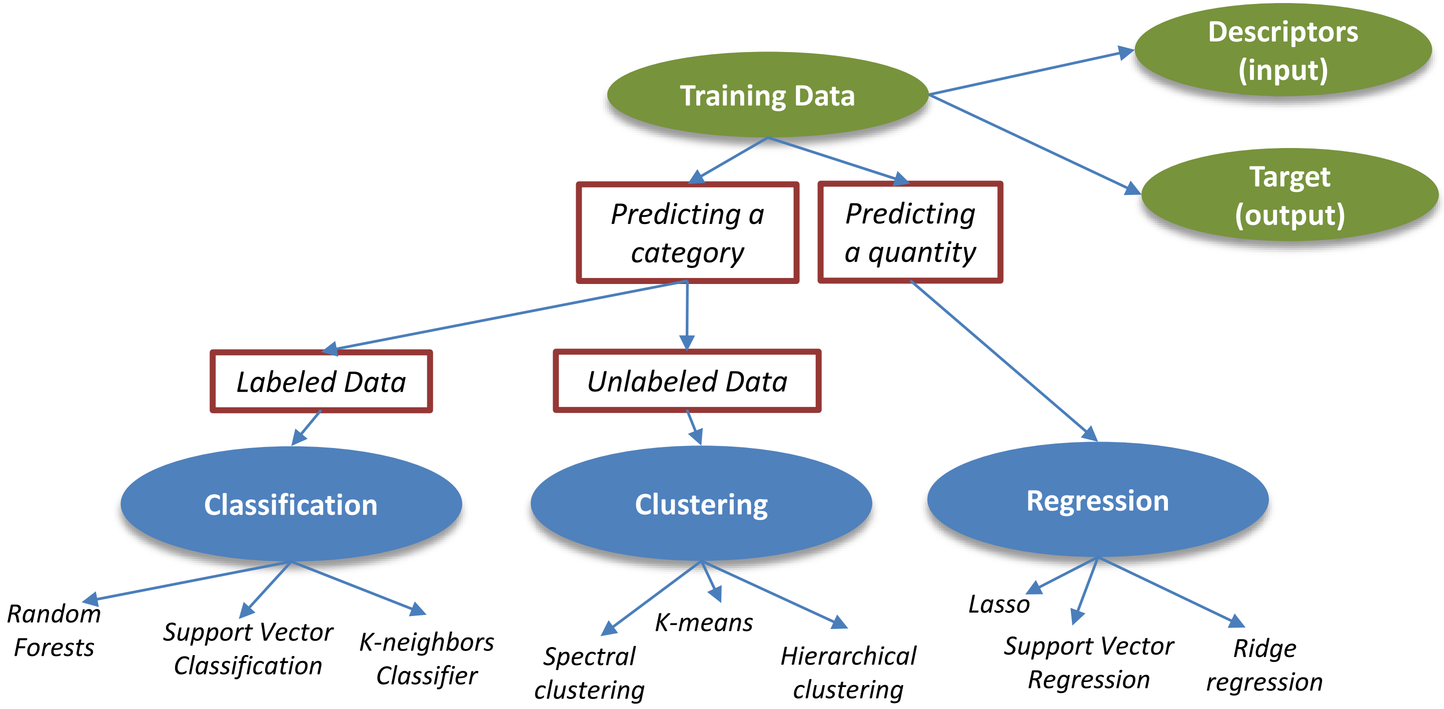
Mentions in Google Books Database



- Quantitative Structure-Activity Relationships (QSAR) models have been used for over 50 years to predict the physical and biological properties of chemicals.
- The field has advanced from simple regression methods to sophisticated machine learning techniques for the analysis of very large datasets comprising thousands of diverse molecular structures.
- The scientific QSAR community has been on the forefront of the use of machine learning methods, having developed:
  - New chemical structural descriptor sets
  - Many recommendations for best practices, including model validation

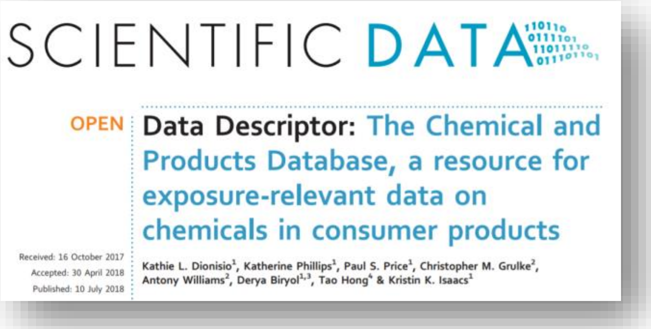
Machine Learning Overview

- Machine learning is ideally suited to look at many factors simultaneously.
- It can identify patterns in large datasets and build corresponding predictive models.
- A major challenge is determining the most appropriate method for the problem.



Portions adapted from https://scikit-learn.org

Training and Descriptor Sets for Chemical Exposure



SCIENTIFIC DATA

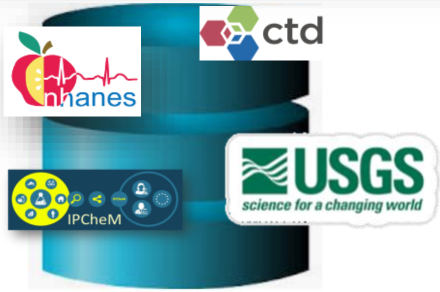
OPEN

Data Descriptor: The Chemical and Products Database, a resource for exposure-relevant data on chemicals in consumer products

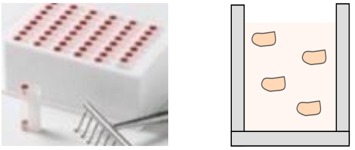
Received: 16 October 2017
Accepted: 30 April 2018
Published: 10 July 2018

Kathie L. Dionisio[1], Katherine Phillips[1], Paul S. Price[1], Christopher M. Grulke[2], Antony Williams[2], Derya Biryol[1,3], Tao Hong[4] & Kristin K. Isaacs[1]

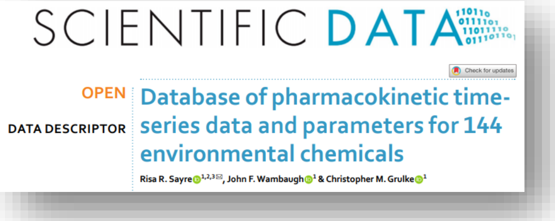
New quantitative and qualitative chemical use descriptors from EPA's Chemicals and Products Database (CPDat, Dionisio et al. 2018)



Traditional (targeted) monitoring data for various environmental media from publicly available monitoring databases



***In-vitro* protein binding and clearance (Wetmore et al. 2015, Pearce et al. 2017, Wambaugh et al. 2019a.)**



SCIENTIFIC DATA

Check for updates

OPEN

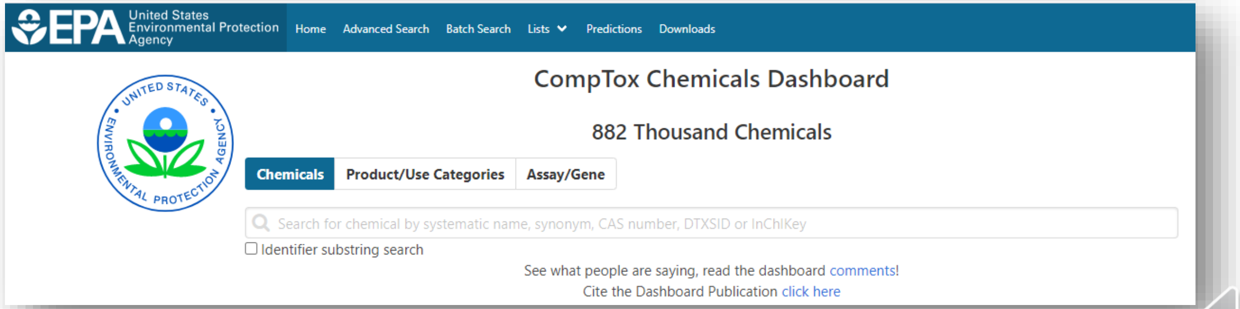
DATA DESCRIPTOR

Database of pharmacokinetic time-series data and parameters for 144 environmental chemicals

Risa R. Sayre[1,2,3], John F. Wambaugh[1] & Christopher M. Grulke[1]

***In-vivo* toxicokinetic parameters collected from the literature (Sayre et al. 2020)**

- **Models are only as good as the underlying data!**
- In EPA-ORD's ExpoCast project, we are compiling the datasets that enable extrapolation of target information to data-poor chemicals using machine learning.
- Also currently developing IT infrastructure for automated and manual curation, QA, provenance tracking, and dissemination of these data (**Poster P-117**).
- Our goal is to be able to ultimately provide all these data publicly via the CompTox Chemicals Dashboard. (https://comptox.epa.gov/dashboard)



CompTox Chemicals Dashboard

882 Thousand Chemicals

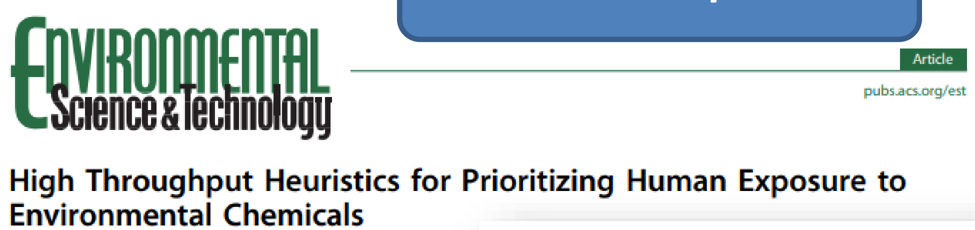
Search for chemical by systematic name, synonym, CAS number, DTXSID or InChIKey

□ Identifier substring search

See what people are saying, read the dashboard comments!
Cite the Dashboard Publication click here

Training and Descriptor Sets for Chemical Exposure

Use Descriptors

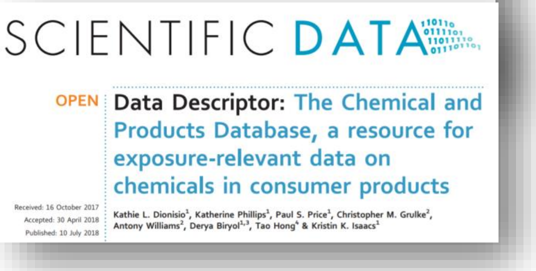

Environmental Science & Technology

Article

pubs.acs.org/est

High Throughput Heuristics for Prioritizing Human Exposure to Environmental Chemicals

John F. Wambaugh,[*,†] Anran Wang,[†,§,∥] Kathie L.
Richard Judson,[†] and R. Woodrow Setzer[†]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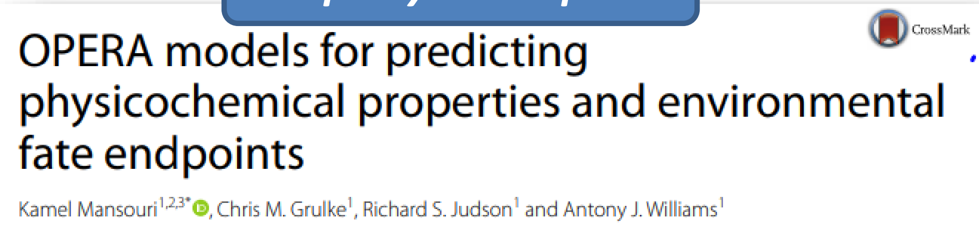
- We use a variety of chemical descriptor sets for our exposure models.
- Different descriptor sets contain unique information that can inform predictive models.
- OPERA and ToxPrint descriptors can be easily downloaded for thousands of substances using the batch search utility of the CompTox Chemicals Dashboard.

Property Descriptors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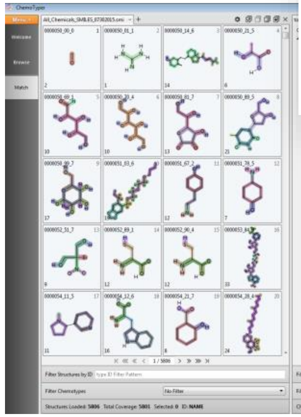
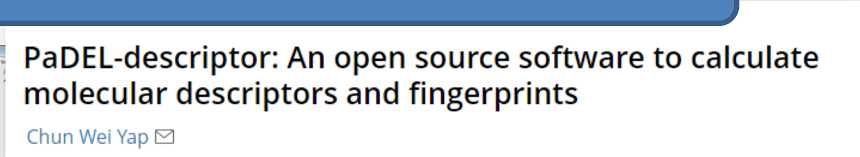
OPERA models for predicting physicochemical properties and environmental fate endpoints

Kamel Mansouri[1,2,3*], Chris M. Grulke[1], Richard S. Judson[1] and Antony J. Williams[1]

https://github.com/kmansouri/OPERA

Structural/Molecular Descriptors



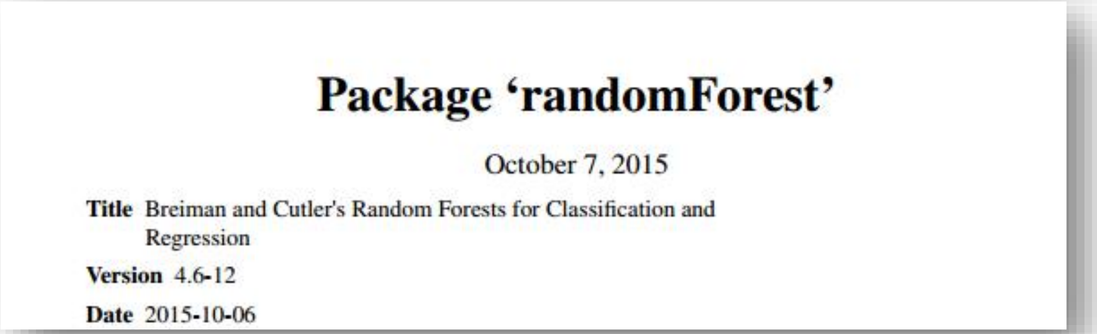

PaDEL-descriptor: An open source software to calculate molecular descriptors and fingerprints

Chun Wei Yap ✉

ToxPrint - A Public Set of Chemotypes

Method of Random Forests

- Ensemble average over many decision trees
- Randomly select subset of descriptors and grow ‘unpruned’ tree, repeat many times
- Model returns a probability equal to fraction of trees returning a positive classification
- Importance of descriptors can be quantified



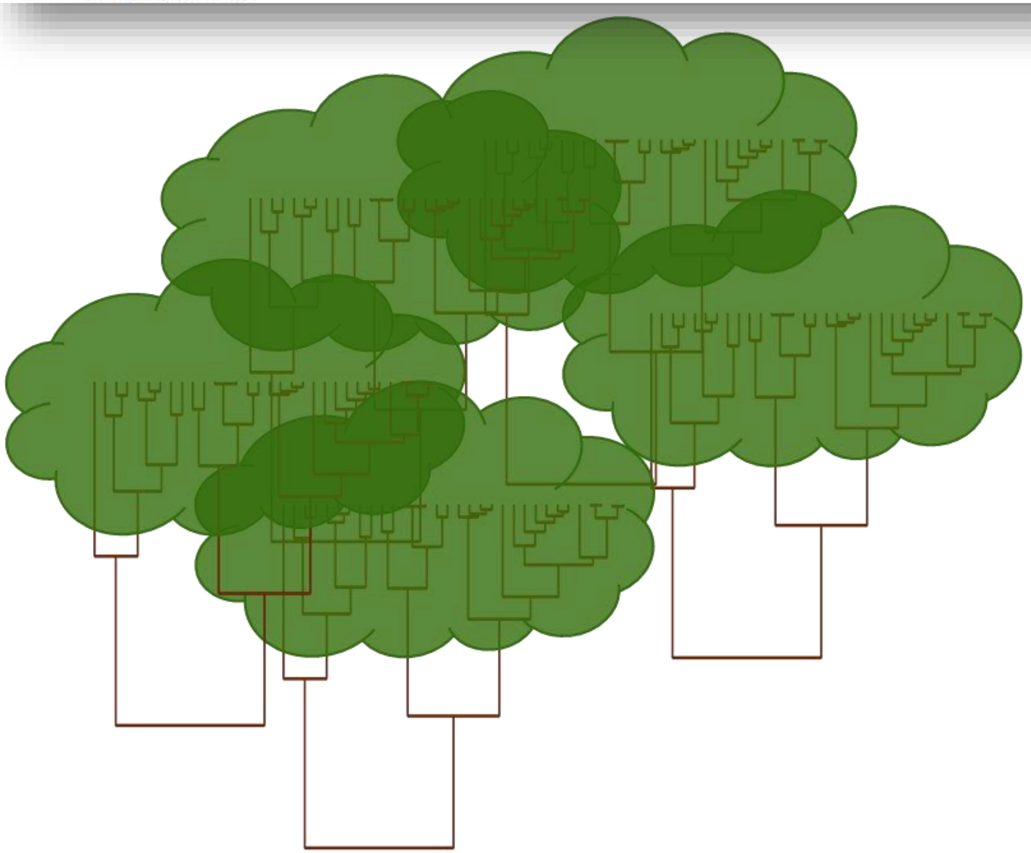
Package ‘randomForest’

October 7, 2015

Title Breiman and Cutler's Random Forests for Classification and Regression

Version 4.6-12

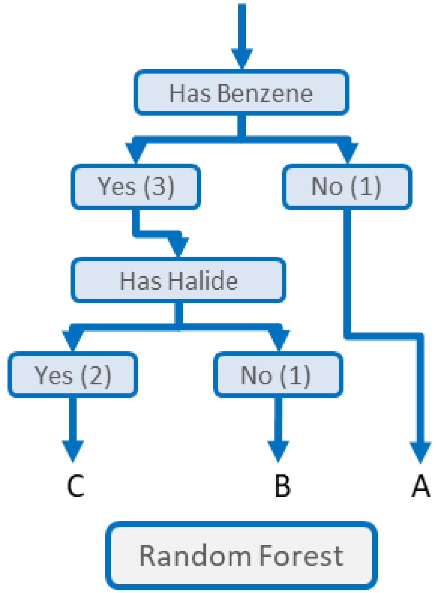
Date 2015-10-06



Method of Random Forests

Train Model

	Target	Descriptors			
		Has Metal	Has Halide	Has Benzene	Has Alkyne
Chemical 1	A	0	1	0	0
Chemical 2	B	0	0	1	1
Chemical 3	C	0	1	1	0
Chemical 4	C	1	1	1	1



Validate models

- Does model work beyond the training set?
- Does the model perform better than one built using random data?

Figure from Katherine Phillips

Method of Random Forests

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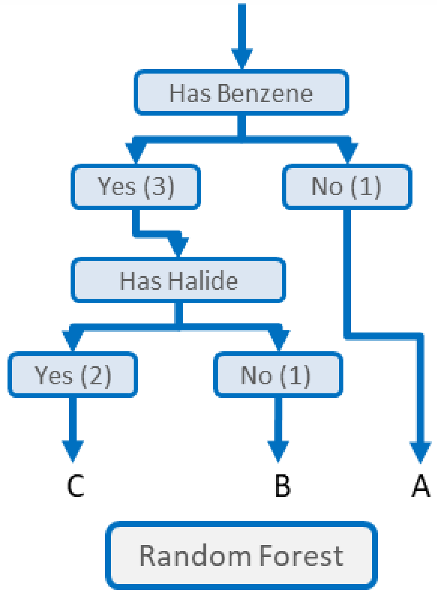


Validate models
- Does model work beyond the training set?
- Does the model perform better than one built using random data?

Predict Model

	Descriptors			
Chemical 5	0	1	1	0
Chemical 6	0	1	0	0
Chemical 7	0	0	1	1

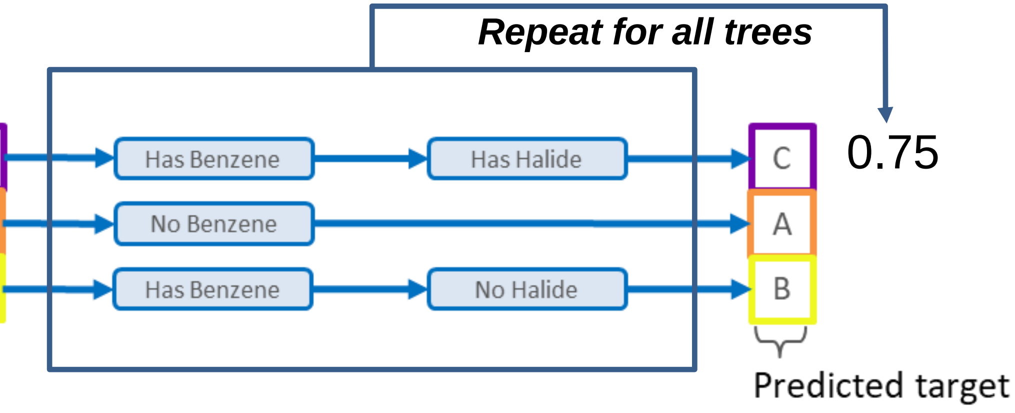
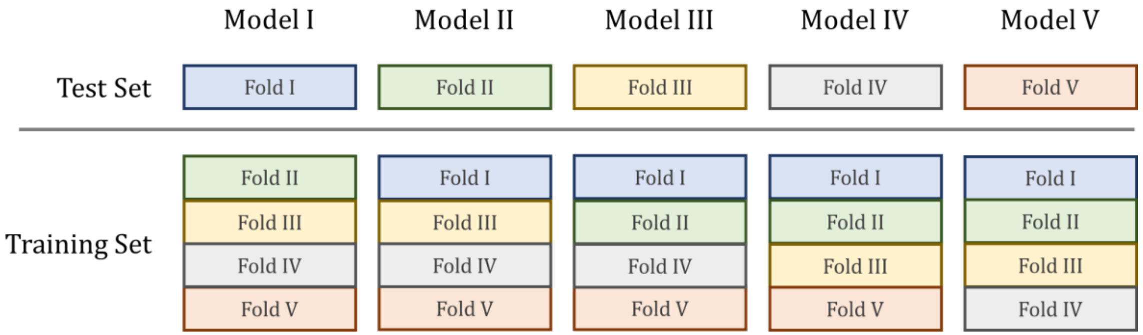


Figure from Katherine Phillips

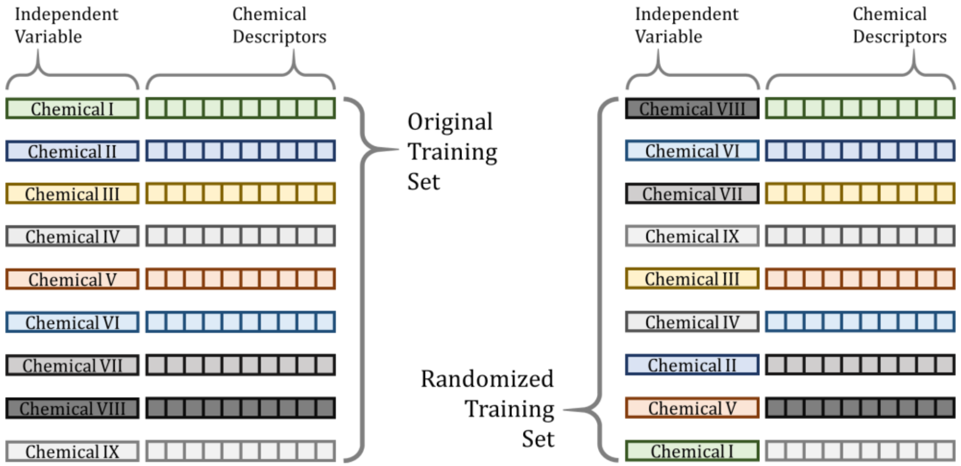
Model Validation and Applicability Domain (AD)

5-fold cross validation



	Model I	Model II	Model III	Model IV	Model V
Test Set	Fold I	Fold II	Fold III	Fold IV	Fold V
Training Set	Fold II Fold III Fold IV Fold V	Fold I Fold III Fold IV Fold V	Fold I Fold II Fold IV Fold V	Fold I Fold II Fold III Fold V	Fold I Fold II Fold III Fold IV

Y-randomization



Independent Variable	Chemical Descriptors		Independent Variable	Chemical Descriptors
Chemical I		Original Training Set	Chemical VIII	
Chemical II			Chemical VI	
Chemical III			Chemical VII	
Chemical IV			Chemical IX	
Chemical V			Chemical III	
Chemical VI			Chemical IV	
Chemical VII			Chemical II	
Chemical VIII		Randomized Training Set	Chemical V	
Chemical IX			Chemical I	

- Validation approaches:
  - 5-fold cross validation (build the model 5 times withholding a different subset of the data each time for testing)
  - Y-randomization (build the model using randomized target assignment to descriptors - does the true model outperform the randomized version?)
  - Evaluation with true external training sets

Figure from Katherine Phillips

Model Validation and Applicability Domain (AD)

AD: The response and chemical structure space in which the model makes predictions with a given reliability

Methods for Assessing AD in Chemical Space

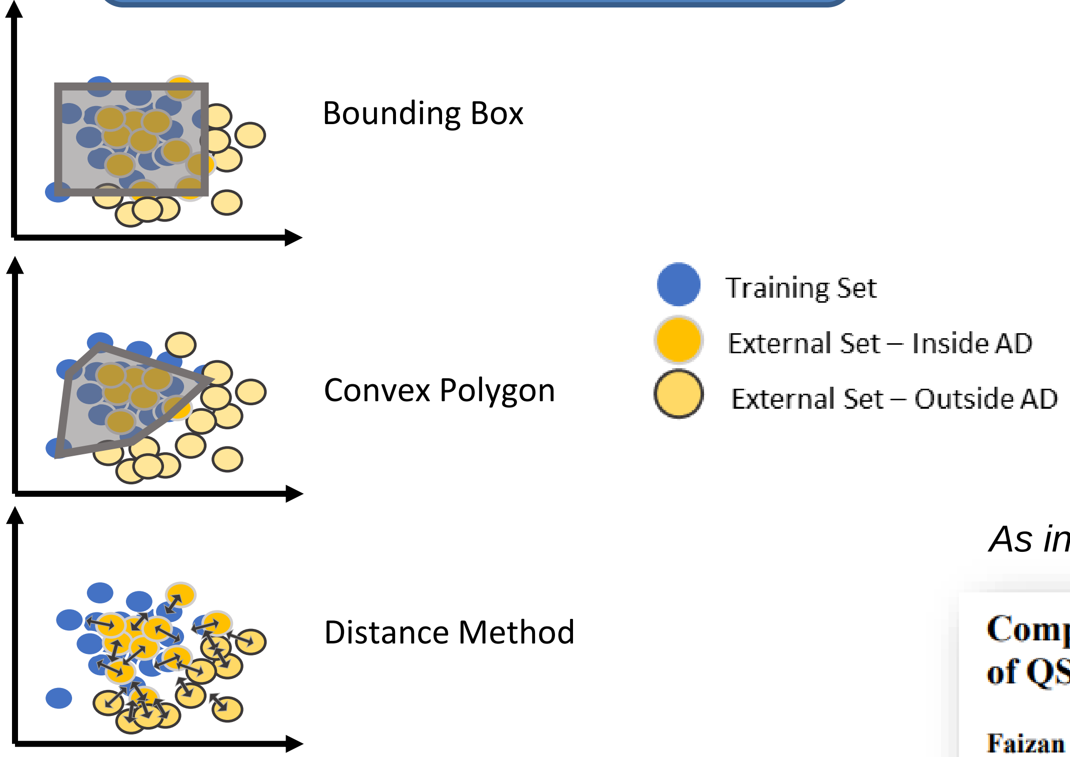
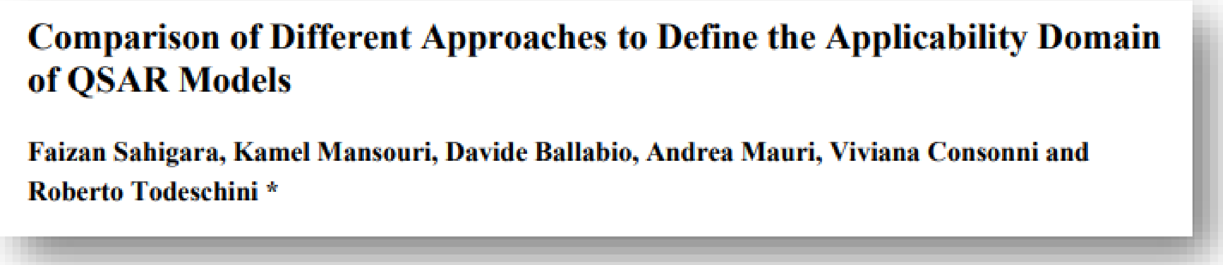


Figure from Katherine Phillips

- QSAR/Machine learning best-practices include an emphasis on model validation and the need to define **model applicability domain** (AD) in the chemistry space (Tropsha et al. 2007)
- Knowledge of the AD is required for assessing confidence in predictions for new chemicals and quantifying the utility of additional data.

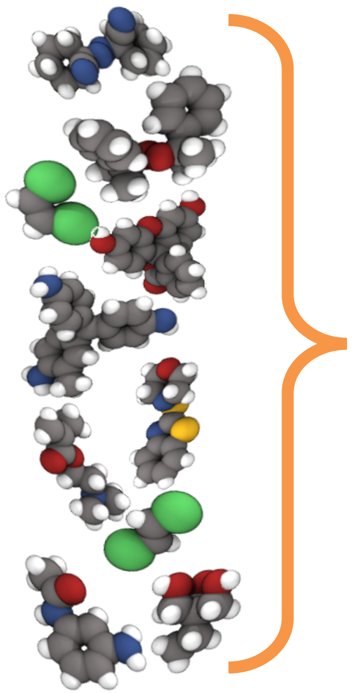
As in Sahigara et al., Molecules (2012):

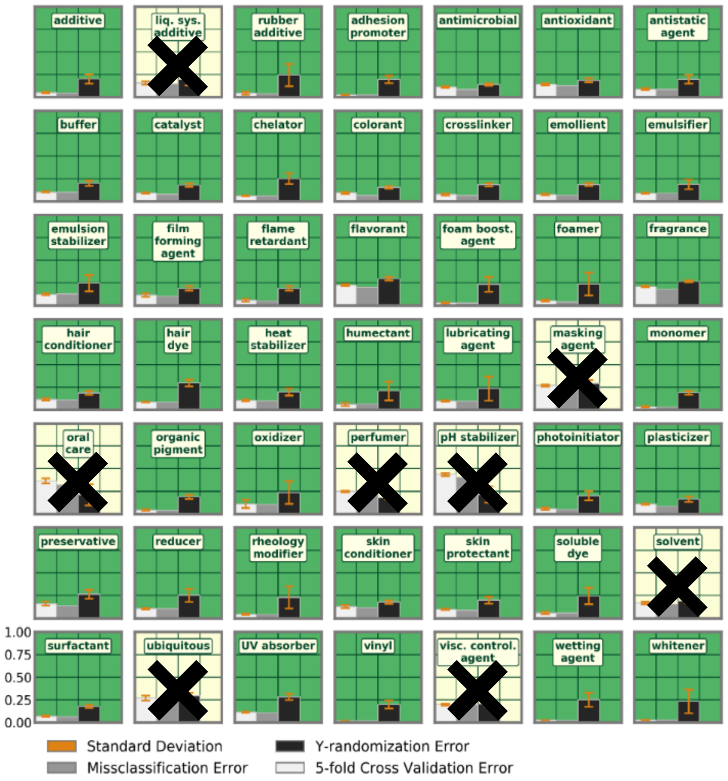


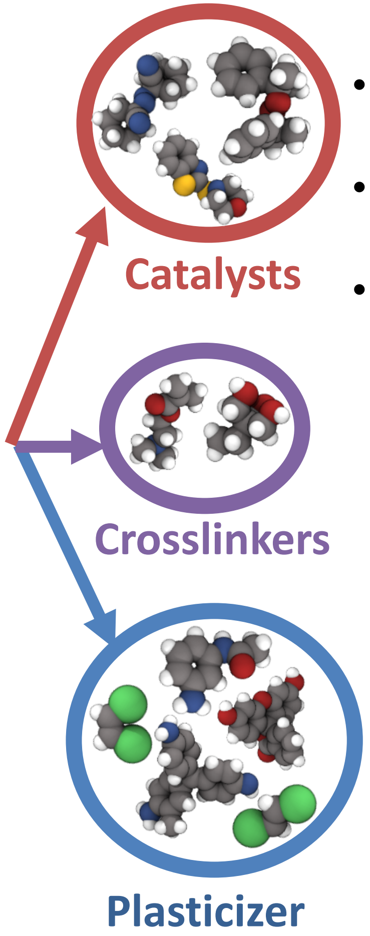
Comparison of Different Approaches to Define the Applicability Domain of QSAR Models

Faizan Sahigara, Kamel Mansouri, Davide Ballabio, Andrea Mauri, Viviana Consonni and Roberto Todeschini *

Chemical Functional Use





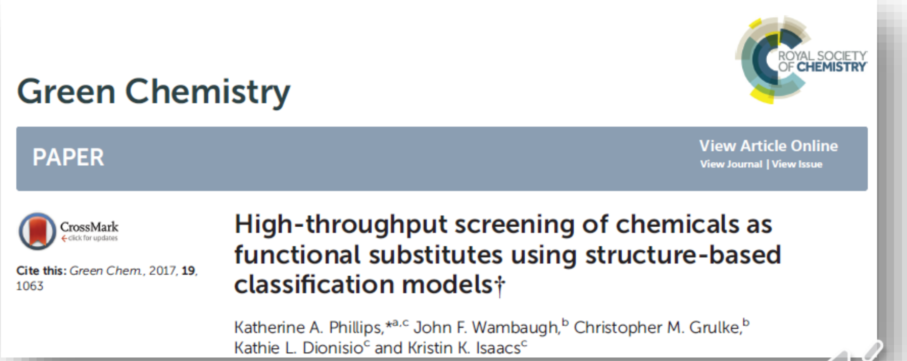


Catalysts

Crosslinkers

Plasticizer

- Quantitative Structure-Use Relationships (QSURs)
- Built from a training set of over 15,000 reported functions
- Used to inform screening of chemical libraries for potential alternatives with lower toxicity
- Used in non-targeted analysis workflows for ground truthing tentatively identified chemicals



Green Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

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Cite this: *Green Chem.*, 2017, **19**, 1063

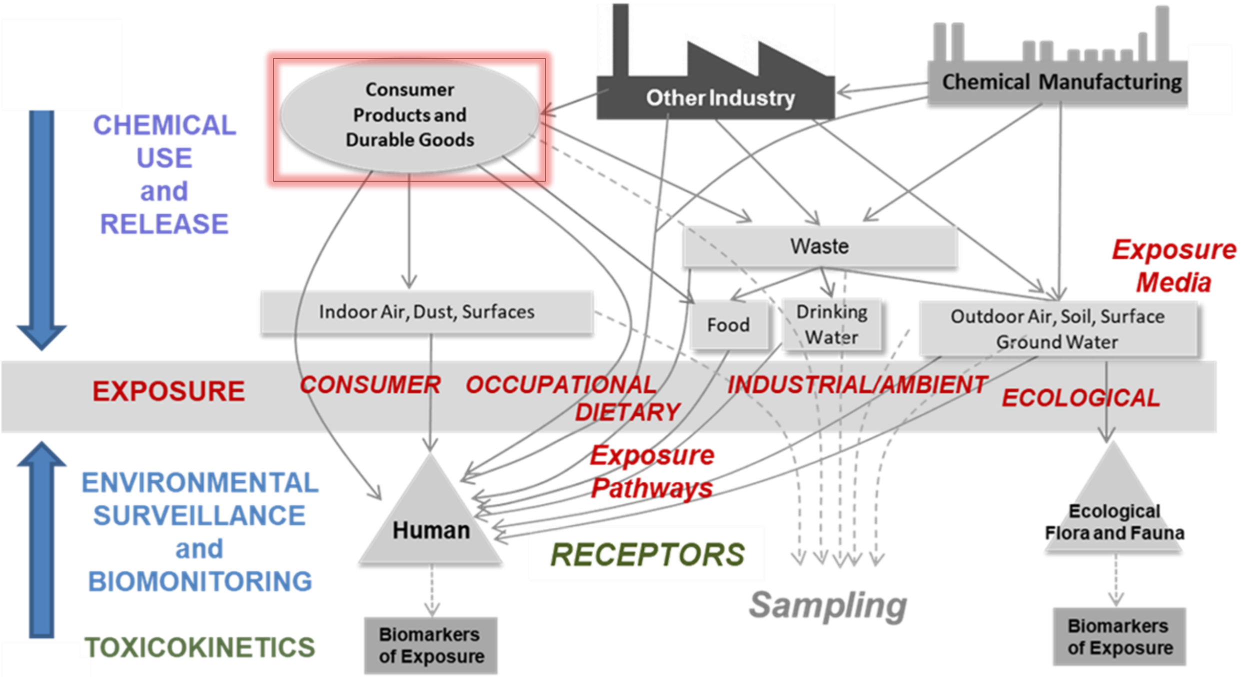
High-throughput screening of chemicals as functional substitutes using structure-based classification models†

Katherine A. Phillips,[*a,c] John F. Wambaugh,[b] Christopher M. Grulke,[b] Kathie L. Dionisio[c] and Kristin K. Isaacs[c]

Phillips et al., *Green Chem.*, 2017

Applying Machine Learning to Other Exposure Domains

- Using functional use predictions to estimate quantitative chemical weight fractions in consumer formulations (Isaacs et al., 2016) and articles
- Using Natural Language Processing Support Vector Classification models to assign 100,000 consumer product ingredient documents to harmonized categories for modeling



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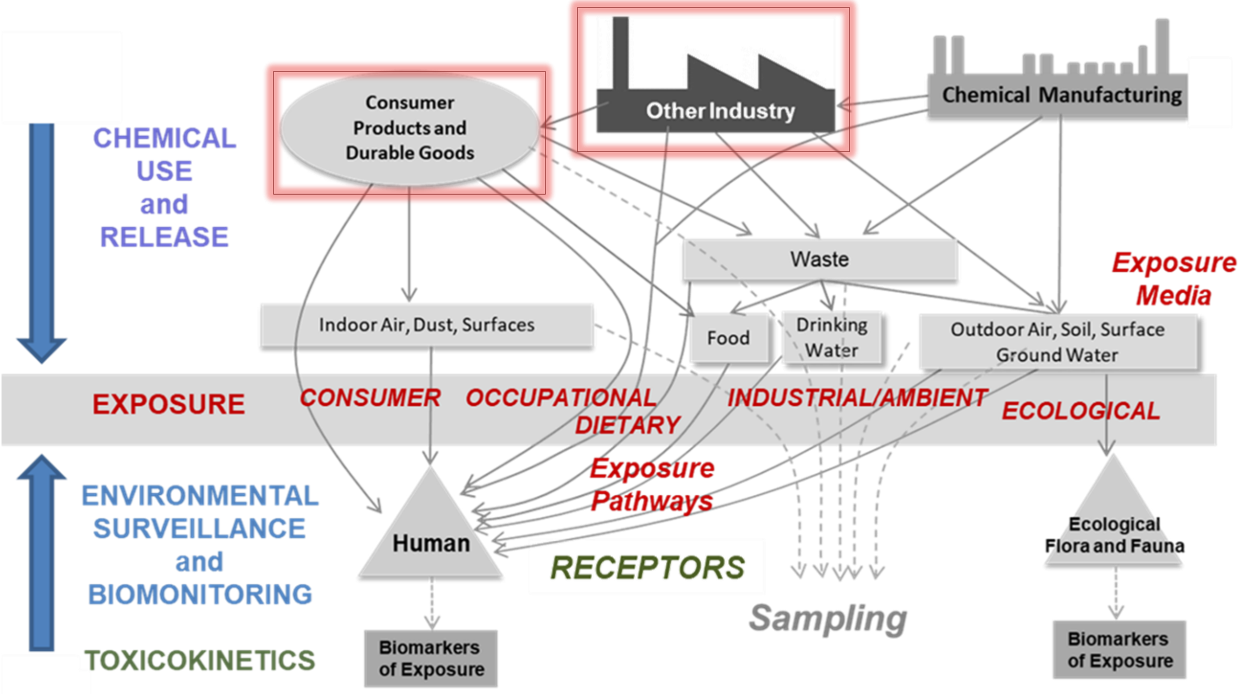

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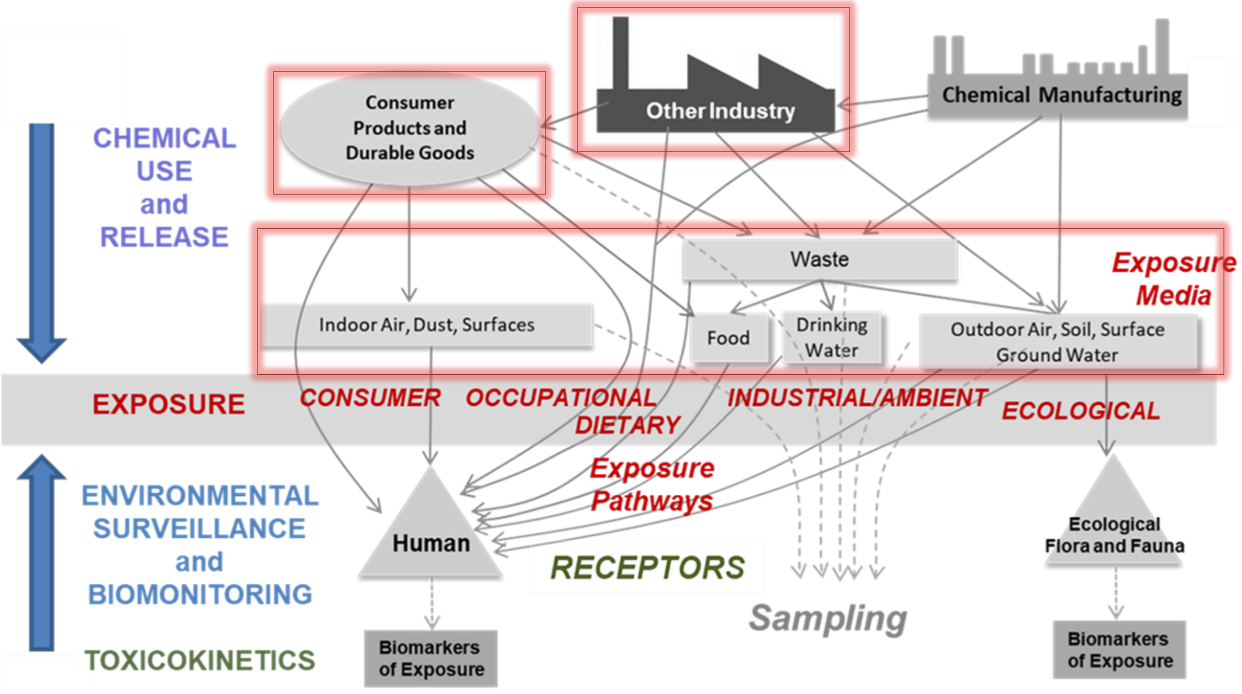

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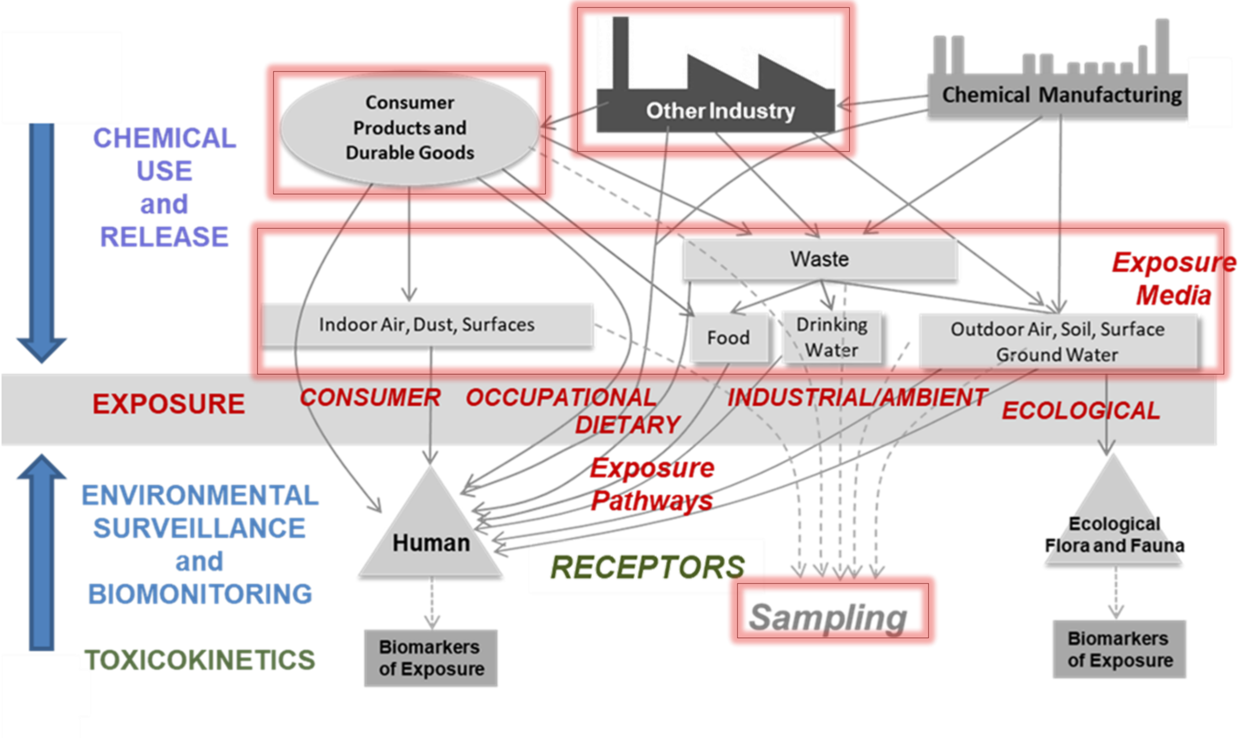
- Prediction of method amenability in high-resolution mass spectrometry (ORD Center for Computational Toxicology and Exposure)



CHEMICAL USE and RELEASE

Consumer Products and Durable Goods

Other Industry

Chemical Manufacturing

Waste

Exposure Media

Indoor Air, Dust, Surfaces

Food

Drinking Water

Outdoor Air, Soil, Surface Ground Water

EXPOSURE

CONSUMER

OCCUPATIONAL

DIETARY

INDUSTRIAL/AMBIENT

ECOLOGICAL

Exposure Pathways

ENVIRONMENTAL SURVEILLANCE and BIOMONITORING

TOXICOKINETICS

Human

RECEPTORS

Sampling

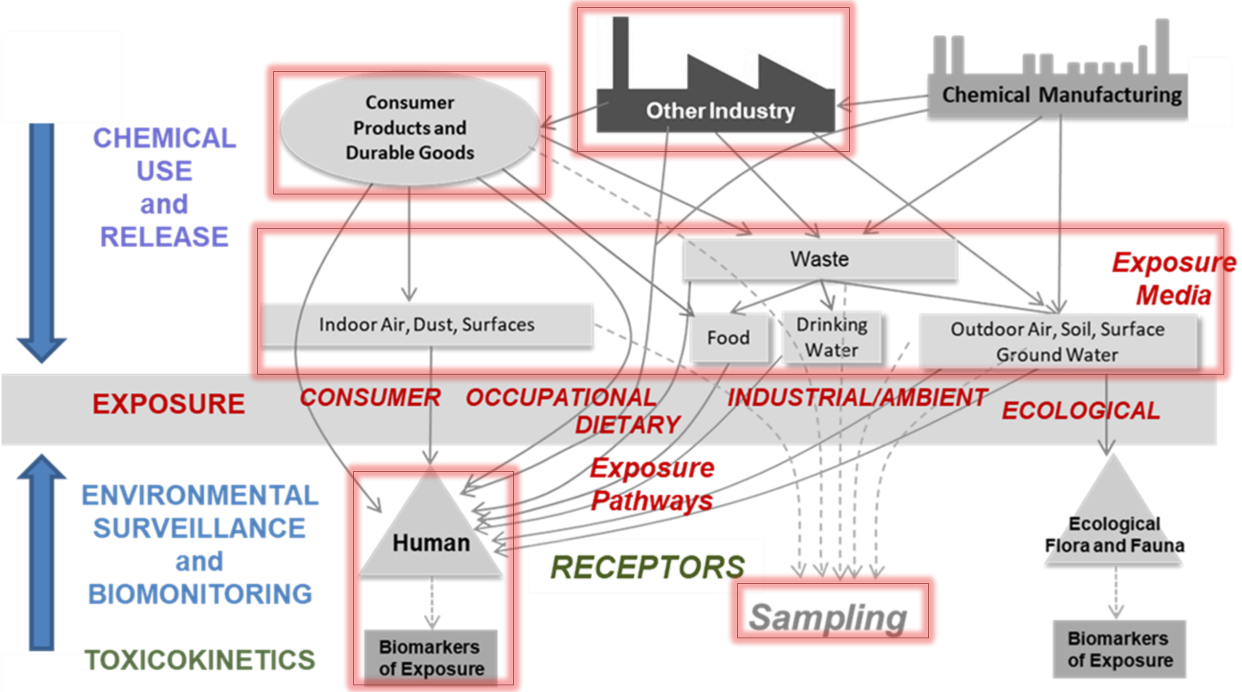
Ecological Flora and Fauna

Biomarkers of Exposure

Biomarkers of Exposure

Applying Machine Learning to Other Exposure Domains

- Using functional use predictions to estimate quantitative chemical weight fractions in consumer formulations (Isaacs et al., 2016) and articles
- Using Natural Language Processing Support Vector Classification models to assign 100,000 consumer product ingredient documents to harmonized categories for modeling
- Prediction of chemical releases associated with industrial scenarios and processes (ORD Center for Environmental Solutions & Emergency Response)
- Prediction of chemical occurrence in 26 different types of environmental and biological media.
- Prediction of method amenability in high-resolution mass spectrometry (ORD Center for Computational Toxicology and Exposure)
- In-silico machine learning models for toxicokinetic parameters: protein binding and clearance for environmental chemicals



Human SEEM Model (3rd Generation) Collaboration

Systematic **E**mpirical **E**valuation of **M**odels

Jon Arnot, Deborah H. Bennett, Peter P. Egeghy, Peter Fantke, Lei Huang, Kristin Isaacs, Olivier Jolliet, Hyeong-Moo Shin, Katherine A. Phillips, Caroline Ring, R. Woodrow Setzer, John F. Wambaugh, Johnny Westgate

Predictor (including Models)	Reference(s)	Chemicals	Pathways
EPA Inventory Update Reporting and Chemical Data Reporting (CDR) (2015)	US EPA (2018)	7856	All
Stockholm Convention of Banned Persistent Organic Pollutants (2017)	Lallas (2001)	248	Far-Field Industrial and Pesticide
EPA Pesticide Reregistration Eligibility Documents (REDs) Exposure Assessments (Through 2015)	Wetmore et al. (2012, 2015)	239	Far-Field Pesticide
United Nations Environment Program and Society for Environmental Toxicology and Chemistry toxicity model (USEtox) Industrial Scenario (2.0)	Rosenbaum et al. (2008)	8167	Far-Field Industrial
USEtox Pesticide Scenario (2.0)	Fantke et al. (2011, 2012, 2016)	940	Far-Field Pesticide
Risk Assessment IDentification And Ranking (RAIDAR) Far-Field (2.02)	Arnot et al. (2008)	8167	Far-Field Pesticide
EPA Stochastic Human Exposure Dose Simulator High Throughput (SHEDS-HT) Near-Field Direct (2017)	Isaacs (2017)	7511	Far-Field Industrial and Pesticide
SHEDS-HT Near-field Indirect (2017)	Isaacs (2017)	1119	Residential
Fugacity-based INdoor Exposure (FINE) (2017)	Bennett et al. (2004), Shin et al. (2012)	645	Residential
RAIDAR-ICE Near-Field (0.803)	Arnot et al., (2014), Zhang et al. (2014)	1221	Residential
USEtox Residential Scenario (2.0)	Jolliet et al. (2015), Huang et al. (2016,2017)	615	Residential
USEtox Dietary Scenario (2.0)	Jolliet et al. (2015), Huang et al. (2016), Ernstoff et al. (2017)	8167	Dietary

Material from John Wambaugh

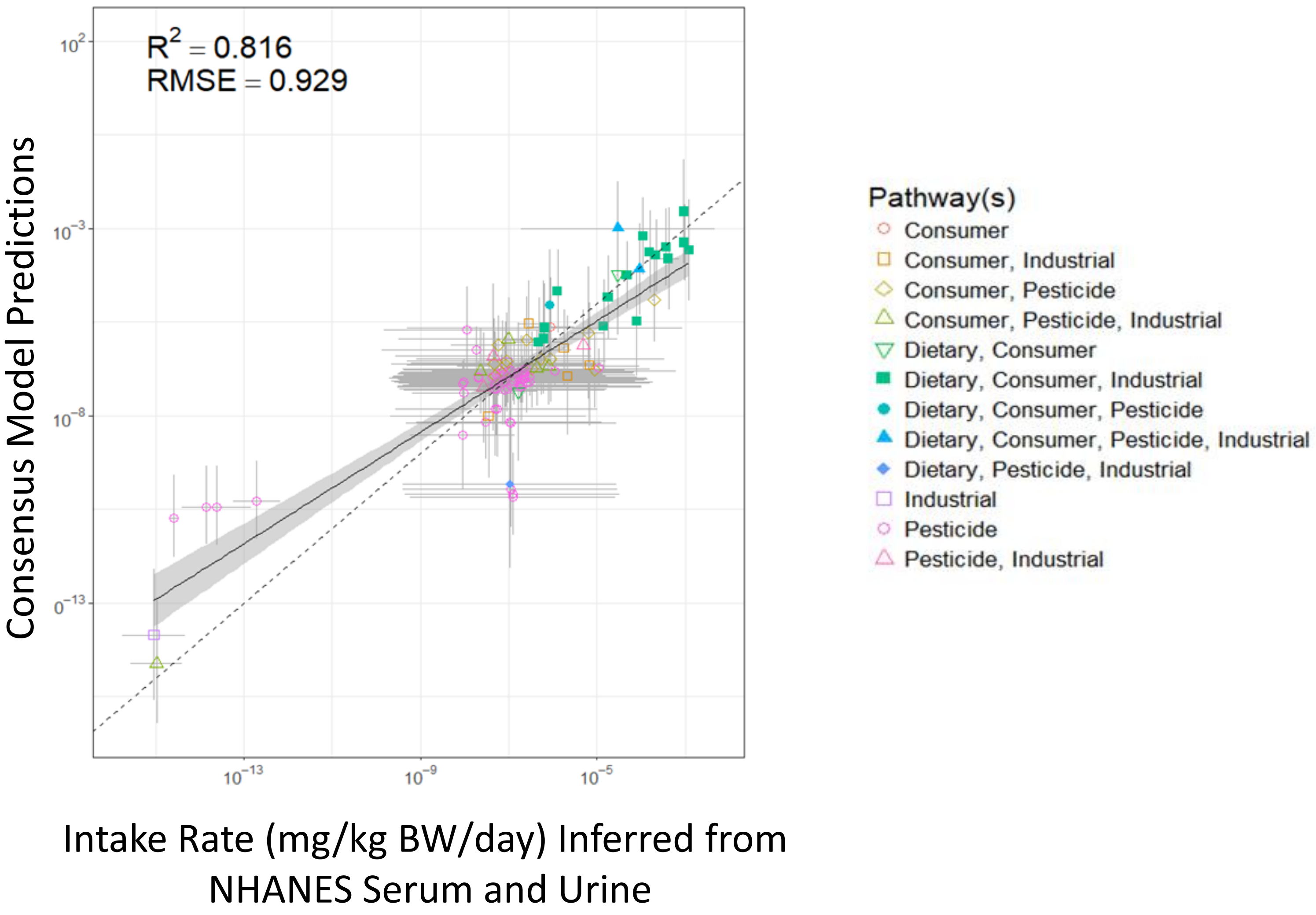
Pathway Prediction Enabled Consensus Modeling of Exposure

Ring et al., 2019

- Consumer (Near-Field), Industrial, Pesticide, Dietary

- Each chemical may have exposure by multiple pathways

- **Machine learning models were built for each of four exposure pathways**



Material from John Wambaugh

Predicting Exposure Pathway with Machine Learning

We use the method of Random Forests to relate chemical structure and properties to exposure pathway

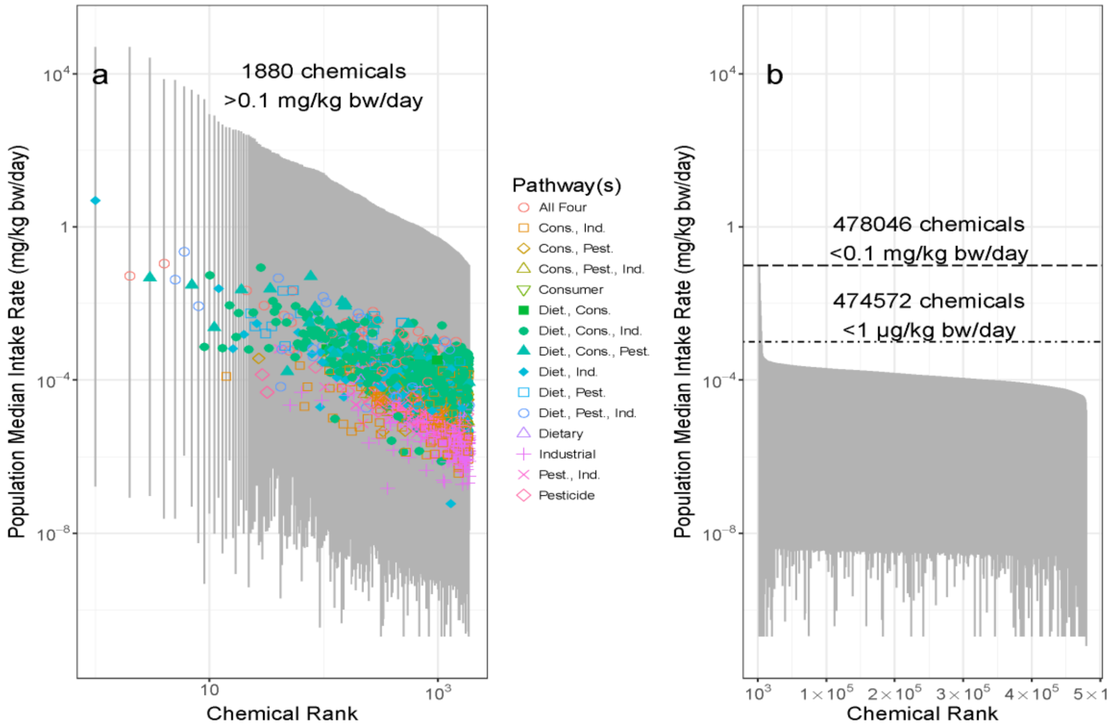
	NHANES Chemicals	Positives	Negatives	OOB Error Rate	Positives Error Rate	Balanced Accuracy	Sources of Positives	Sources of Negatives
Dietary	24	2523	8865	27	32	73	FDA CEDI, ExpoCast, CPDat (Food, Food Additive, Food Contact), NHANES Curation	Pharmapendium, CPDat (non-food), NHANES Curation
Near-Field	**49**	1622	567	26	24	74	CPDat (consumer_use, building_material), ExpoCast, NHANES Curation	CPDat (Agricultural, Industrial), FDA CEDI, NHANES Curation
Far-Field Pesticide	**94**	1480	6522	21	36	80	REDs, Swiss Pesticides, Stockholm Convention, CPDat (Pesticide), NHANES Curation	Pharmapendium, Industrial Positives, NHANES Curation
Far Field Industrial	**42**	5089	2913	19	16	81	CDR HPV, USGS Water Occurrence, NORMAN PFAS, Stockholm Convention, CPDat (Industrial, Industrial_Fluid), NHANES Curation	Pharmapendium, Pesticide Positives, NHANES Curation

Material from John Wambaugh

Pathway Prediction Enabled Consensus Modeling of Exposure

Ring et al., 2019

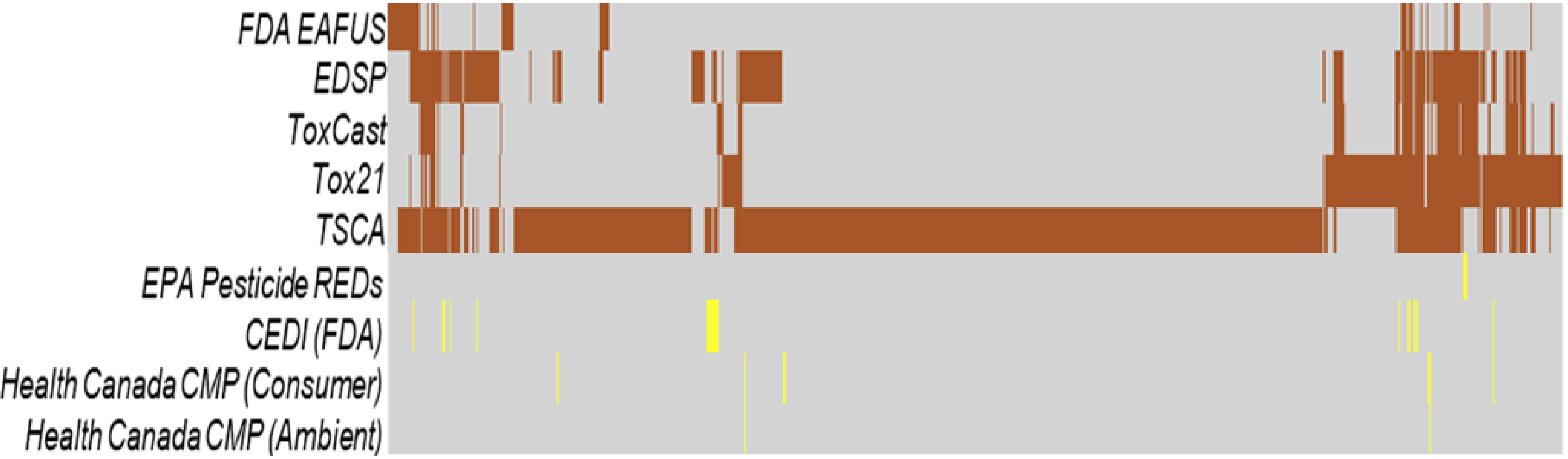
- **Machine learning models were built for each of four exposure pathways**
- Pathway predictions can be used for large chemical libraries
- Use prediction (and accuracy of prediction) as a prior for Bayesian analysis
- Each chemical may have exposure by multiple pathways



Of 687,359 chemicals evaluated, 30% have less than a 50% probability for any of the four pathways and are considered outside the applicability domain.

Material from John Wambaugh

How Have ML Models Improved the Exposure-Relevant Data Landscape?



38,344 Inventory Chemicals

- Examined coverage of chemical inventories
- Regulatory lists
  - EPA Toxic Substance Control Act Non-Confidential Active Inventory
  - EPA Endocrine Disruptor Screening Program
  - FDA Everything Added to Food in the US (EAFUS)
- Chemicals tested in high-throughput screening
  - ToxCast
  - Tox21

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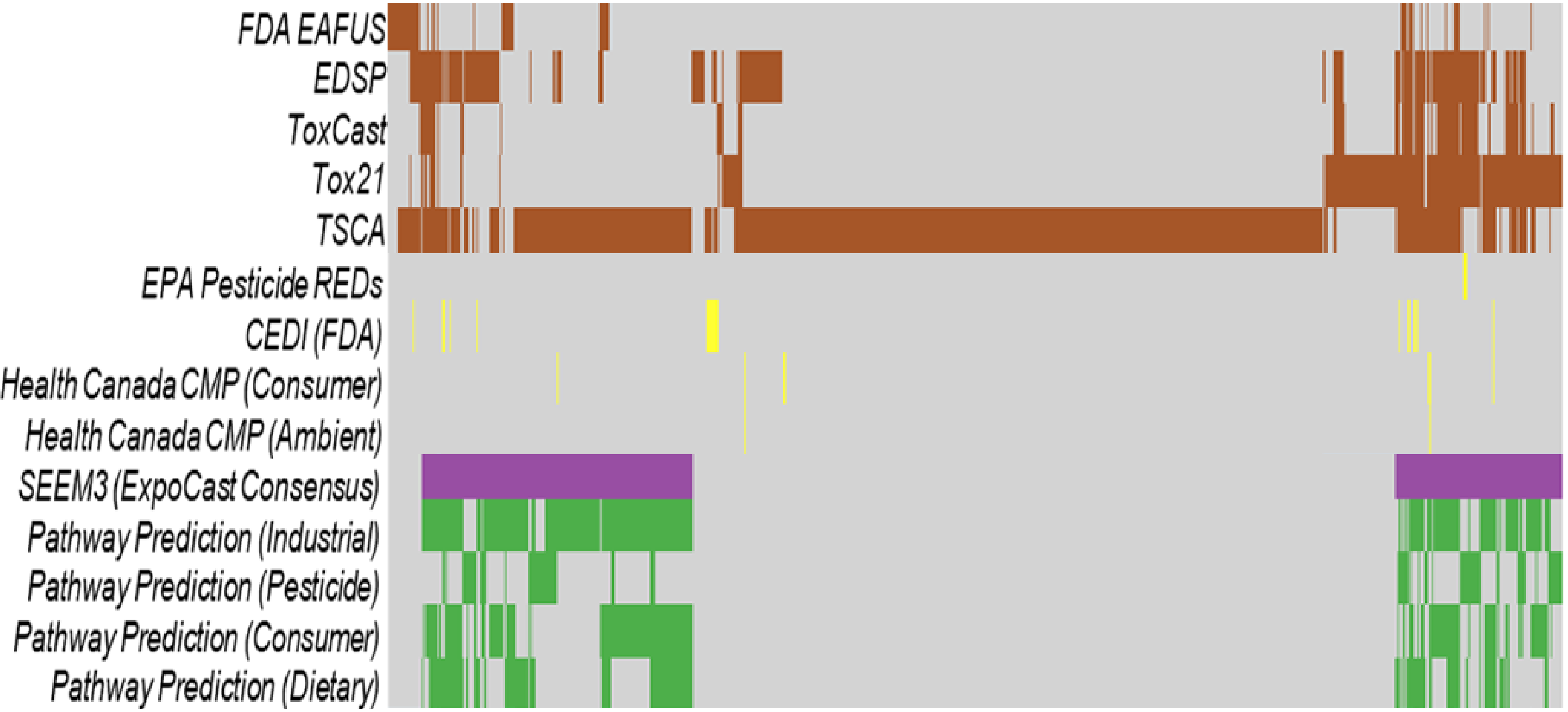

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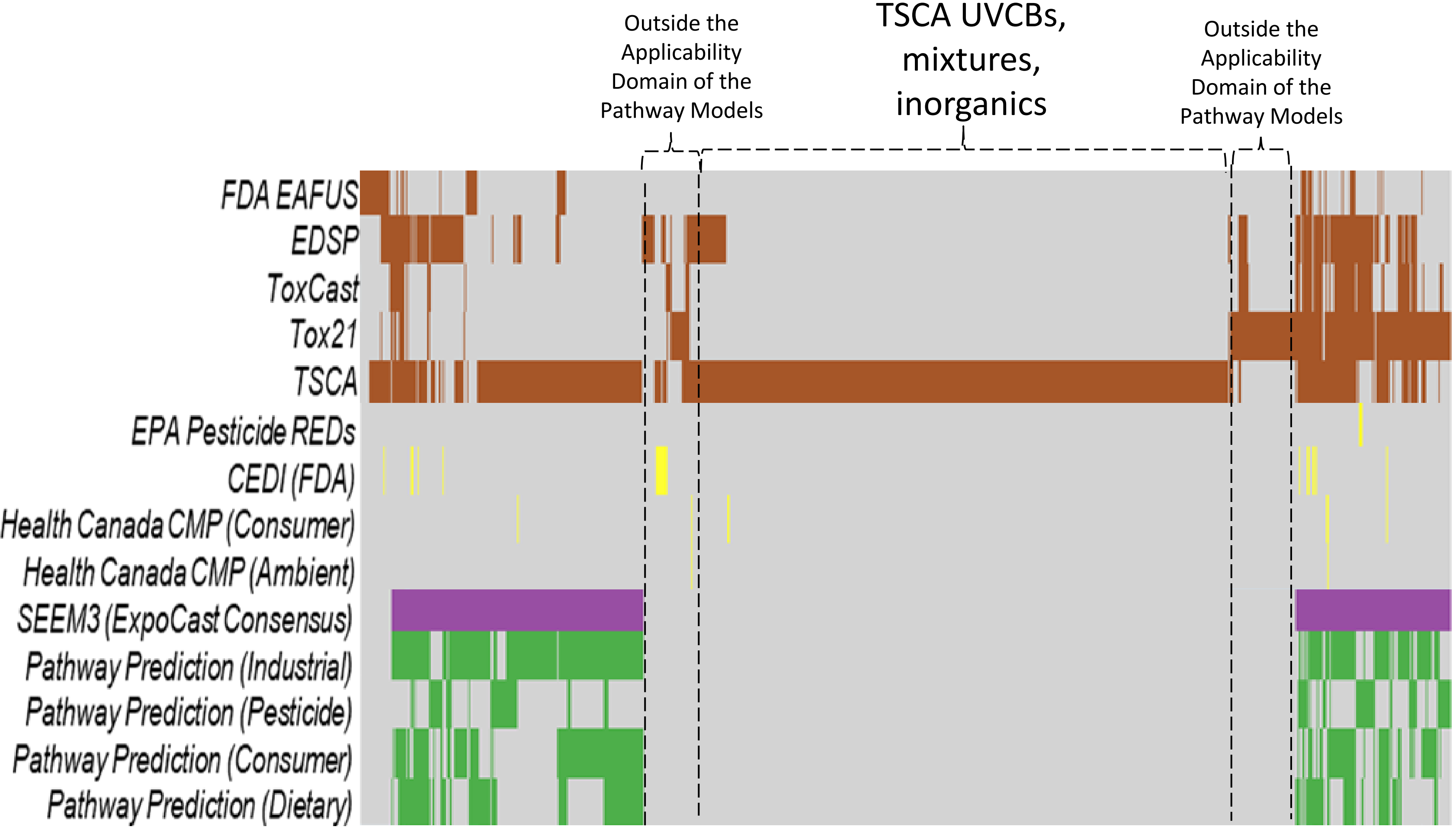

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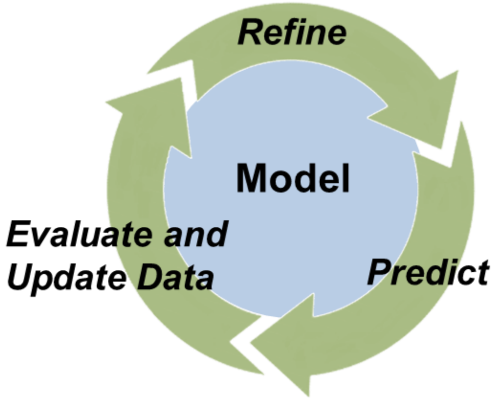
Strategies for Regulatory Acceptance

- **Challenges**:
  - Transparency and reproducibility
  - Determination of fit-for-purpose: How is suitability assessed? What criteria?
- **Strategies**:
  - Learning from QSAR: Development of documentation and reporting standards
    - Training data, modeling methods, AD, results (predictions), performance metrics
    - Data accessibility
    - Versioning
    - Iterative development frameworks
  - Integration into tiered workflow case studies (demonstration of value added when no other data are available)
  - Continued external validation (with datasets of regulatory relevance)
  - Characterization of uncertainty



Summary

- Machine learning is a powerful tool for extrapolating existing information to chemicals lacking data.
- We are building the training sets and machine-learning based predictive tools to estimate exposure-relevant information from chemical descriptors.
- We aim to develop workflows that allow for validation of model performance, characterization of chemical domain of applicability, and incorporation of new information as data become available.
- These new approach methodologies are improving our coverage of key chemical inventories.
- The predictions from these models provide defensible methods for filling knowledge gaps in process-based models, analytical workflows, chemical prioritization, and other risk-based evaluations.

ExpoCast Project (Exposure Forecasting)

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