Systematic Empirical Evaluation of Models to Inform Risk Prioritization

John F. Wambaugh[1], Kristin K. Isaacs[2], Katherine A. Phillips[2], Caroline L. Ring[1], Jon A. Arnot[3,4,5], Deborah H. Bennett[6], Peter P. Egeghy[2], Peter Fantke[7], Lei Huang[8], Olivier Jolliet[8], Hyeong-Moo Shin[9], John N. Westgate[3], R. Woodrow Setzer[1]

[1]*National Center for Computational Toxicology and* [2]*National Exposure Research Laboratory, Office of Research and Development, United States Environmental Protection Agency, Research Triangle Park, North Carolina 27711*

[3]ARC Arnot Research and Consulting, 36 Sproat Ave. Toronto, ON, Canada, M4M 1W4

[4]Department of Physical & Environmental Sciences, University of Toronto Scarborough 1265 Military Trail, Toronto, ON, Canada, M1C 1A4

[5]Department of Pharmacology and Toxicology, University of Toronto, 1 King's College Cir, Toronto, ON, Canada, M5S 1A8

[6]Center for Health and the Environment, University of California, Davis, 95616

[7]*Quantitative Sustainability Assessment Division, Department of Management Engineering, Technical University of Denmark, 2800 Kgs. Lyngby, Denmark*

[8]Department of Environmental Health Sciences, University of Michigan, Ann Arbor, Michigan, 48109

[9]*Department of Earth and Environmental Sciences, University of Texas, Arlington, Texas, 76019*

Consensus Modeling of Chemical Exposure

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https://orcid.org/0000-0002-4024-534X

United States Environmental Protection Agency

Chemical Regulation in the United States

- Park *et al.* (2012): At least 3221 chemical signatures in pooled human blood samples, many appear to be exogenous
- A tapestry of laws covers the chemicals people are exposed to in the United States (Breyer, 2009)
- Different testing requirements exist for food additives, pharmaceuticals, and pesticide active ingredients (NRC, 2007)

November 29, 2014

United States Environmental Protection Agency

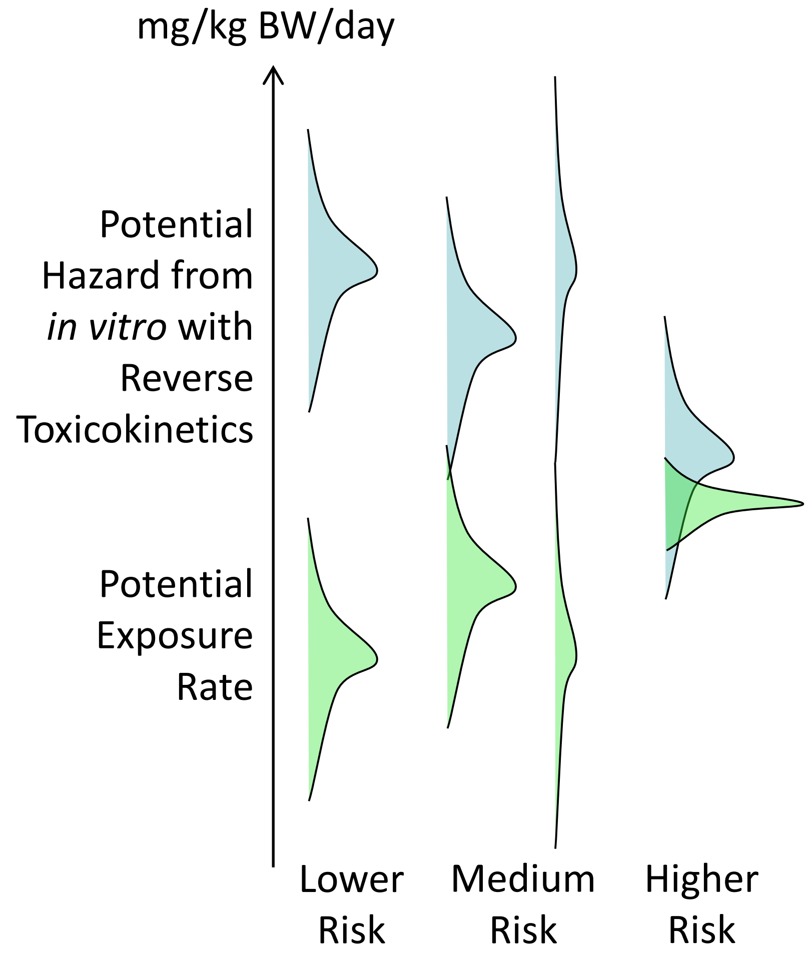
Chemical Regulation in the United States

- Most other chemicals, ranging from industrial waste to dyes to packing materials, are covered by the Toxic Substances Control Act (TSCA)
  - Thousands of chemicals on the market were either “grandfathered” in or were allowed without experimental assessment of hazard, toxicokinetics, or exposure
  - Thousands of new chemical use submissions are made to the EPA every year
- TSCA was updated in June, 2016 to allow evaluation of these and other chemicals
  - Methods are being developed to inform the prioritization of these existing and new chemicals for testing

November 29, 2014

Chemical Risk = Hazard x Exposure

- National Research Council (1983) identified chemical risk as a function of both inherent hazard and exposure
- To address thousands of chemicals, new approach methodologies (NAMs) to inform prioritization of chemicals for additional study
- **High throughput risk prioritization** needs:
  1. high throughput **hazard** characterization (from HTT project)
  2. high throughput **exposure** forecasts
  3. high throughput **toxicokinetics** (*i.e.*, dosimetry) linking hazard and exposure
- All of these methods are uncertain, but if that uncertainty can be quantified, we can make informed decisions

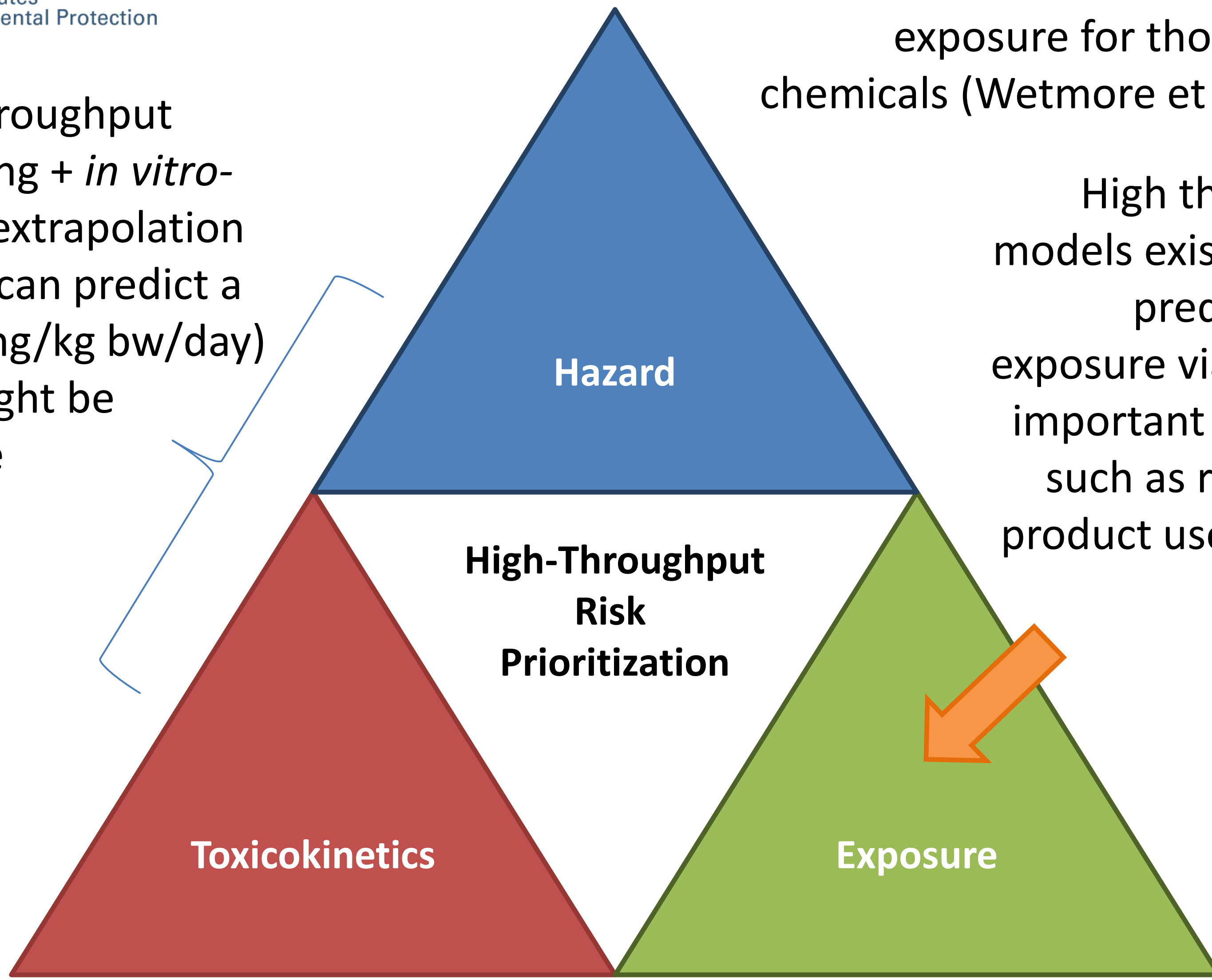


New Exposure Data and Models

Need methods to forecast exposure for thousands of chemicals (Wetmore et al., 2015)

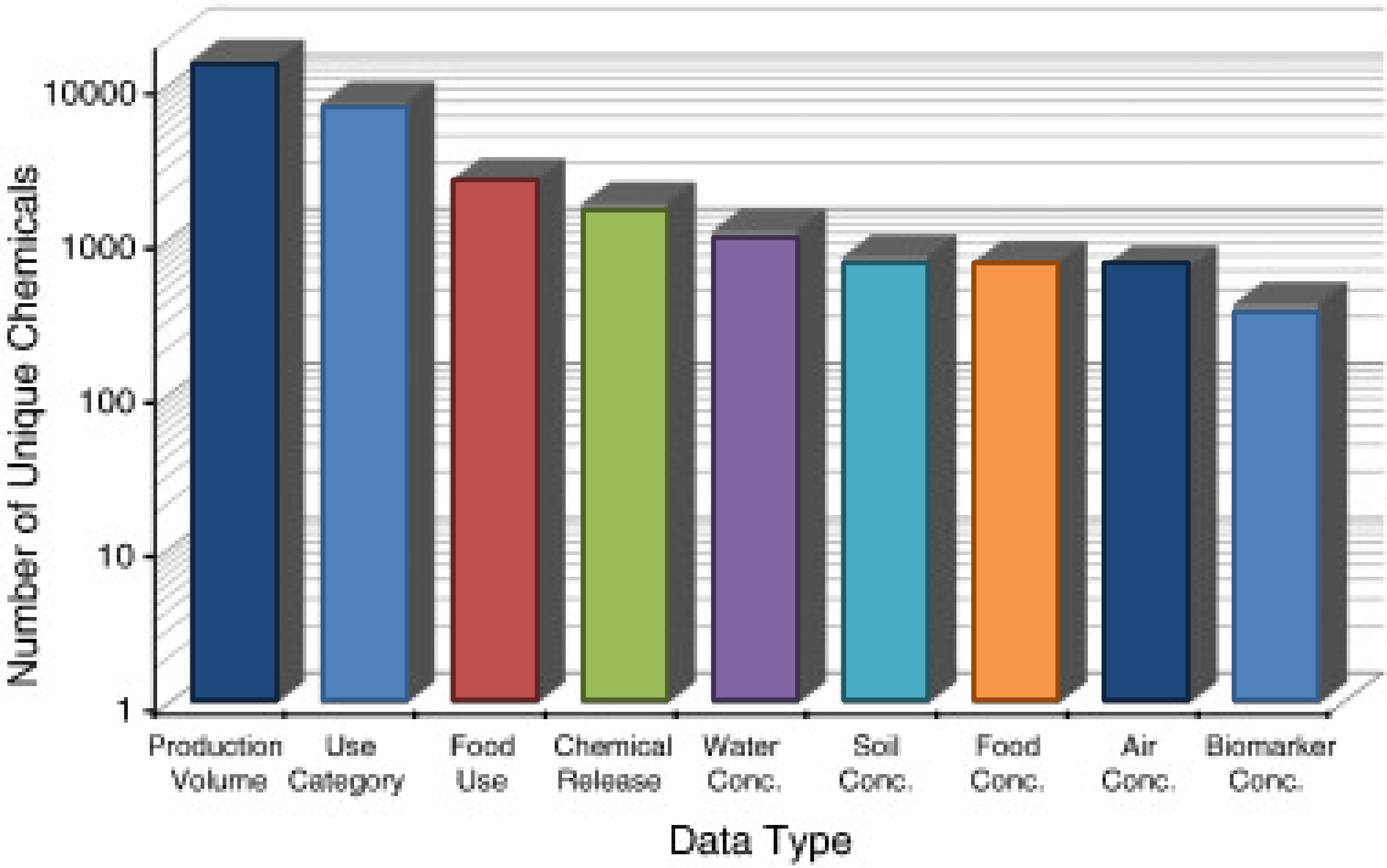
High throughput screening + *in vitro-in vivo* extrapolation (IVIVE) can predict a dose (mg/kg bw/day) that might be adverse

High throughput models exist to make predictions of exposure via specific, important pathways such as residential product use and diet



Limited Available Data for Exposure Estimation

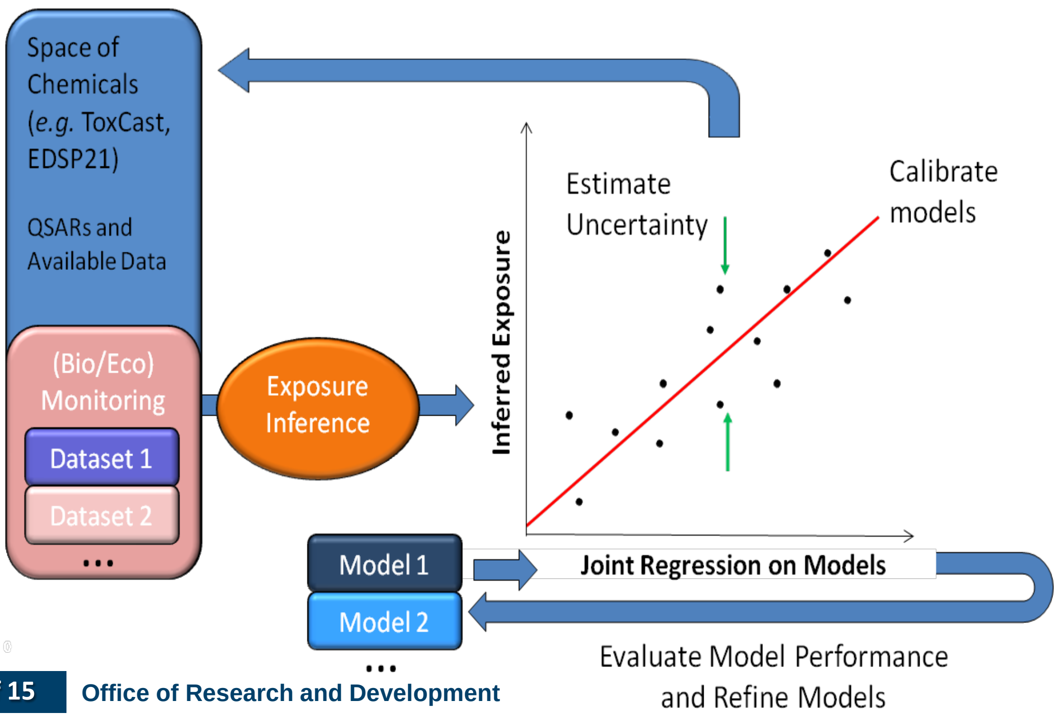
Most chemicals lack public exposure-related data beyond production volume (Egeghy et al., 2012)

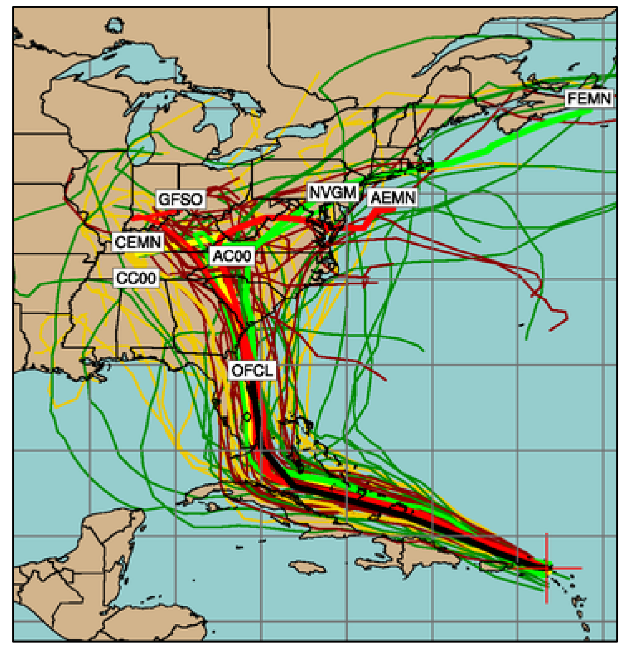


Can we use models to generate the exposure information we need?

Consensus Exposure Predictions with the SEEM Framework

- Different exposure models incorporate **knowledge**, **assumptions**, and **data** (MacLeod et al., 2010)
- We incorporate multiple models (including SHEDS-HT, ExpoDat) into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM)** (Wambaugh et al., 2013, 2014)
- Evaluation is similar to a sensitivity analysis: What models are working? What data are most needed?





Hurricane Path Prediction is an Example of Integrating Multiple Models

Collaboration on High Throughput Exposure Predictions

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

Predictor	Reference(s)	Chemicals Predicted	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

Knowledge of Exposure Pathways Limits High Throughput Exposure Models

United States Environmental Protection Agency

"In particular, the assumption that 100% of [quantity emitted, applied, or ingested] is being applied to each individual use scenario is a very conservative assumption for many compound / use scenario pairs."

Environmental Science & Technology

Article

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Risk-Based High-Throughput Chemical Screening and Prioritization using Exposure Models and in Vitro Bioactivity Assays

Hyeong-Moo Shin,[*,†] Alexi Ernstoff,[‡,§] Jon A. Arnot,[∥,⊥,#] Barbara A. Wetmore,[∇] Susan A. Csiszar,[§] Peter Fantke,[‡] Xianming Zhang,[○] Thomas E. McKone,[◆,¶] Olivier Jolliet,[§] and Deborah H. Bennett[†]

[†]Department of Public Health Sciences, University of California, Davis, California 95616, United States

[‡]Quantitative Sustainability Assessment Division, Department of Management Engineering, Technical University of Denmark, Kgs. Lyngby 2800, Denmark

[§]Department of Environmental Health Sciences, University of Michigan, Ann Arbor, Michigan 48109, United States

[∥]ARC Arnot Research and Consulting, Toronto, Ontario M4M 1W4 , Canada

[⊥]Department of Physical and Environmental Sciences, University of Toronto, Scarborough, Toronto, Ontario M1C 1A4, Canada

[#]Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario M5S 1A8, Canada

[∇]The Hamner Institutes for Health Sciences, Research Triangle Park, North Carolina 27709, United States

[○]Harvard School of Public Health and School of Engineering and Applied Sciences, Harvard University, Cambridge, Massachusetts 02138, United States

[◆]Environmental Energy Technologies Division, Lawrence Berkeley National Laboratory, Berkeley, California 94720 , United States

[¶]School of Public Health, University of California, Berkeley, California 94720, United States

Supporting Information

ABSTRACT: We present a risk-based high-throughput screening

Potential exposure from exposure

Potential hazard from in vitro

Predicting Pathways

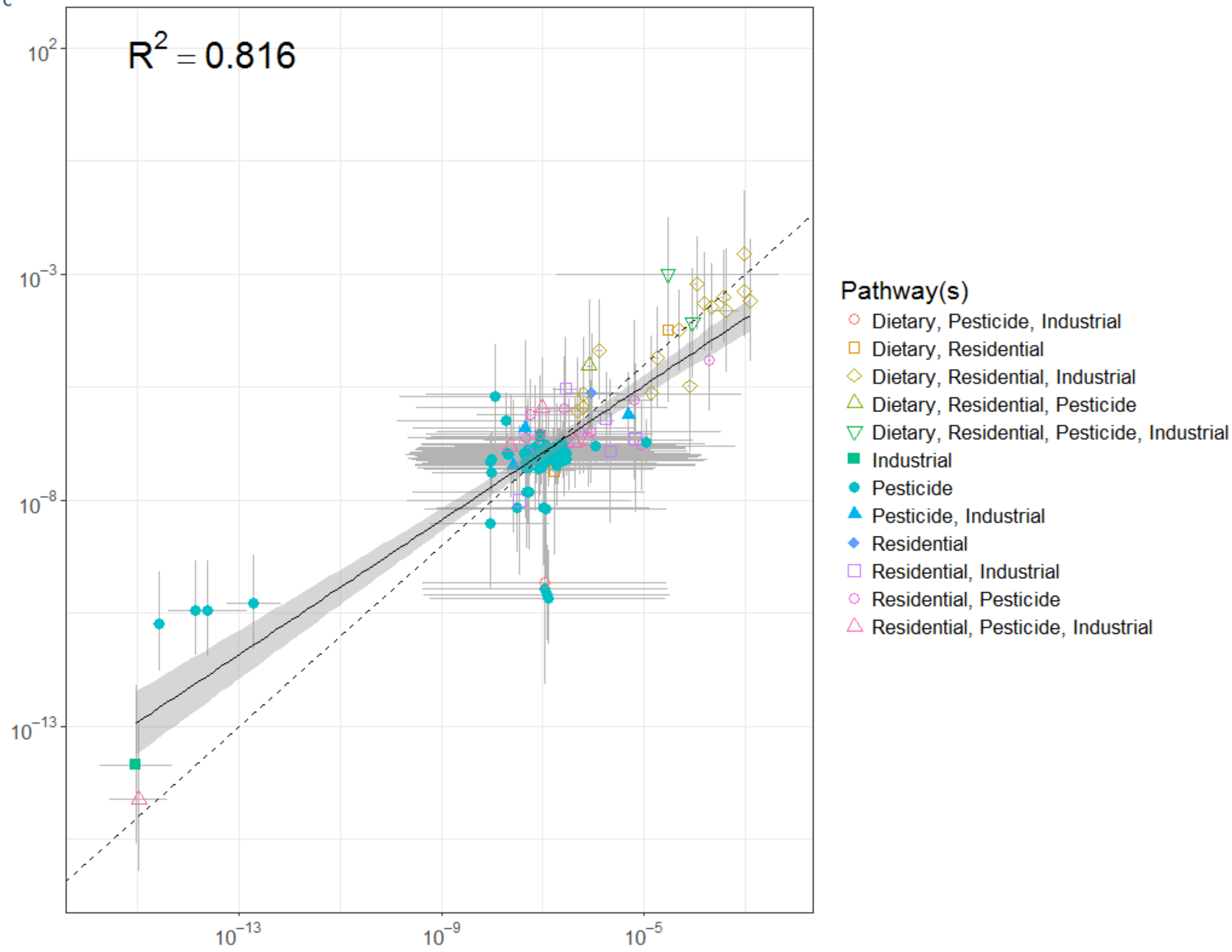
We use the method of Random Forests to relate chemical structure and properties to exposure pathway

	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

Ring et al., submitted

Pathway-Based Consensus Modeling

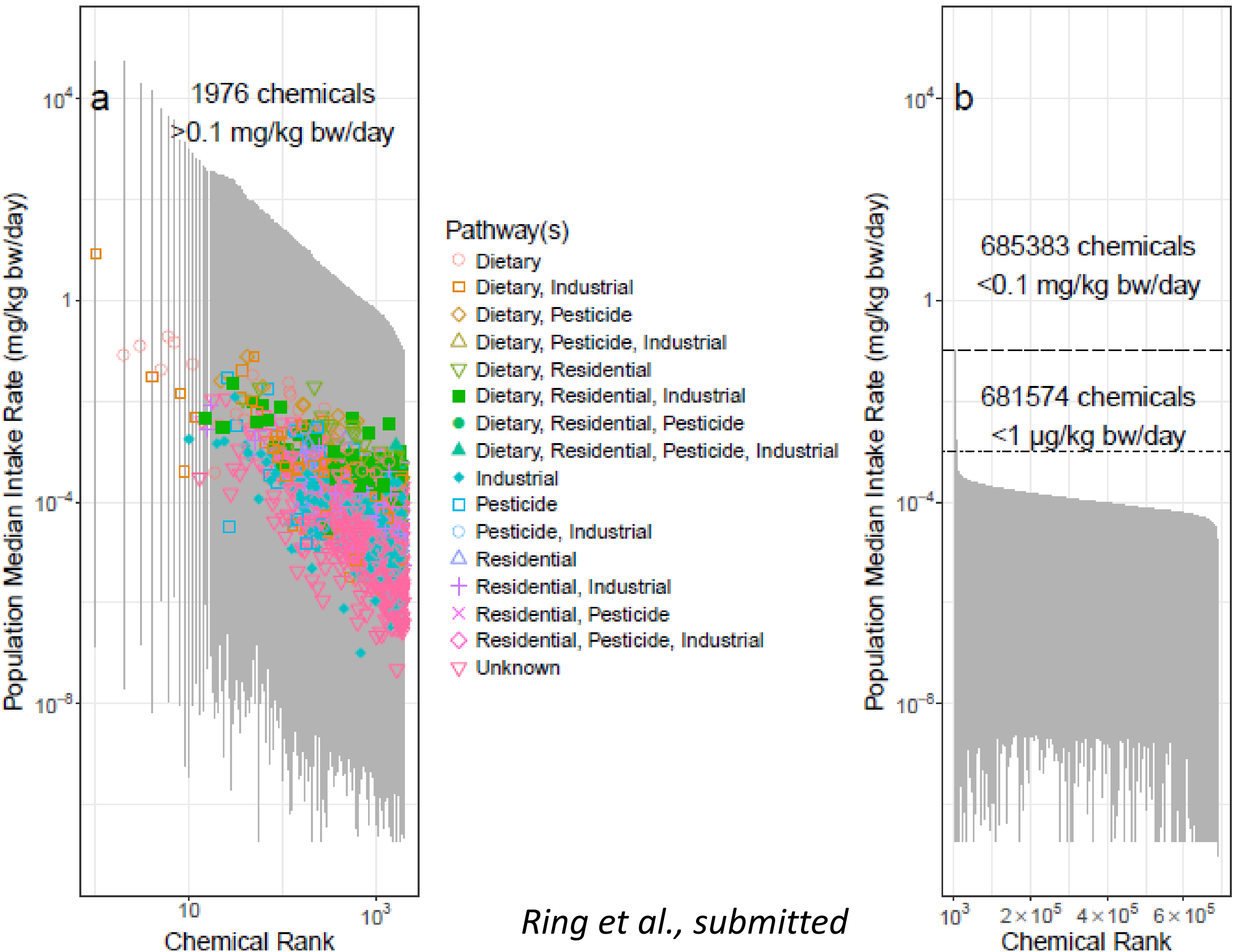
United States Environmental Protection Agency



Intake Rate (mg/kg BW/day) Inferred from NHANES Serum and Urine

Ring et al., submitted

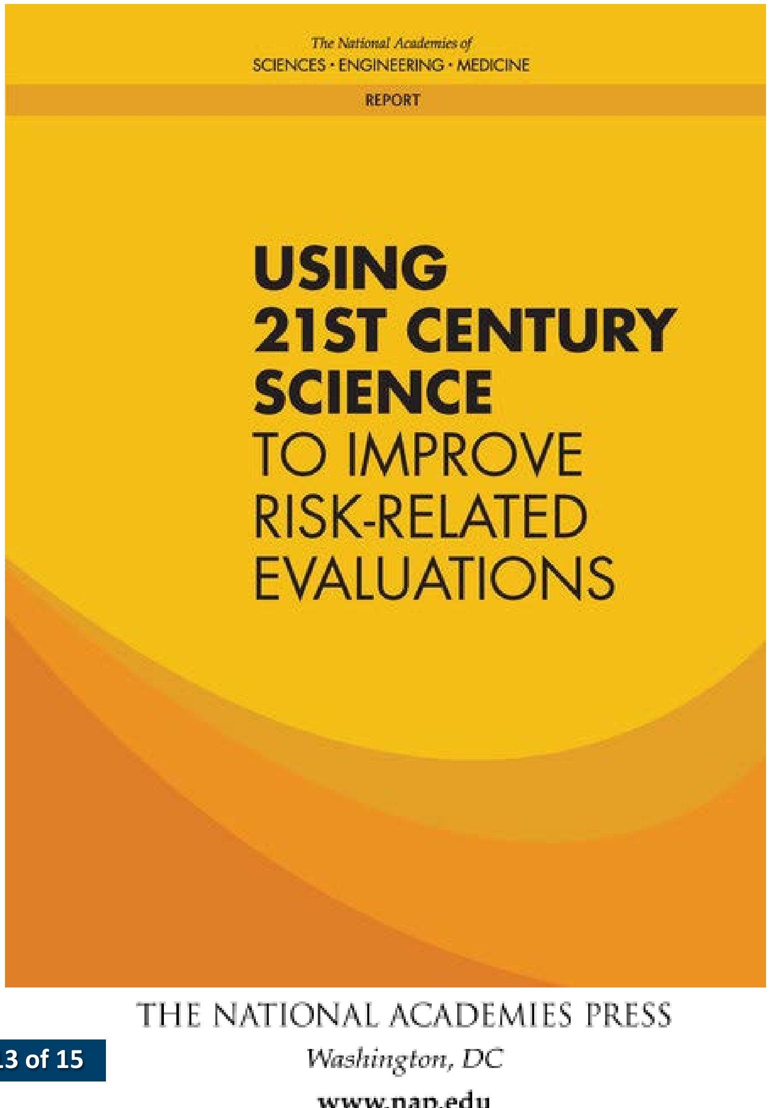
Consensus Modeling of Median Chemical Intake



Ring et al., submitted

Risk Assessment in the 21st Century

EPA United States Environmental Protection Agency



"Translation of high-throughput data into risk-based rankings is an important application of exposure data for chemical priority-setting. Recent advances in high-throughput toxicity assessment, notably the ToxCast and Tox21 programs (see Chapter 1), and in high-throughput computational exposure assessment (Wambaugh et al. 2013, 2014) have enabled first-tier risk-based rankings of chemicals on the basis of margins of exposure…"

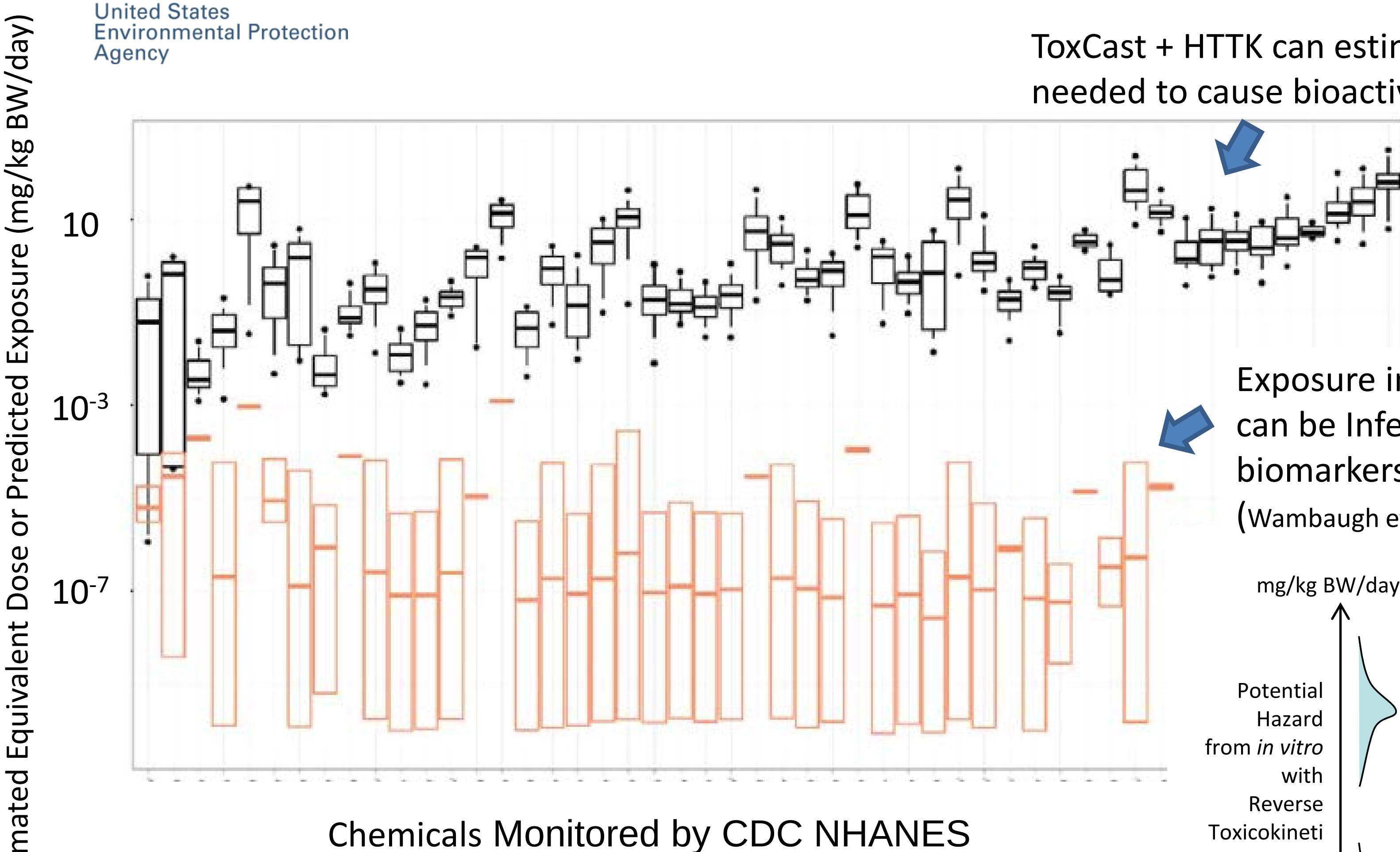
"…The committee sees the potential for the application of **computational exposure science** to be highly valuable and credible for comparison and **priority-setting among chemicals in a risk-based context**."

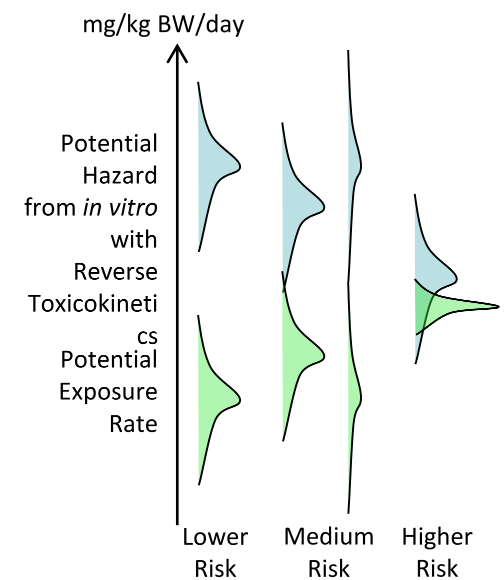
January 5, 2017

Selecting Candidates for Prioritization

ToxCast + HTTK can estimate doses needed to cause bioactivity

Exposure intake rates can be Inferred from biomarkers (Wambaugh et al., 2014)



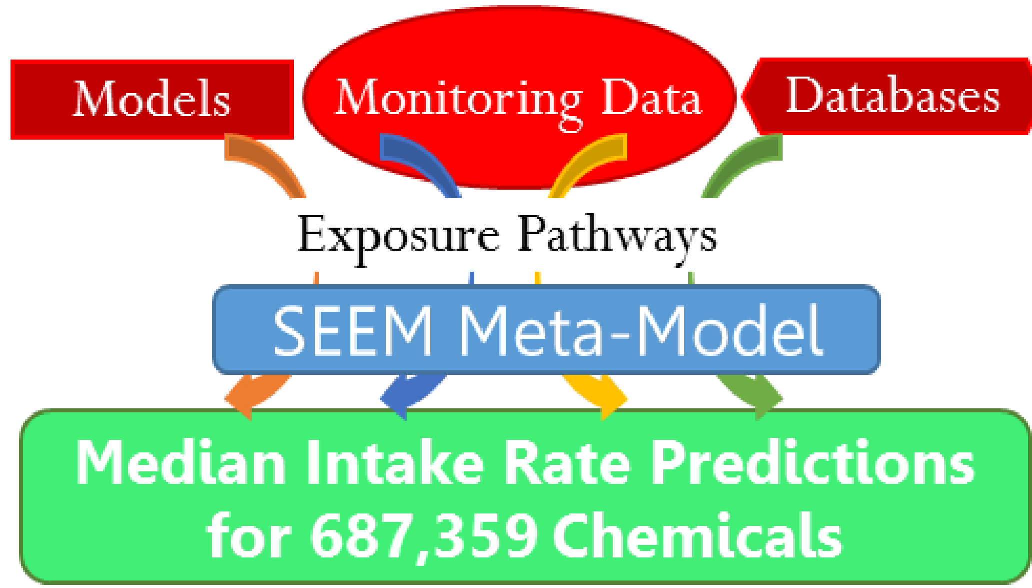


National Health and Nutrition Examination Survey (NHANES) is an ongoing survey that covers ~10,000 people every two years

Ring *et al*. (2017)

Conclusions

- We would like to know more about the risk posed by thousands of chemicals in the environment – which ones should we start with?
- New machine learning tools provide improved high throughput exposure estimates by matching chemicals to exposure pathways and associated calibrated exposure models. A collaboration of exposure researchers has developed databases and mathematical models allowing for high-throughput exposure (HTE) forecasting



- Exposure predictors (data and models) have been grouped into four pathways (residential, dietary, pesticidal, and industrial) and calibrated via Bayesian multivariate regression using human intake rates inferred for 114 chemicals from a large bio-monitoring survey.
- Machine learning models based on chemical structure and physico-chemical properties predict whether or not each pathway is relevant to a library of over 680,000 chemicals, allowing an exposure estimate for each chemical based on the calibrated predictors.

 Office of Research and Development

Chemical Safety for Sustainability (CSS) Research Program

Rapid Exposure and Dosimetry (RED) Project

NCCT
Chris Grulke
Greg Honda*
Richard Judson
Matthew Linakis*
Andrew McEachran*
Ann Richard
Risa Sayre*
Woody Setzer
Rusty Thomas
John Wambaugh
Antony Williams

NRMRL
Xiaoyu Liu

NHEERL
Linda Adams
Christopher Ecklund
Marina Evans
Mike Hughes
Jane Ellen Simmons

NERL
Cody Addington*
Craig Barber
Namdi Brandon*
Peter Egeghy
Hongtai Huang*
Kristin Isaacs
Ashley Jackson*
Charles Lowe*
Dawn Mills*
Seth Newton
Katherine Phillips
Paul Price
Jeanette Reyes*
Randolph Singh*
Jon Sobus
John Streicher*
Mark Strynar
Mike Tornero-Velez
Elin Ulrich
Dan Vallero
Barbara Wetmore

Lead CSS Matrix Interfaces:
John Kenneke (NERL)
John Cowden (NCCT)

***Trainees**

Collaborators

Arnot Research and Consulting
Jon Arnot
Johnny Westgate
Institut National de l'Environnement et des Risques (INERIS)
Frederic Bois
Integrated Laboratory Systems
Kamel Mansouri
National Toxicology Program
Mike Devito
Steve Ferguson
Nisha Sipes
Ramboll
Harvey Clewell
ScitoVation
Chantel Nicolas
Silent Spring Institute
Robin Dodson
Southwest Research Institute
Alice Yau
Kristin Favela
Summit Toxicology
Lesa Aylward
Technical University of Denmark
Peter Fantke
Tox Strategies
Caroline Ring
Miyoung Yoon
Unilever
Beate Nicol
Cecilie Rendal
Ian Sorrell
United States Air Force
Heather Pangburn
University of California, Davis
Deborah Bennett
University of Michigan
Lei Huang
Olivier Jolliet
University of Texas, Arlington
Hyeong-Moo Shin

References

- Arnot, J. A.; Zhang, X.; Kircanski, I.; Hughes, L.; Armitage, J. Develop Sub-Module for Direct Human Exposures to Consumer Products. Technical Report for the U.S. Environmental Protection Agency; ARC Arnot Research & Consulting, Inc.: Toronto, ON, Canada, 2014.
- Bennett, D. H.; Furtaw, E. J., Fugacity-based indoor residential pesticide fate model. Environmental Science & Technology 2004, 38, (7), 2142-2152.
- Borgelt, C. (2012). Frequent item set mining. Wiley Interdisciplinary Reviews: Data Mining and Knowledge Discovery, 2(6), 437-456.
- Breiman, L. (2001). Random forests. Machine learning, 45(1), 5-32.
- Breyer, Stephen. Breaking the vicious circle: Toward effective risk regulation. Harvard University Press, 2009
- Diamond JM. Assembly of species communities. Pp. 342–444 in Cody ML, Diamond JM (eds). Ecology and Evolution of Communities. Cambridge, MA: Belkap Press, 1975.
- Egeghy, P. P., et al. (2012). The exposure data landscape for manufactured chemicals. Science of the Total Environment, 414, 159-166.
- Ernstoff, A. S.; Fantke, P.; Huang, L.; Jolliet, O., High-throughput migration modelling for estimating exposure to chemicals in food packaging in screening and prioritization tools. Food and Chemical Toxicology 2017, 109, 428-438.
- Filer, Dayne L.. "The ToxCast analysis pipeline: An R package for processing and modeling chemical screening data." US Environmental Protection Agency: http://www. epa. gov/ncct/toxcast/files/MySQL% 20Database/Pipeline_Overview. pdf (2014)
- Goldsmith, M. R., et al. (2014). Development of a consumer product ingredient database for chemical exposure screening and prioritization. Food and chemical toxicology, 65, 269-279.
- Huang, L.; Ernstoff, A.; Fantke, P.; Csiszar, S. A.; Jolliet, O., A review of models for near-field exposure pathways of chemicals in consumer products. Science of The Total Environment 2017, 574, 1182-1208.
- Huang, L.; Jolliet, O., A parsimonious model for the release of volatile organic compounds (VOCs) encapsulated in products. Atmospheric Environment 2016, 127, 223-235.
- Jolliet, O.; Ernstoff, A. S.; Csiszar, S. A.; Fantke, P., Defining Product Intake Fraction to Quantify and Compare Exposure to Consumer Products. Environmental Science & Technology 2015, 49, (15), 8924-8931.
- Judson, R. S., Magpantay, F. M., Chickarmane, V., Haskell, C., Tania, N., Taylor, J., ... & Houck, K. A. (2015). Integrated model of chemical perturbations of a biological pathway using 18 in vitro high-throughput screening assays for the estrogen receptor. Toxicological Sciences, 148(1), 137-154.
- Kaewkhaw, R., et al. (2016). Treatment paradigms for retinal and macular diseases using 3-D retina cultures derived from human reporter pluripotent stem cell linestreatment design using PSC-Derived 3-D retina cultures. Investigative ophthalmology & visual science, 57(5), ORSFl1-ORSFl11.
- Kapraun, Dustin et al., “A Method for Identifying Prevalent Chemical Combinations in the US Population,” Environmental Health Perspectives, 2017
- Kavlock, Robert, et al. "Update on EPA’s ToxCast program: providing high throughput decision support tools for chemical risk management." Chemical research in toxicology 25.7 (2012): 1287-1302.
- MacLeod, Matthew, et al. "The state of multimedia mass-balance modeling in environmental science and decision-making." (2010): 8360-8364
- National Academies of Sciences, Engineering, and Medicine. (2017). Using 21st century science to improve risk-related evaluations. National Academies Press.
- National Research Council. (1983). Risk Assessment in the Federal Government: Managing the Process Working Papers. National Academies Press.
- National Research Council. (2007) Toxicity testing in the 21st century: a vision and a strategy. National Academies Press.
- O’Connell, S. G., Kincl, L. D., & Anderson, K. A. (2014). Silicone wristbands as personal passive samplers. Environmental science & technology, 48(6), 3327-3335.
- Park, Youngja, H., et al. “High-performance metabolic profiling of plasma from seven mammalian species for simultaneous environmental chemical surveillance and bioeffect monitoring.” Toxicology 295:47-55 (2012)
- Pearce, Robert, et al. “httk: R Package for High-Throughput Toxicokinetics.” Journal of Statistical Software, 2017
- Phillips, Katherine A., et al. "High-throughput screening of chemicals as functional substitutes using structure-based classification models." Green Chemistry (2017).
- Phillips, Katherine A., et al. “Suspect Screening Analysis of Chemicals in Consumer Products”, accepted at Environmental Science & Technology.
- Rotroff, Daniel, et al., (2010) “Incorporating human dosimetry and exposure into high-throughput in vitro toxicity screening.” Tox. Sciences 117(2), 348-58
- Schmidt, Charles W. "TOX 21: new dimensions of toxicity testing." Environmental health perspectives 117.8 (2009): A348.
- Shin, H.-M.; McKone, T. E.; Bennett, D. H., Intake Fraction for the Indoor Environment: A Tool for Prioritizing Indoor Chemical Sources. Environmental Science & Technology 2012, 46, (18), 10063-10072.
- Shin, Hyeong-Moo, et al. "Risk-based high-throughput chemical screening and prioritization using exposure models and in vitro bioactivity assays." Environmental science & technology 49.11 (2015): 6760-6771.
- Wallace et al., “The TEAM Study: Personal exposures to toxic substances in air, drinking water, and breath of 400 residents of New Jersey, North Carolina, and North Dakota .” Environmental Research 43: 209-307 (1987)
- Tornero-Velez et al. (2012) “Biogeographical Analysis of Chemical Co-Occurrence to Identify Priorities for Mixtures Research”: Risk Analysis, 32(2) 224-236
- Wambaugh, John F., et al. "High-throughput models for exposure-based chemical prioritization in the ExpoCast project." Environmental science & technology 47.15 (2013): 8479-848.
- Wambaugh, John F., et al. "High Throughput Heuristics for Prioritizing Human Exposure to Environmental Chemicals." Environmental science & technology (2014).
- Wambaugh, John F., et al. “Evaluating In Vitro-In Vivo Extrapolation" accepted at Toxicological Sciences,.
- Wang, Y.-H. (2010). “Confidence Assessment of the Simcyp Time-Based Approach and a Static Mathematical Model in Predicting Clinical Drug-Drug Interactions for Mechanism-Based CYP3A Inhibitors.” Drug Metabolism and Disposition 38(7), 1094-1104
- Wetmore, Barbara A., et al. "Integration of dosimetry, exposure and high-throughput screening data in chemical toxicity assessment." Toxicological Sciences (2012): kfr254.
- Wetmore, Barbara A., et al. "Incorporating High-Throughput Exposure Predictions with Dosimetry-Adjusted In Vitro Bioactivity to Inform Chemical Toxicity Testing." Toxicological Sciences 148.1 (2015): 121-136.
- Zhang, X.; Arnot, J. A.; Wania, F., Model for screening-level assessment of near-field human exposure to neutral organic chemicals released indoors. Environmental science & technology 2014, 48, (20), 12312-12319.