EPA United States Environmental Protection Agency

Triaging Exposure Data and Modeling Needs for Exogenous Chemicals: *Comparing High-Throughput and Traditional Exposure Estimates*

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Accelerating the Pace of Chemical Risk Assessment
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United States Environmental Protection Agency

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Contributors

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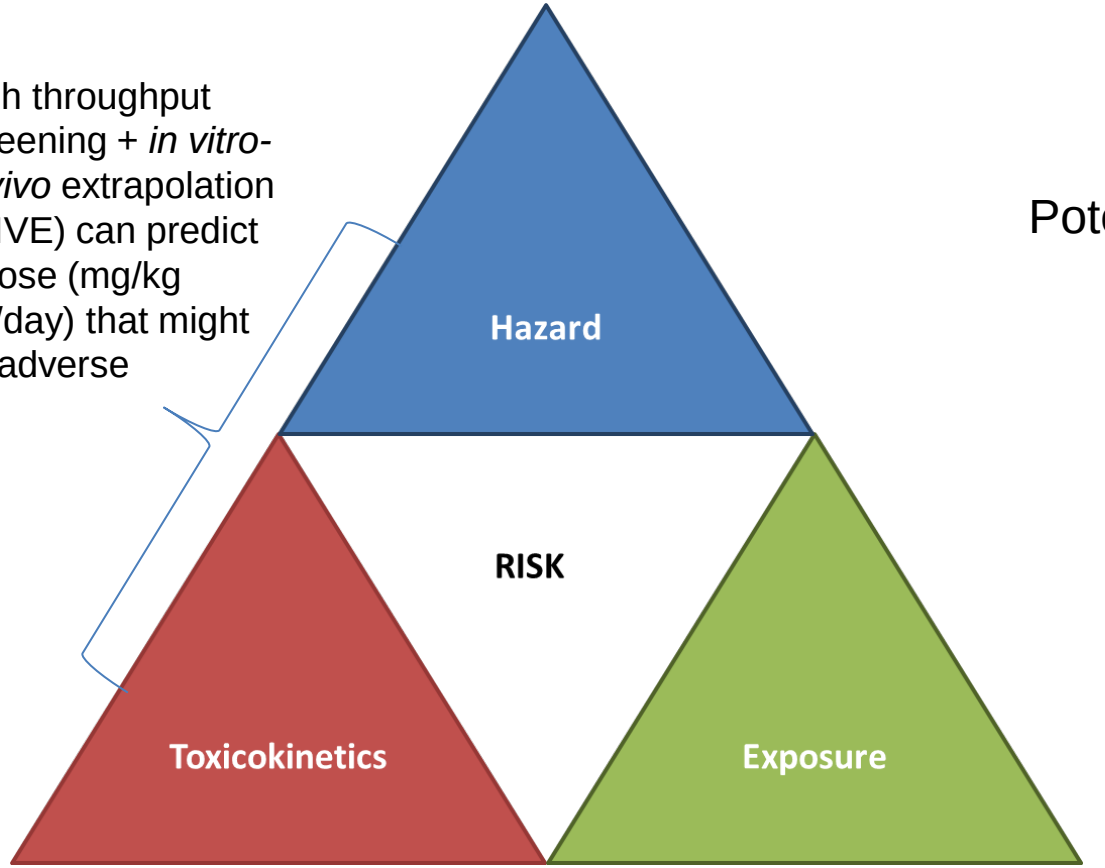
Overview

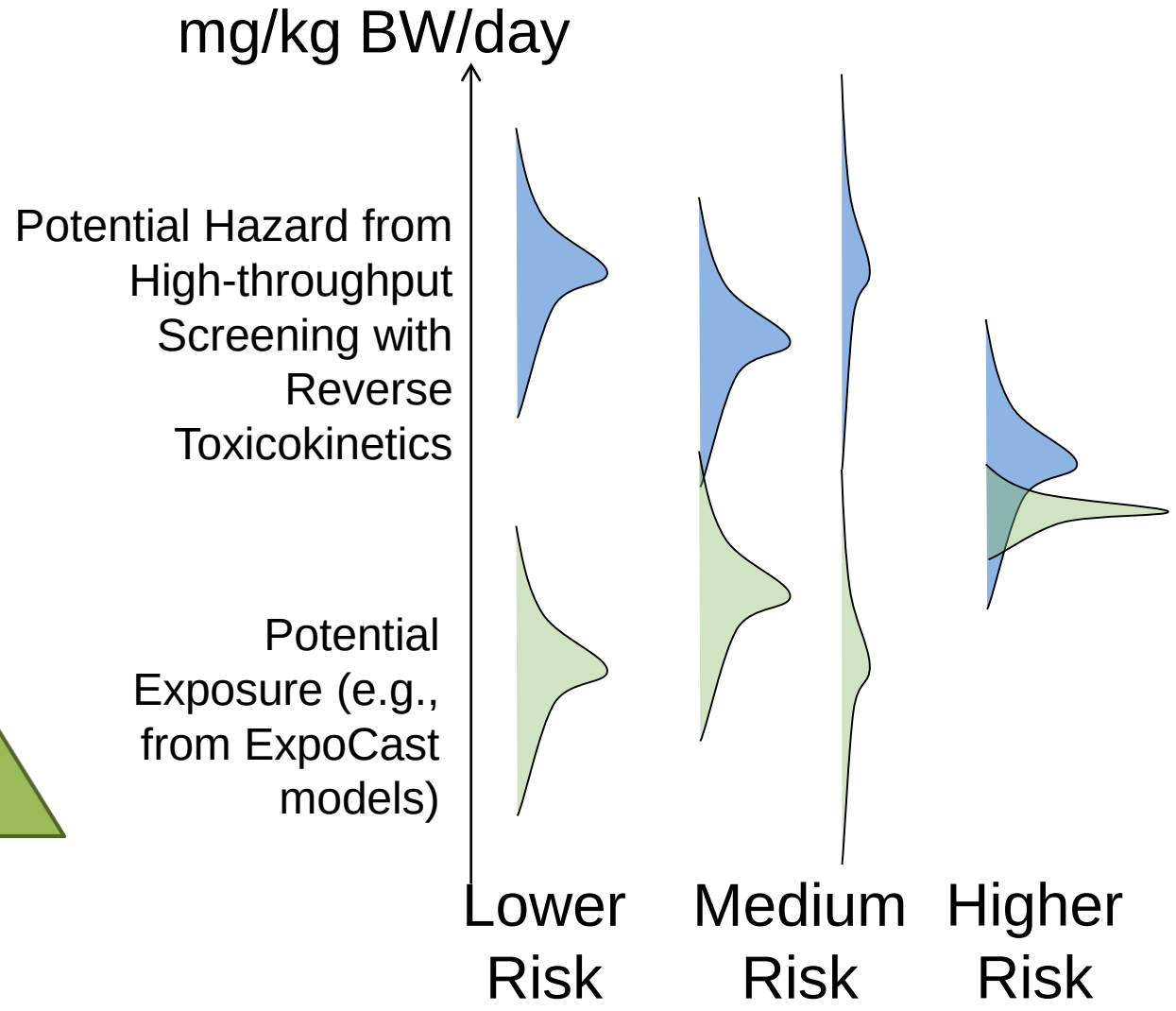
- Motivation: The need for high-throughput (HT) new approach methods (NAM) for exposure
- NAM for filling gaps in exposure data and multi-pathway exposure estimates in EPA's ExpoCast project
- Current Case Study: Comparison with traditional exposure estimates performed under the Canadian Chemicals Management Plan (CMP)
  - CMP Exposure assessments
  - ExpoCast HT models
  - Challenges
  - Relevant Comparisons
- Conclusions and Recommendations

Santé Canada Health Canada

Risk is Multifaceted

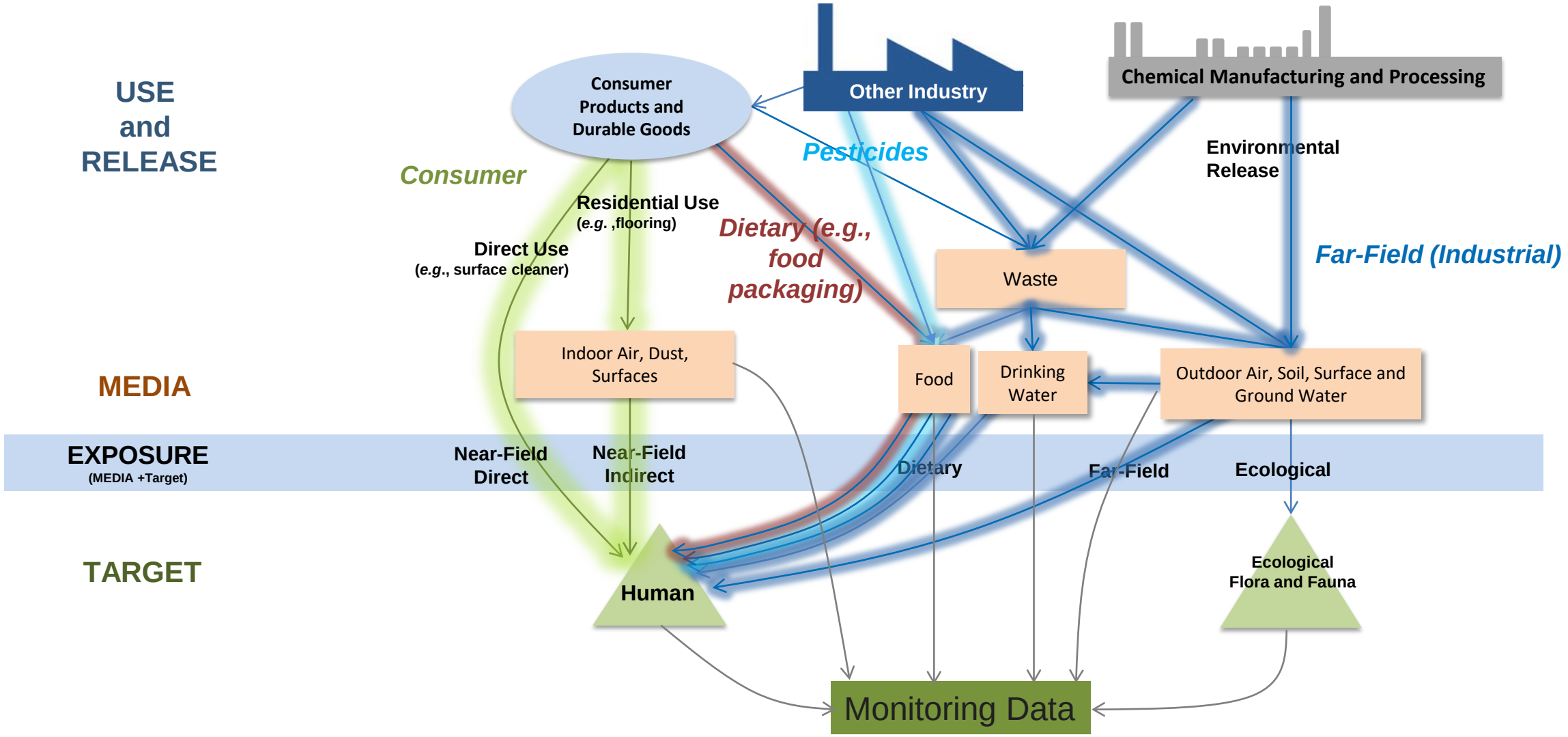
High throughput screening + *in vitro-in vivo* extrapolation (IVIVE) can predict a dose (mg/kg bw/day) that might be adverse



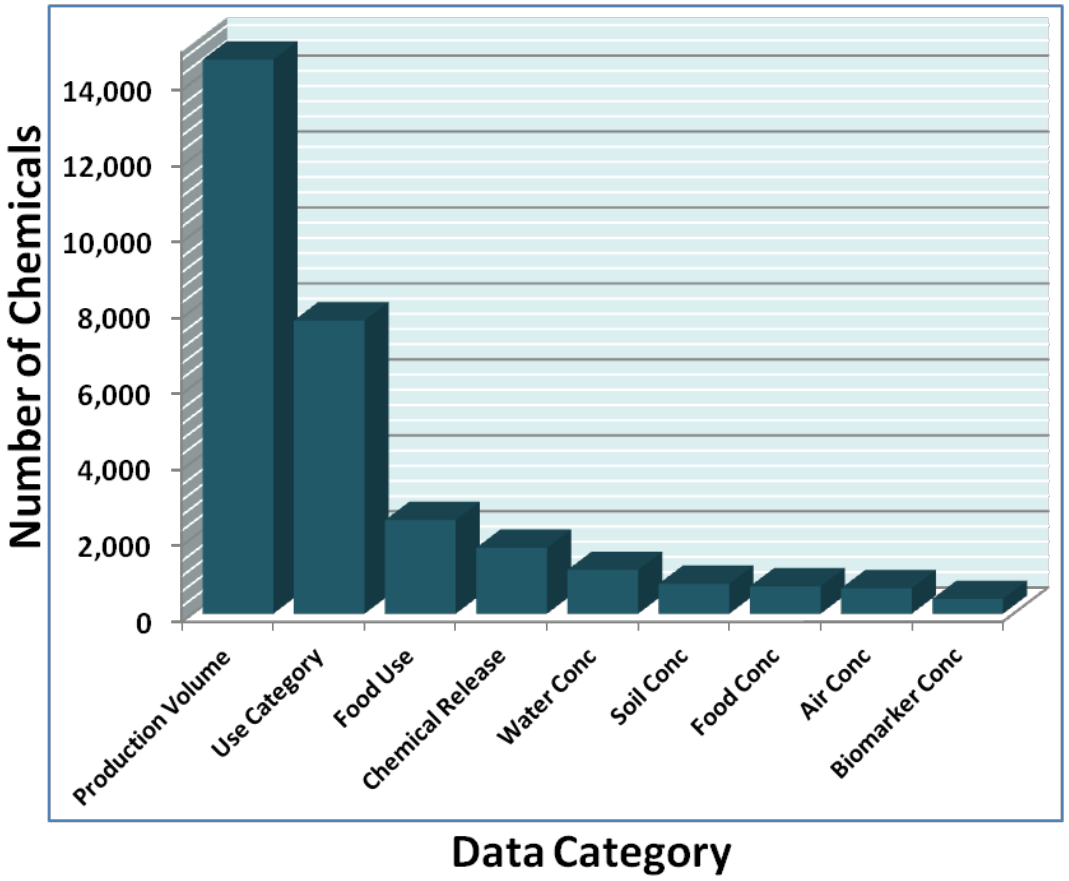


Exposure Pathways

"Exposure pathway": The course an agent takes from the source to the target (Zartarian et al., 2005)

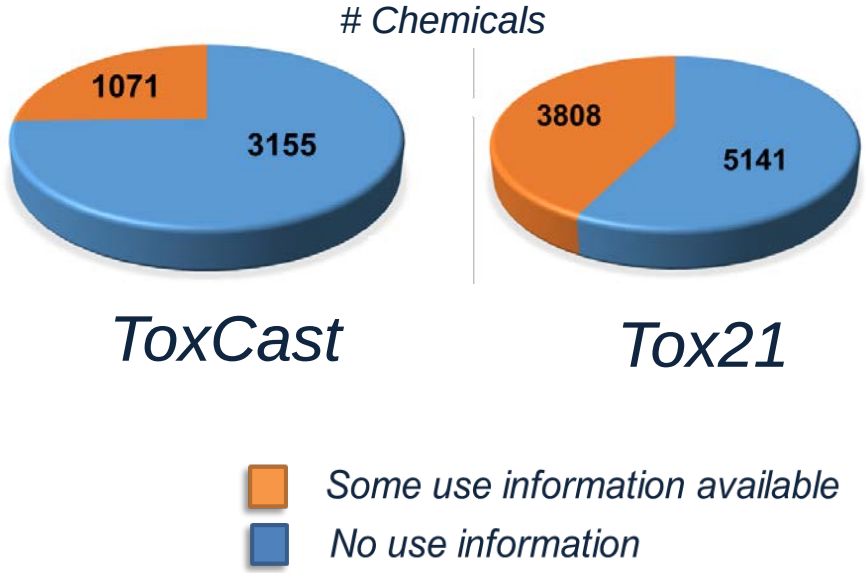


Data Critical to Exposure Estimation Are Often Limited



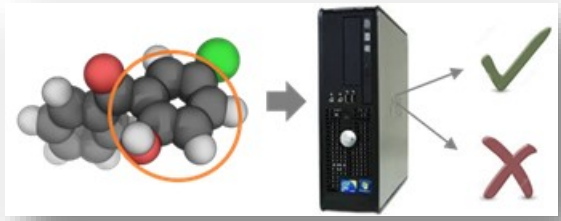
Egeghy P., et al. (2012) The exposure data landscape for manufactured chemicals. Science of the Total Environment

Use data for chemicals being tested via high throughput screening at EPA

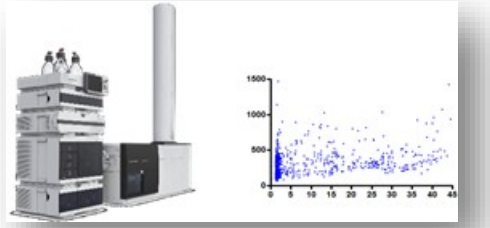


Filling Gaps in Exposure Information: New Approach Methods in EPA's ExpoCast Project

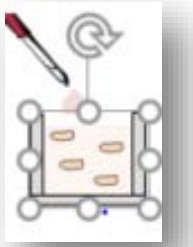
- Use of structure-based machine-learning QSAR models to predict exposure information
  - Functional use
  - Exposure pathways
  - Media occurrence or concentration

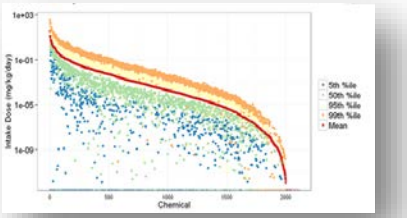


- Non-targeted monitoring of environmental or biological media



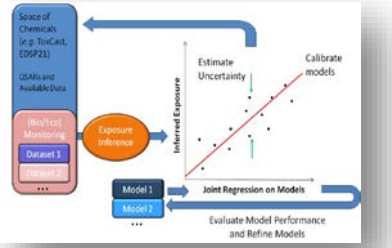
- High-throughput toxicokinetics
  - *In-vitro* studies
  - *In-silico* models and tools





- Rapidly parameterized consumer exposure models (CPDat/SHEDS-HT)

- Consensus multi-pathway modeling approaches (e.g., ExpoCast SEEM)



APCRA Exposure NAM Evaluation Activities

- APCRA 2017
  - Exposure NAM landscaping exercise across chemical use, release, monitoring, toxicokinetic, and exposure domains
- APCRA 2018: Case Studies
  - Comparison of high-throughput QSARs for chemical functional use to EPA Chemical Data Reporting and to reported information from ECHA
  - Comparison of high-throughput QSARs for chemical media occurrence (environmental/biomonitoring) to external datasets from the European Commission Information Platform for Chemical Monitoring and other sources
  - **Comparison with traditional exposure estimates performed under the Canadian Chemicals Management Plan to ExpoCast HT consumer and multipathway consensus exposure predictions**

Chemicals Management Plan (CMP)

- The CMP was designed in 2006 to help Canada meet goals set by the World Summit on Sustainable Development for the sound management of chemicals by 2020
  - Accomplished by addressing 4,300 priority substances that are in commerce in Canada
  - CMP also includes the pre-market assessment of new substances (4,500 notifications assessed since 2006)
- Under these programs, risk assessments are carried out, which consider exposure to the general population
- The CMP has also developed mechanisms to gather information from industry and identify priorities for research, monitoring/surveillance as well as risk assessment based on new information

Material from Angelika Zidek

CMP Human Health Exposure Analysis

- Compilation of over 3000 exposure estimates for ~700 substances
  - Volumes reported imported or manufactured in Canada
  - Exposure estimates by route (oral, dermal, inhalation)
  - Exposure estimates by source, and sub-population:
    - Food
    - Drinking water
    - Indoor air
    - Outdoor air
    - Soil/dust
    - Consumer product

Material from Angelika Zidek

High-throughput Stochastic Human Exposure and Dose Simulation Model (SHEDS-HT)

- High-throughput model for simulating population exposures to chemicals in consumer products via multiple product types, scenarios, and routes
- **Rapidly parameterized** route-specific algorithms based on product category (e.g., spray paint, surface cleaner, toothpaste)
- **Product chemical concentrations** from EPA's Chemical and Products Database (CPDat)
- Public R package, code, and default input files for consumer products (derived from CPDat) available at:

https://github.com/HumanExposure/SHEDSHTRPackage

Package 'ShedsHT'

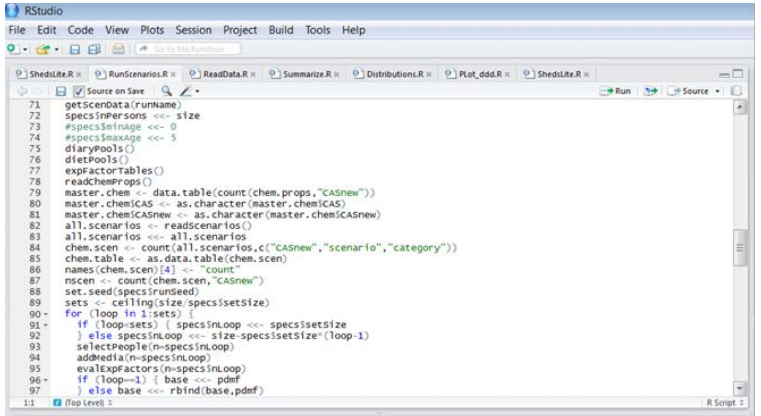
September 9, 2016

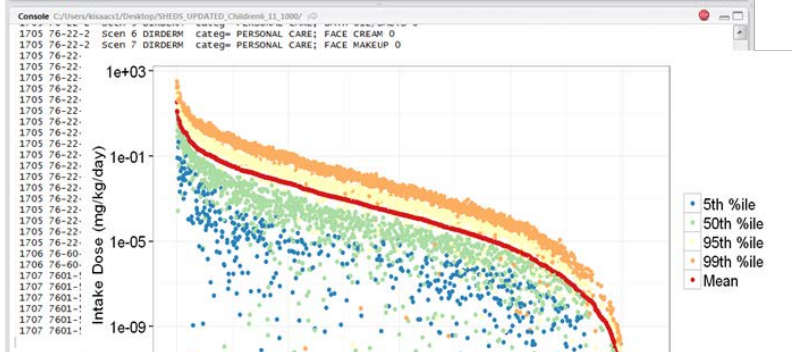
Title To run the SHEDS-HT screening model for estimating human exposure to chemicals.

Version 0.1.1

Author Kristin Isaacs [aut, cre]

Maintainer Kristin Isaacs <isaacs.kristin@epa.gov>





ENVIRONMENTAL Science & Technology

SHEDS-HT: An Integrated Probabilistic Exposure Model for Prioritizing Exposures to Chemicals with Near-Field and Dietary Sources

Kristin K. Isaacs,*,† W. Graham Glen,‡ Peter Egeghy,† Michael-Rock Goldsmith,§,○ Luther Smith,‡ Daniel Vallero,† Raina Brooks,∥ Christopher M. Grulke,⊥,○ and Halûk Özkaynak†

†U.S. Environmental Protection Agency, Office of Research and Development, National Exposure Research Laboratory, 109 T.W. Alexander Drive, Research Triangle Park, North Carolina 27709, United States

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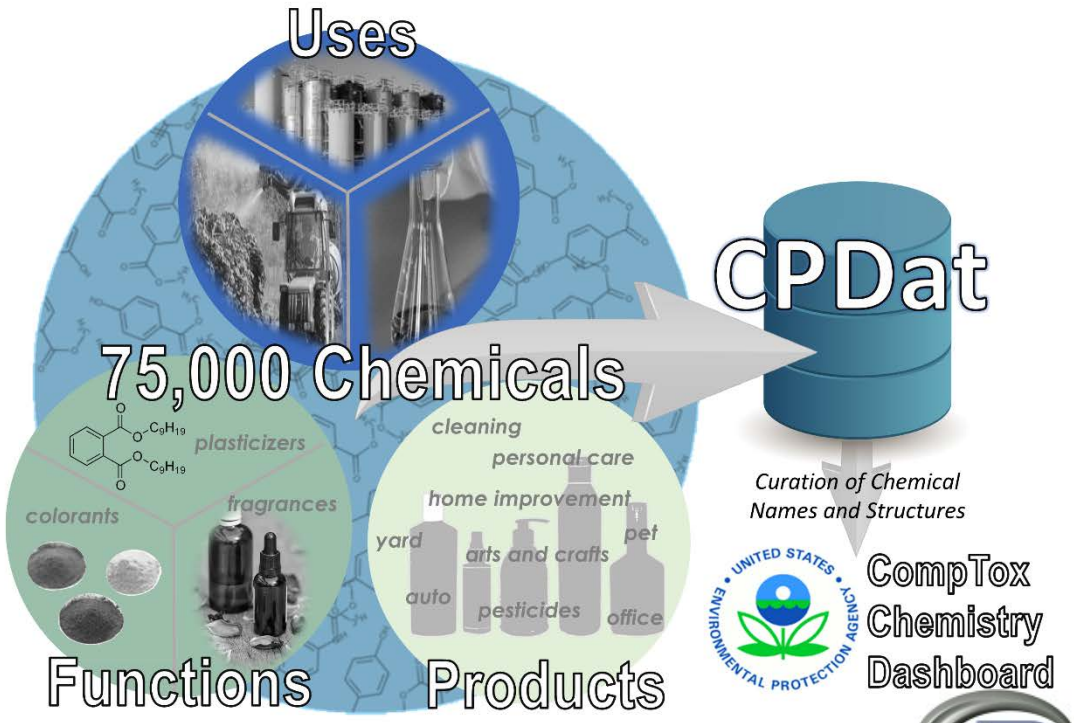
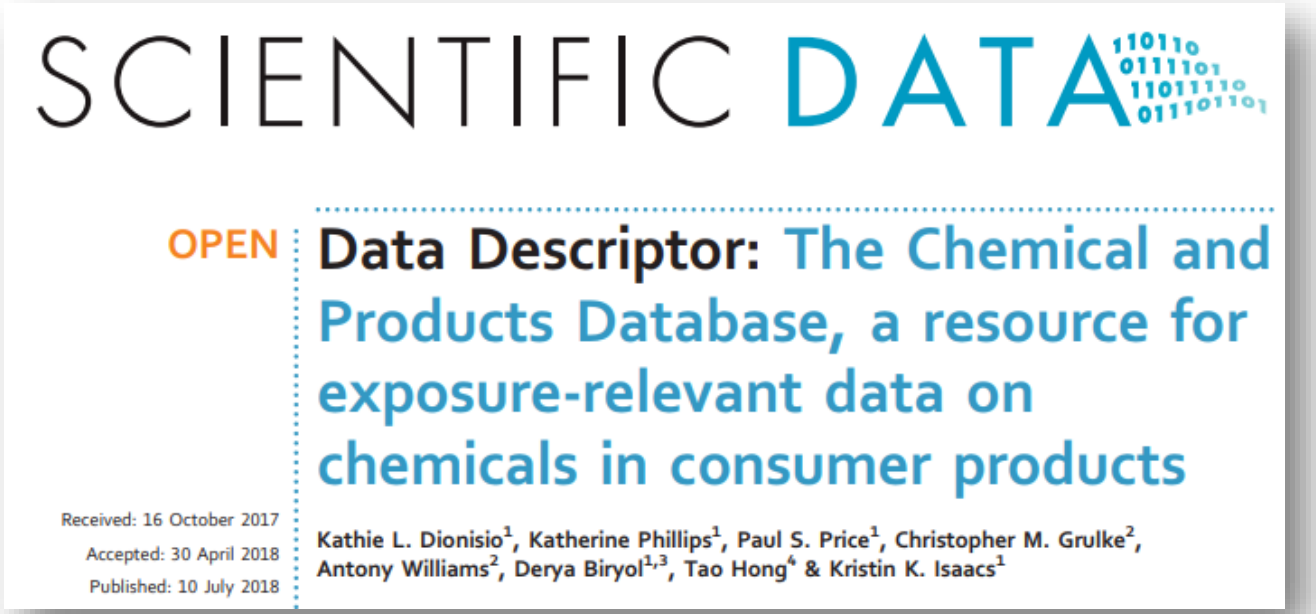
Chemical and Products Database (CPDat)

- New database of chemical and product information
- General uses, functional uses, product ingredients and compositions
- Data on 75,000 chemicals **and 15,000 consumer products** (via SDS sheets)
- Data available via individual chemical search or via bulk download via the CompTox Chemistry Dashboard




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

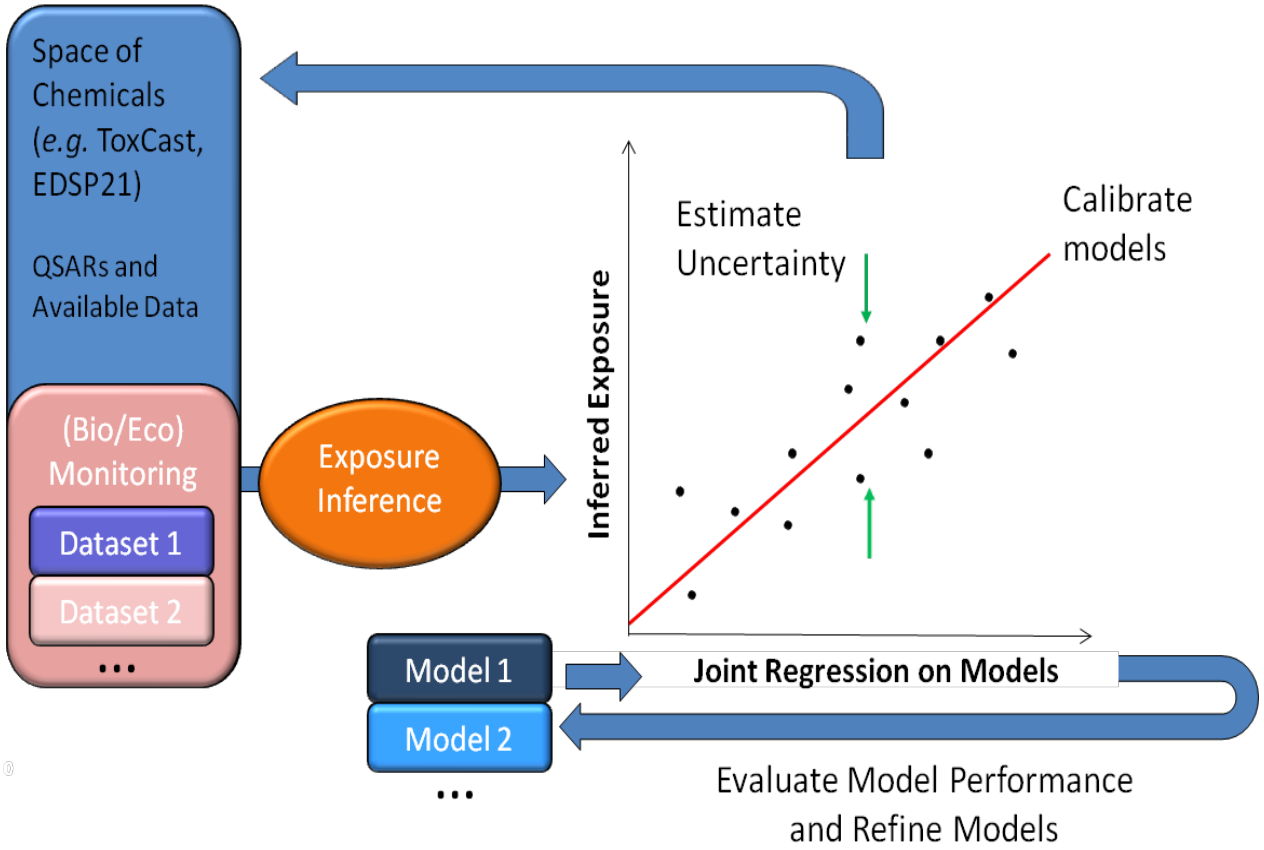
Kathie L. Dionisio[1], Katherine Phillips[1], Paul S. Price[1], Christopher M. Grulke[2], Antony Williams[2], Derya Biryol[1,3], Tao Hong[4] & Kristin K. Isaacs[1]

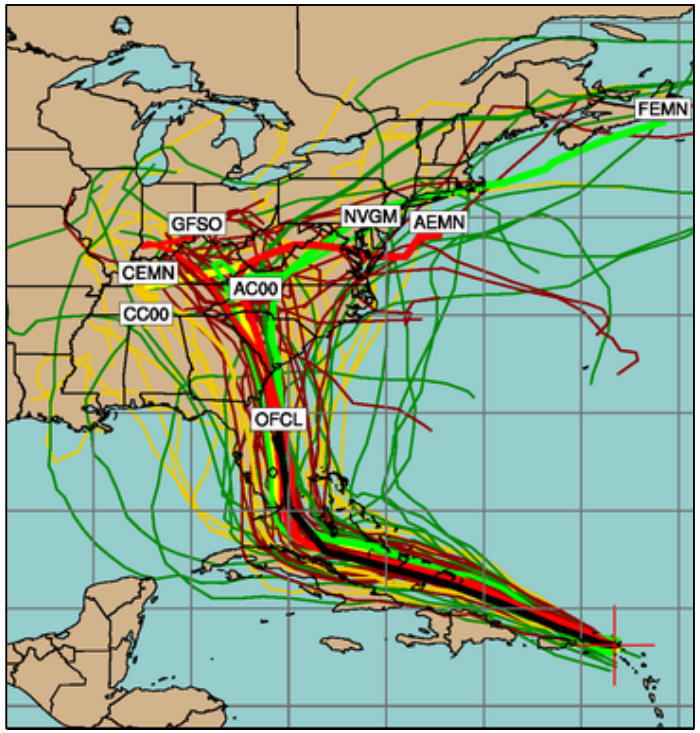
Package 'CPDat'

https://comptox.epa.gov/dashboard/

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?





Adapted from John Wambaugh

Collaboration on High Throughput Exposure Predictions: "SEEM3"

Predictor	Reference(s)	Chemicals Predicted	Pathways/Sources Covered by the Model/Predictor
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)	8167	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 Simulation Model- 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	Consumer
High-Throughput Dietary Exposure Model for Food Contact Substances (2017)	Biryol et al. (2017)	940	Dietary (Food Packaging)
Fugacity-based INdoor Exposure (FINE) (2017)	Bennett et al. (2004), Shin et al. (2012)	645	Consumer
RAIDAR-ICE Near-Field (0.803)	Arnot et al., (2014), Zhang et al. (2014)	1221	Consumer
USEtox Residential Scenario (2.0)	Jolliet et al. (2015), Huang et al. (2016,2017)	615	Consumer
USEtox Dietary Scenario (2.0)	Jolliet et al. (2015), Huang et al. (2016), Ernstoff et al. (2017)	8167	Dietary (Food Packaging)

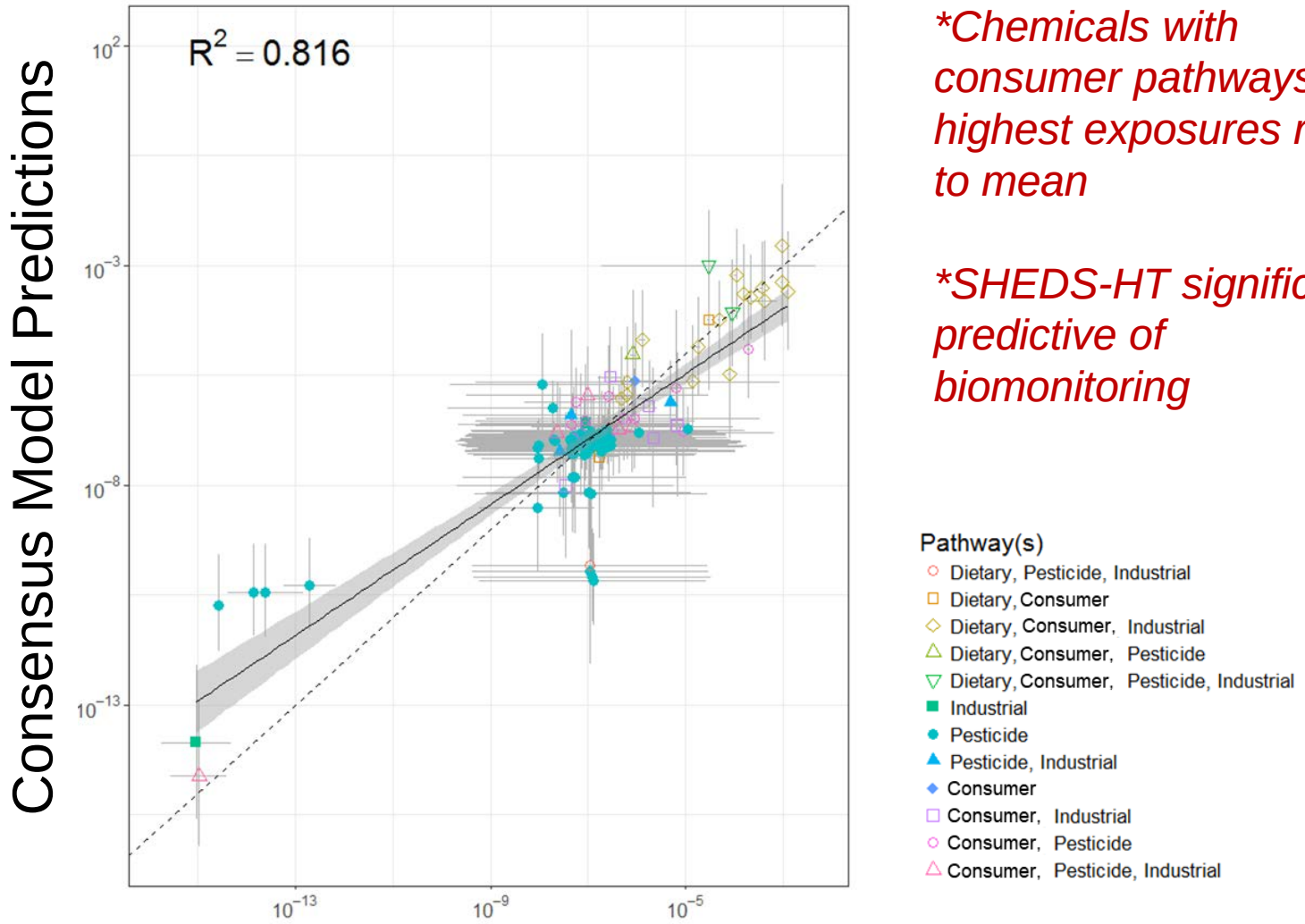
Jon Arnot, Deborah H. Bennett, Peter P. Egeghy, Peter Fantke, Lei Huang, Kristin K. Isaacs, Olivier Jolliet, Hyeong-Moo Shin, Katherine A. Phillips, Caroline Ring, R. Woodrow Setzer, John F. Wambaugh, Johnny Westgate

Ring et al., in revision

Adapted from John Wambaugh

Building the Consensus Model

- Models evaluated against chemicals in NHANES with same pathways
- Bayesian multivariate regression using exposures inferred from NHANES biomonitoring data
- Regression incorporated pathway information
- Pathways predicted with machine-learning based models, allowing application of regression model to large chemical libraries



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

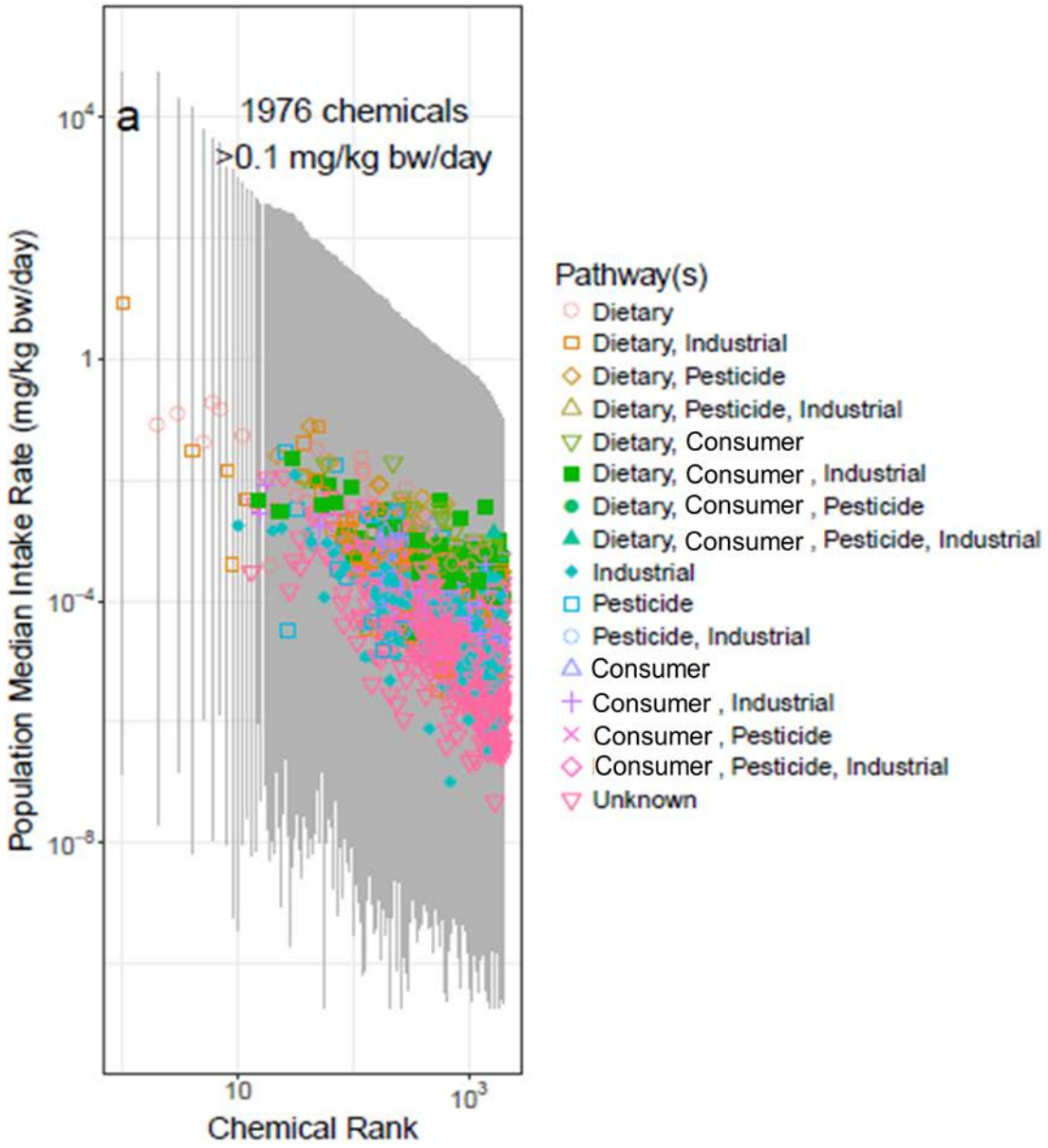
**Chemicals with consumer pathways had highest exposures relative to mean*

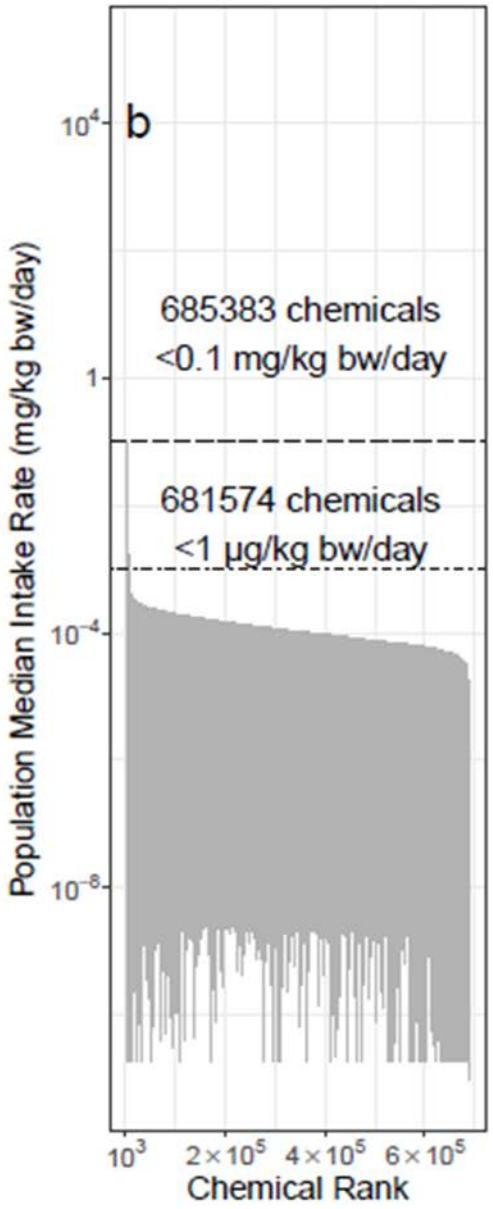
**SHEDS-HT significantly predictive of biomonitoring*

Ring et al., in revision

Adapted from John Wambaugh

Consensus Modeling of Median Chemical Intake Exposure





Ring et al., in revision

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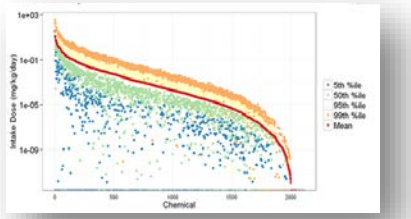
Comparison of NAMs and CMP: A Challenge

What metrics to compare?

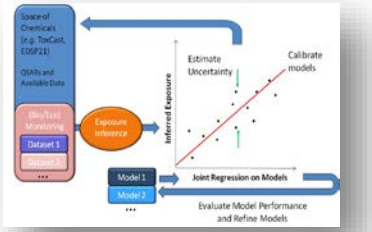
What chemicals?



SHEDS-HT

CMP Consumer

CMP Environmental Media



SEEM3

	SHEDS-HT	CMP Consumer	CMP Environmental Media	SEEM3
Pathways	*Consumer*	*Consumer*	*Dietary (food), Far-field, Indoor air and dust (partial consumer)*	*Consumer, Dietary, Far-field*
Population	*U.S. population (**users/non-users**)*	*Typical **product user***	*Typical individual*	*U.S. population*
Exposure Metric	*Percentiles of aggregate exposure (**all products**)*	*Exposure for **individual products***	*Exposure for each pathway (exposed and non-exposed populations)*	***Population Median***

Comparison of NAMs and CMP: A Challenge

What metrics to compare?

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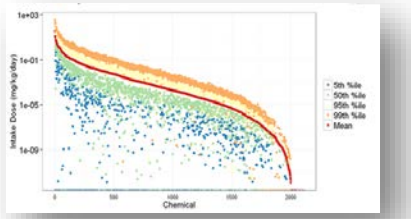
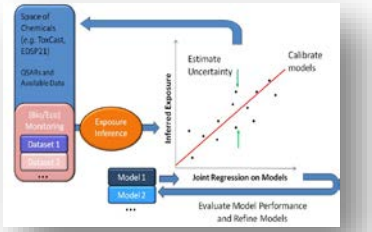


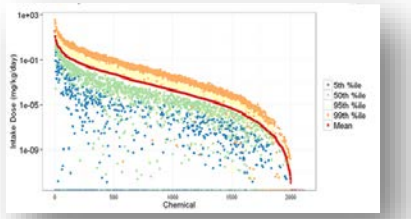


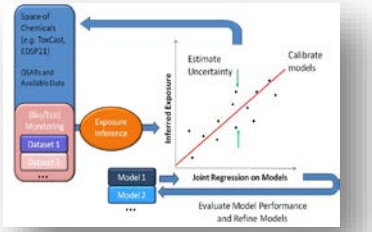
	SHEDS-HT	CMP Consumer	CMP Environmental Media	SEEM3
Pathways	*Consumer*	*Consumer*	*Dietary (food), Far-field, Indoor air and dust (partial consumer)*	*Consumer, Dietary, Far-field*
Population	Re-parameterized SHED-HT into a series of product-specific runs (e.g., "paint") for users only (population prevalence =100%) Examine 5th-95th %ile of *user exposure*	*Typical **product user***	*Typical individual*	*U.S. population*
Exposure Metric		*Exposure for **individual products***	*Exposure for each pathway (exposed and non-exposed populations)*	***Population Median***

Comparison of NAMs and CMP: A Challenge

What metrics to compare?

What chemicals?





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Population	Re-parameterized SHED-HT into a series of product-specific runs (e.g., "paint") for users only (population prevalence =100%)	*Typical **product user***	*Typical individual*	*U.S. population*
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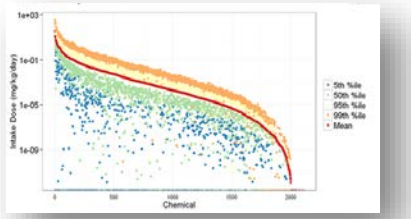
Compare chemical -product combinations

Comparison of NAMs and CMP: A Challenge

What metrics to compare?

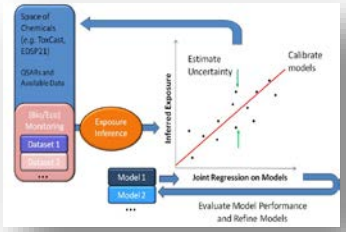
What chemicals?



SHEDS-HT

CMP Consumer

CMP Environmental Media



SEEM3

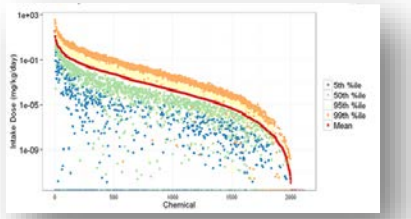
Compare chemical -product combinations

	SHEDS-HT	CMP Consumer	CMP Environmental Media	SEEM3
Pathways	*Consumer*	*Consumer*	*Dietary (food), Far-field, Indoor air and dust (partial consumer)*	*Consumer, Dietary, Far-field*
Population	Re-parameterized SHED-HT into a series of product-specific runs (e.g., "paint") for users only (population prevalence =100%)	*Typical **product user***	Examined total exposure from all media (all represented pathways)	*U.S. population*
Exposure Metric	Examine 5th-95th %ile of *user exposure*	*Exposure for **individual products***		***Population Median***

Comparison of NAMs and CMP: A Challenge

What metrics to compare?

What chemicals?



SHEDS-HT

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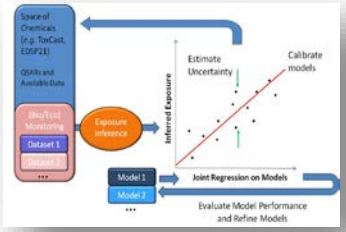


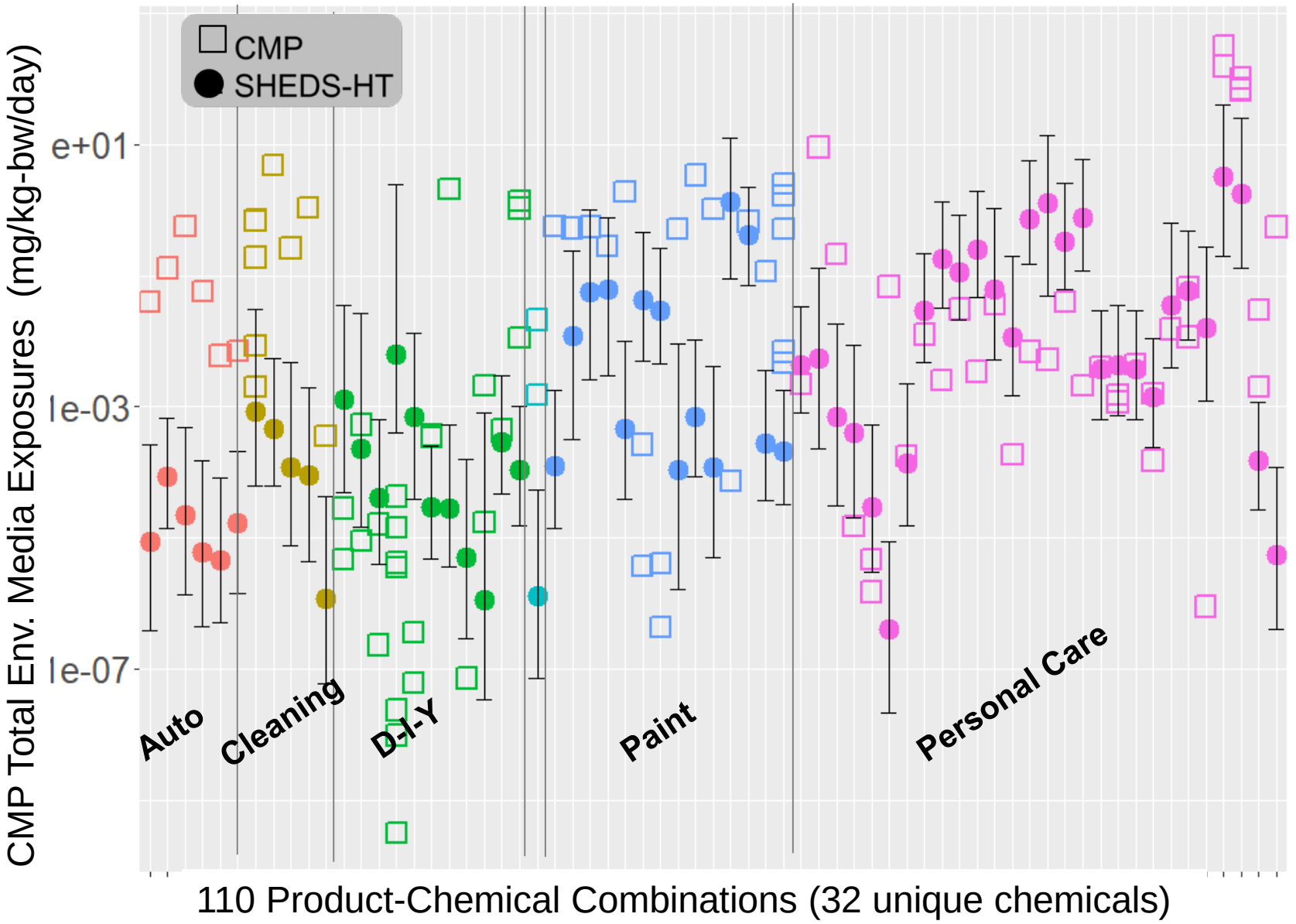
SEEM3

	SHEDS-HT	CMP Consumer	CMP Environmental Media	SEEM3
Pathways	*Consumer*	*Consumer*	*Dietary (food), Far-field, Indoor a[illegible] and dust (p[illegible] consum[illegible]*	*Consumer, Dietary, [illegible]ar-field*
Population	Re-parameterized SHED-HT into a series of product-specific runs (e.g., "paint") for users only (population prevalence =100%)	*Typical **product user***	Examined total exposure from all media (all represented pathways)	*U.S. population*
Exposure Metric	Examine 5th-95th %ile of *user exposure*	*Exposure for **individual products***		***Population Median***

Compare chemical -product combinations

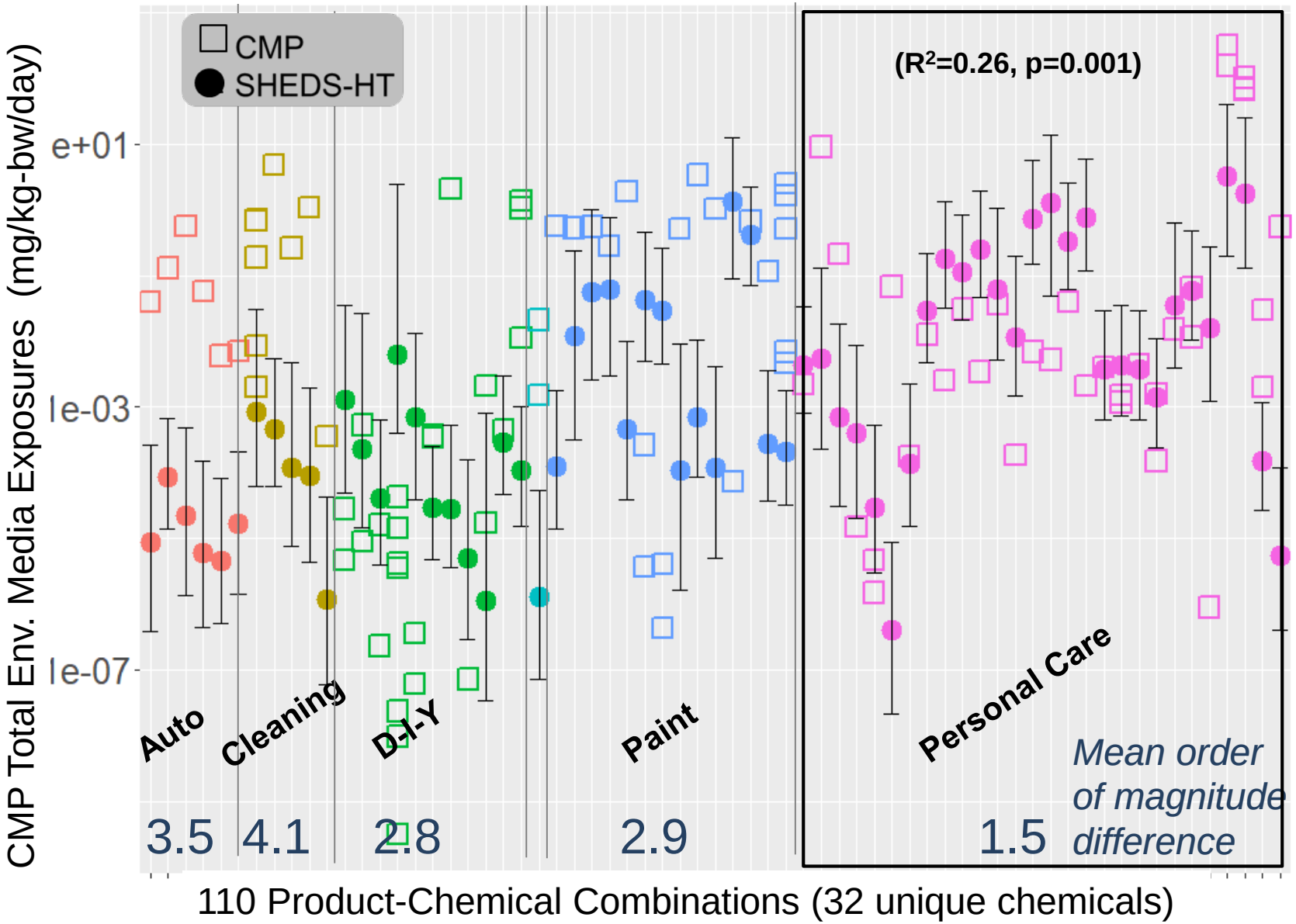
Compare chemicals w/o consumer uses

Consumer Exposure Comparisons



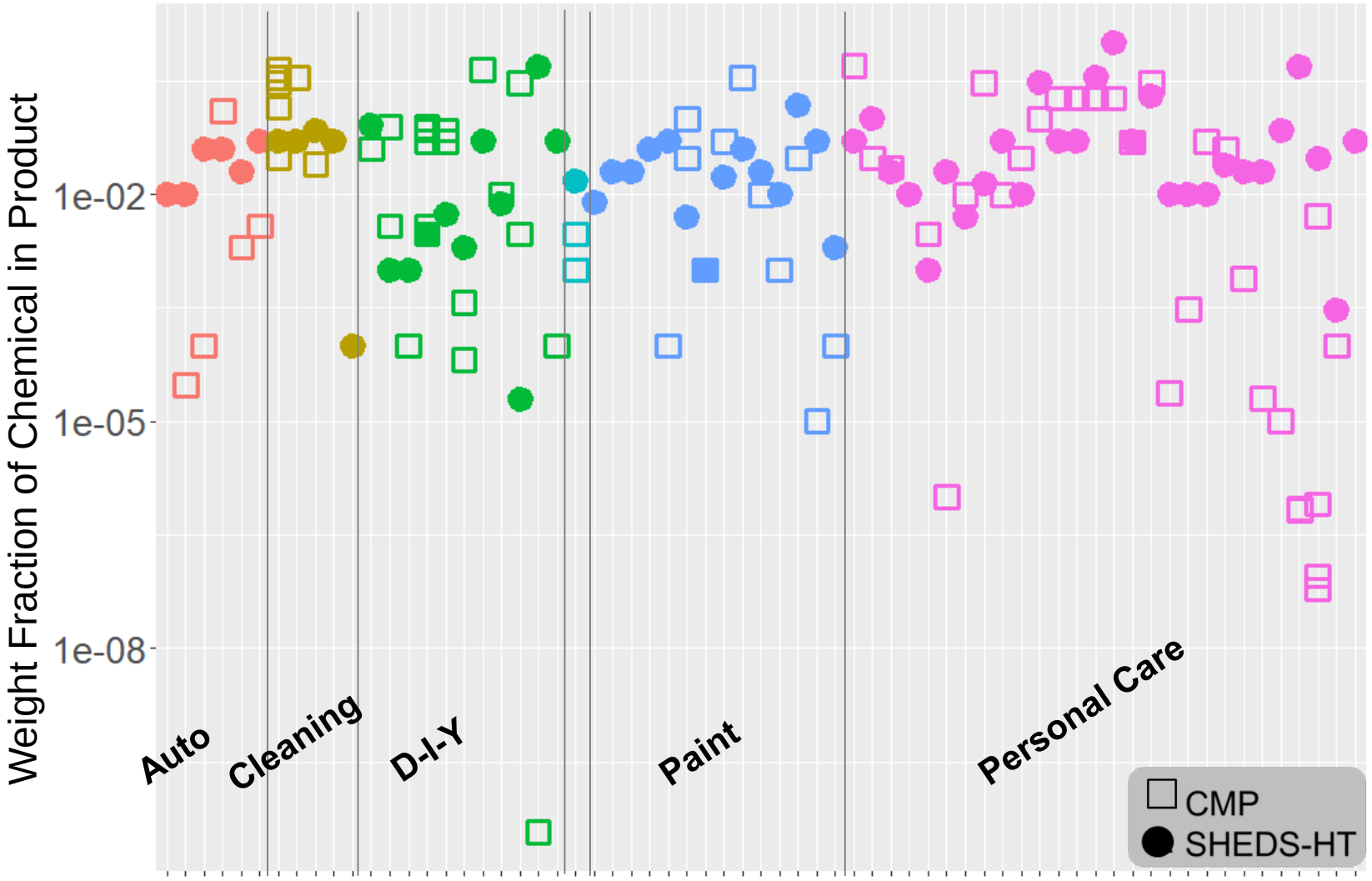
- Matched product as closely as possible; some inconsistencies
- No systematic magnitude differences between SHEDS-HT and CMP, although some categories showed clear patterns

Consumer Exposure Comparisons



- Matched product as closely as possible; some inconsistencies
- No systematic magnitude differences between SHEDS-HT and CMP, although some categories showed clear patterns
- Predictions were most comparable for personal care products (most data-rich category in CPDat)
- Are product concentrations driving the larger differences?

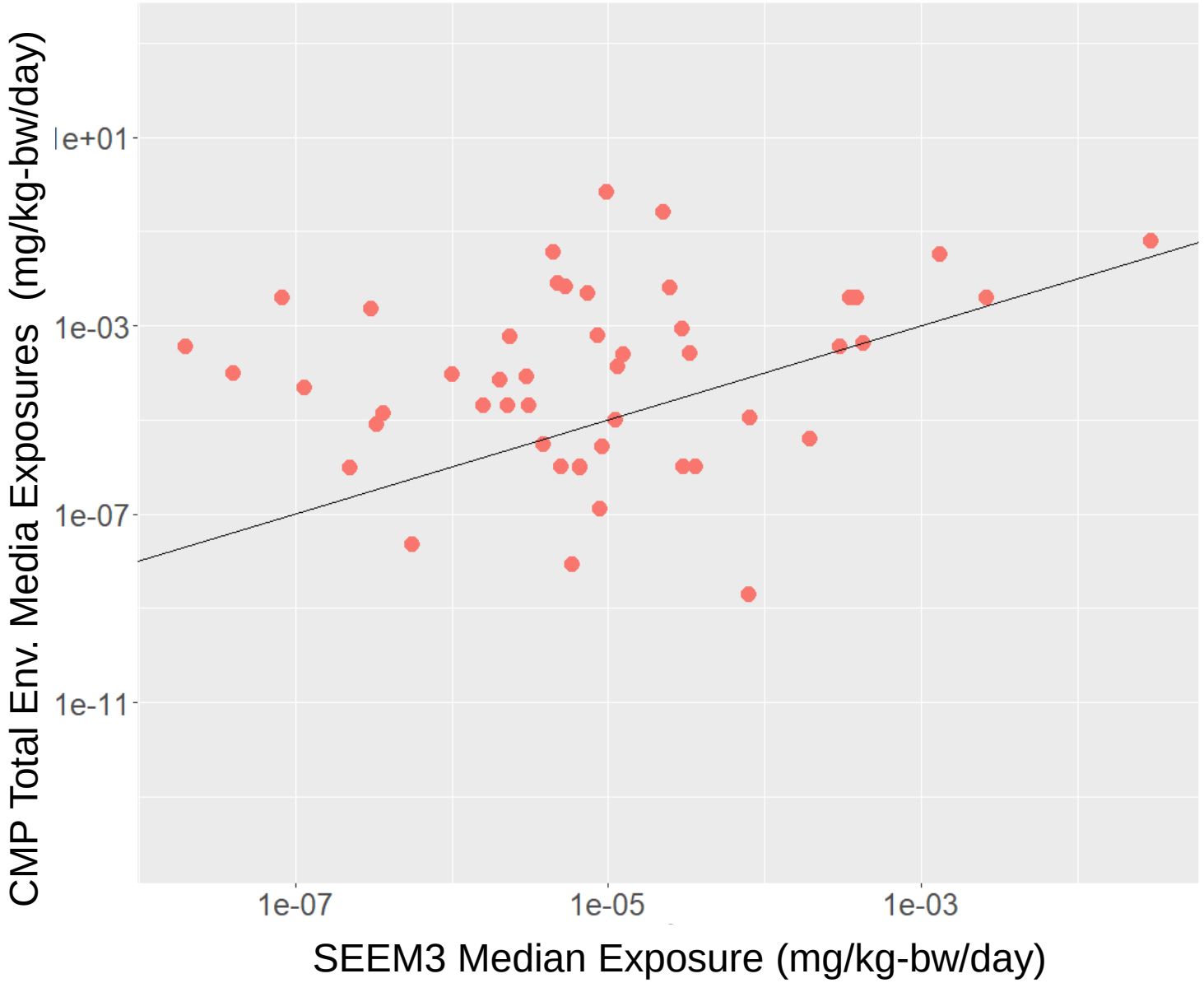
Product Concentration Differences: CPDat Versus CMP



110 Product-Chemical Combinations (32 unique chemicals)

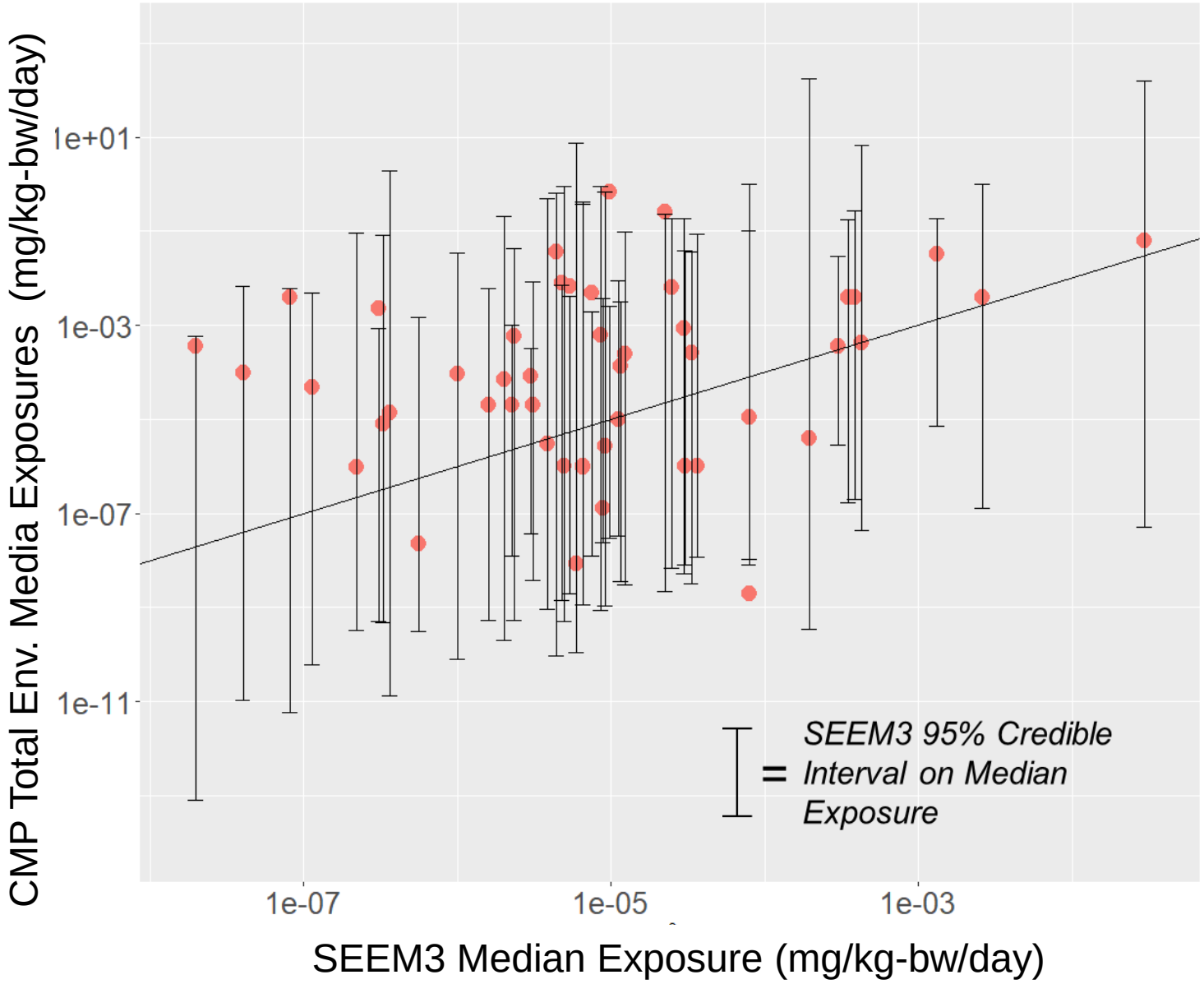
- Compared median CPDat and CMP concentrations where available
- Concentration might be contributing to differences for some categories, but concentration differences were generally smaller than those observed in ultimate exposures
- However, examination of scenario definitions (e.g., durations, amounts) and other decisions/assumptions will be required to fully understand differences
- Likely some lack of congruence between SHEDS and CMP product categories (and thus scenario definitions)

Comparison of SEEM3 with CMP Environmental Media Exposures (Chemicals without Consumer Pathways)



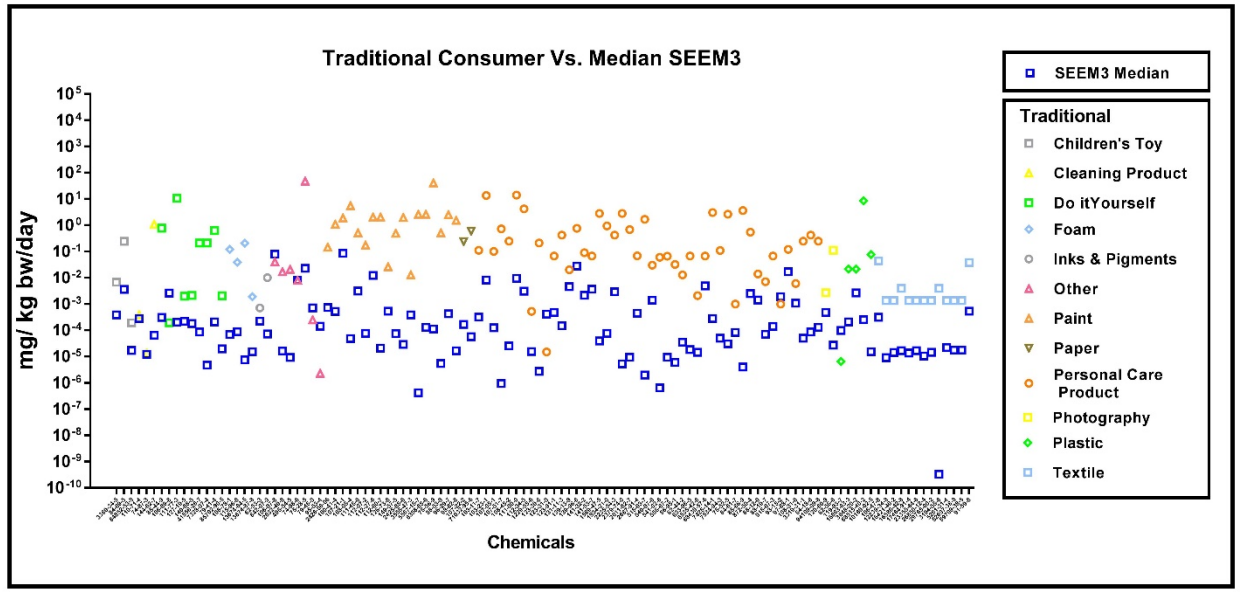
- 48 chemicals could be compared; used age 20-59
- No significant relationship between SEEM median estimates and the CMP environmental estimates for these 48 chemicals, but significant relationship with the 95th% credible interval (R^2=0.1, p<0.0001)

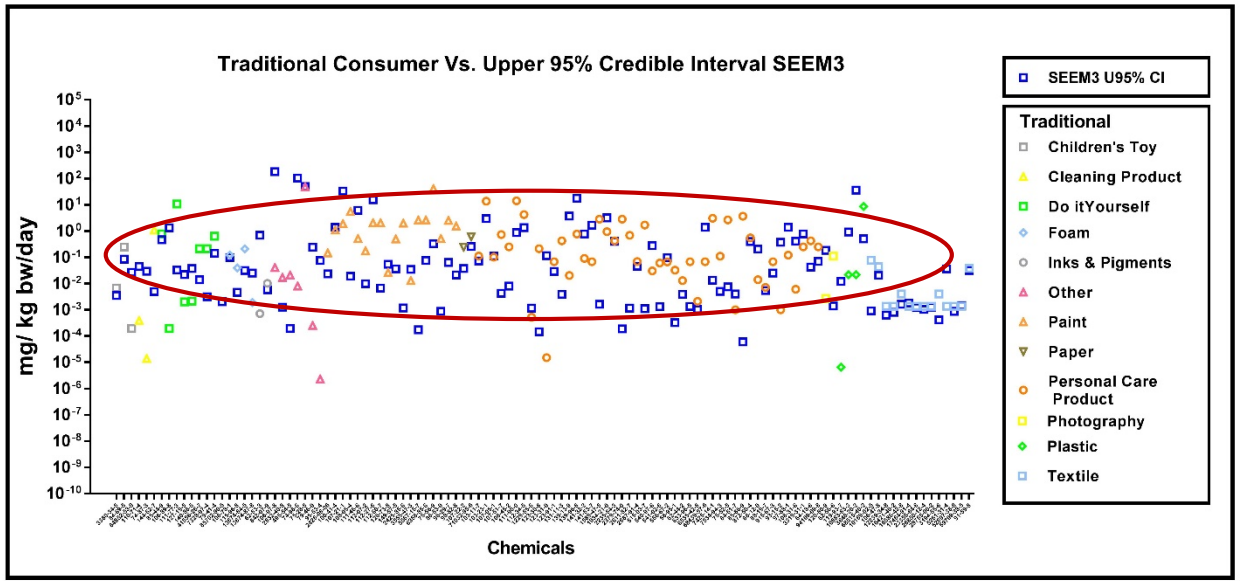
Comparison of SEEM3 with CMP Environmental Media Exposures (Chemicals without Consumer Pathways)



- 48 chemicals could be compared; used age 20-59
- No significant relationship between SEEM median estimates and the CMP environmental estimates for these 48 chemicals, but significant relationship with the 95th% credible interval (R^2=0.1, p<0.0001)
- However, SEEM3 95% credible interval contained CMP estimate for 41 chemicals (six chemicals higher, one lower); 33 chemicals within 2 orders of magnitude of median estimate
- Five of the six “higher” chemicals were within an order of magnitude of the upper bound
- One chemical (furfural) was 2 orders of magnitude higher – CMP assessment included estimates of concentration in food (naturally occurring and process-formed) - not included in SEEM3 pathway models

Other SEEM3 Comparisons (Health Canada)



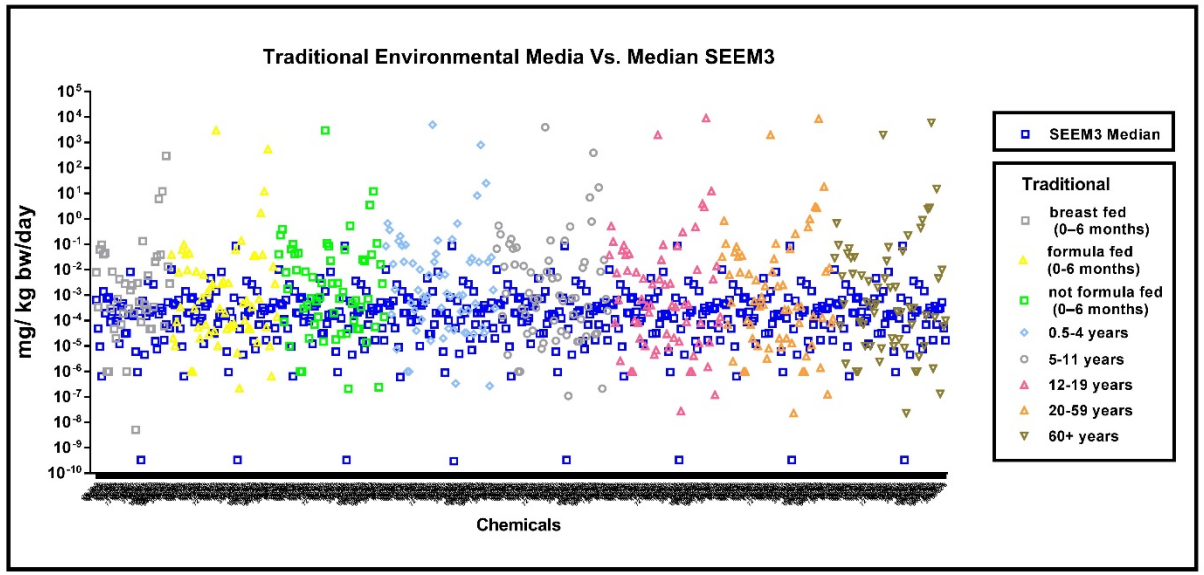


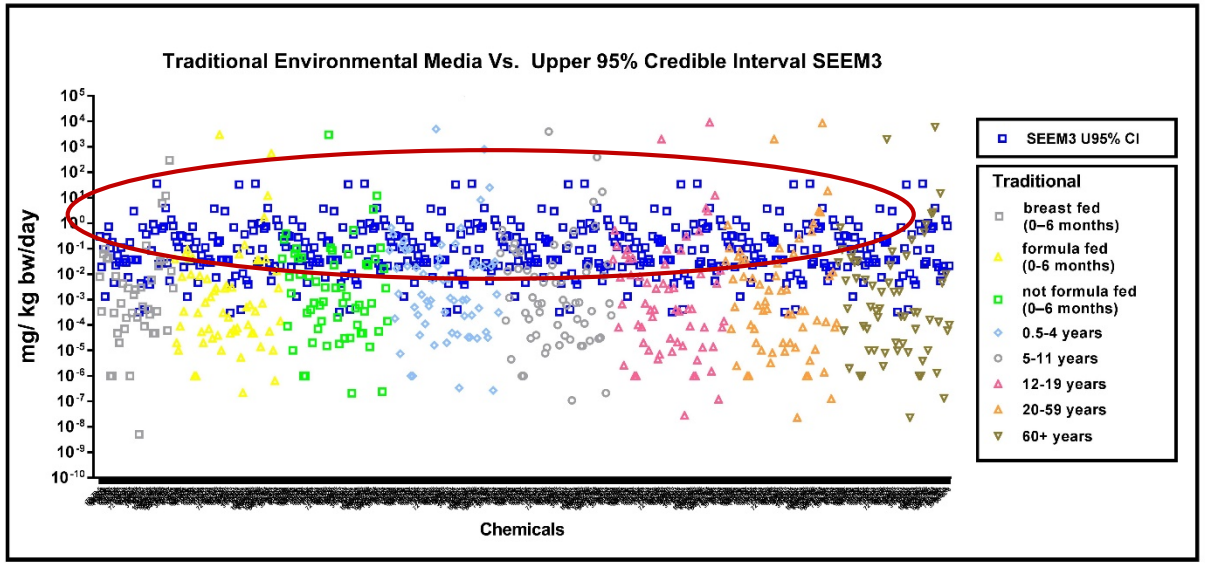
CMP Consumer compared to SEEM3

- For completeness, SEEM3 estimates were compared to traditional consumer estimates
- Upper bound of the 95% credible interval of median did not always encompass the user exposures (not unexpected)
- Should be careful to interpret SEEM3 in appropriate context (average person, not reflective of high exposure percentiles or specific populations)

Material from Angelika Zidek and Reza Farmahin

Other SEEM3 Comparisons (Health Canada)





CMP Environmental compared to SEEM3- 63 chemicals

- CMP environmental estimates were compared with SEEM3 for all chemicals
- Despite some inconsistency in pathway contributions to both metrics, there were very few chemicals above the 95% confidence bounds
- Similarly to earlier example, the chemicals above the interval are chemicals with dietary pathways not currently captured in the SEEM model

Material from Angelika Zidek and Reza Farmahin

Ongoing Activities

- Refined comparisons for SHEDS-HT model
  - Exposure route-specific (e.g., dermal, inhalation, ingestion) comparisons for consumer product exposures
  - Identification of systematic scenario definition differences?
  - Age group comparisons
  - Any lessons learned: could be used to refine SHEDS-HT parameterization/algorithms
- Evaluation of other HT exposure models such as other consumer models included in SEEM3
- Completion and development of additional exposure case studies (e.g., occupational or ecological exposure) to further evaluate performance and limitations of various exposure NAMs in a regulatory context

Conclusions and Recommendations

- Comparing exposure predictions across traditional models/assessments and HT NAMs was challenging given different model structures, purposes, populations, and metrics.
- Estimates for consumer products differed; degree of separation dependent on product category.
  - Personal care products were most comparable (data rich in terms of use, best mapping of product-to-product)
  - Additional exploration of factors driving differences is needed.
  - Harmonization of consumer product categories, scenarios (e.g., use patterns), and other factors across assessment/models tiers can facilitate future evaluations.
    - Harmonization or other alignment will also enhance data sharing capabilities (one of the goals of the APCRA project).

Conclusions and Recommendations

- When uncertainty was considered, the HT SEEM3 estimates of population median exposures were consistent with the traditional environmental media estimates for the majority of the chemicals that could be *most directly compared* (i.e., adults, chemicals without consumer pathways).
- Comparisons between traditional assessments and NAMs for exposure can inform refinement of high-throughput methods (e.g., identification of exposure sources or pathways not currently included and their impact).
- Continued evaluation of HT NAM exposure estimations with traditional assessments and other information (e.g., additional biomonitoring) will aid in establishing fit-for-purpose of exposure NAMs for decision–making (e.g., prioritization, screening, or higher-tier evaluation).

Chemical Safety for Sustainability (CSS) Research Program

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