Defining the Cutting - Edge to the U.S.

EPA's Computational Exposure Science

Presented by Timothy J. Buckley, Ph.D. U.S. EPA Office of Research & Development Center for Computational Toxicology and Exposure (CCTE) Research Triangle Park, NC

Disclaimer: The views expressed in this presentation are those of the authors and do not necessarily represent the views or the policies of the U.S. Environmental Protection Agency.

INTERNATIONAL SOCIETY OF EXPOSURE SCIENC

Declarations of Conflict of Interest

Funding Source(s): Funding for this work came from the U.S. Environmental Protection Agency

Conflict of Interest: Nothing to disclose

Employment: Nothing to disclose

Personal Financial Interests: Nothing to disclose

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Co-Authors

Adam Biales Peter P. Egeghy Ann M. Richard Jon Sobus Elin M. Ulrich Kristin Isaacs

John Wambaugh Caroline Ring Risa R. Sayre Tom Purucker Antony J. Williams Russell S. Thomas

Motivation: Chemical Pollution is an Important Threat to Public Health

- Pollution is known to be a leading public • health threat
- A large proportion of the environmentattributed disease is of unknown etiology (Rappaport, 2016)
- **Effects likely underestimated**
- **Exposure and effects are poorly** understood
- Chemical production and release to the environment vastly outpace ability to test and measure



Pollution disproportionately kills the poor and the vulnerable.

In 2015, diseases caused by pollution were responsible for 9 million premature deaths. That is 16 percent of all global deaths.

Exposures to contaminated air, water and soil kill more people than a high-sodium diet, obesity, alcohol, road accidents, or child and maternal malnutrition. They are also responsible for three times as many deaths as AIDS, tuberculosis, and malaria combined, and for nearly 15 times as many deaths as war and all forms of violence.

Air pollution and climate change are closely linked and share common solutions. Fossil fuel combustion in higher-income countries and the burning of biomass in lower-income countries accounts for 85 percent of airborne

particulate pollution.



Source: Landrigan et al. 2017

is the world's largest environmental cause of disease and premature death

Nearly 92 percent of pollution-related deaths occur in low-income and middle-income countries. Children face the highest risks because small exposures to chemicals in utero and in early childhood can result in lifelong disease, disability, premature death, as well as reduced learning and earning potential.



Major emitters of carbon dioxide are coal-fired power plants, chemical producers, mining operations, and vehicles. Accelerating the switch to cleaner sources of energy will reduce air pollution and improve human and planetary health

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THE LANCET



Motivation: Chemical Pollution is a Major Threat to Public Health

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Genetic Factors Are Not the Major Causes of Chronic Diseases

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Numbers of pollu included in GBD e	rtio
Zone 1: 9-0 mill	ion
Zone 2:none at present	
Zone 3:none	
at present	/

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on-related deaths matesbyzone

Zone 1 Well characterised health effects of well studied pollutants. Data are included in GBD estimates and in this report.

Zone 2

Emerging, but still unquantified, health effects of known pollutants. Data are not included in GBD estimates or in this report.

Zone 3

Inadequately characterised health effects of emerging pollutants. Data are not included in GBD estimates or in this report.

> Source: Landrigan et al., 2017 **#ISES2022LIBSON**

Motivation: Managing the Enormous Number of Chemicals in Commerce

- Pollution is known to be a leading public health threat
- A large proportion of the environment-attributed disease is of unknown etiology
- Effects likely underestimated
- Exposure and effects are poorly understood
- Chemical production and release to the environment vastly outpaces ability to test and measure
 - 350,000 chemicals and mixtures registered for production and use across 19 countries (Wang et al. 2020)
 - The EPA Chemical dashboard lists 37,143 chemicals within its CPDAT, Chemical and Products Database (<u>https://comptox.epa.gov/dashboard/chemical_lists/CPDA</u>)
 - EPA's DSSTox database currently lists 1.2 million substances of environmental health relevance (Grulke et al., 2019)
 - TSCA lists a total of 86,631 chemicals with about half that number (42,039) identified as currently active in U.S. commerce (February 2022)
 - New approaches of assessment are needed

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Motivation: Threat to a Habitable Planet

- Need for improved scientific basis for developing effective hazard screening, monitoring and management options that will avoid transgressing planetary boundary (Rockstrom et al. 2009)
- Current chemical management practices do not address this issue and must therefore be complemented with new approaches (Persson et al. 2013).
- Production and releases of novel entities outstrips global capacity for assessment and monitoring (Persson et al. 2022).
- 4 PFAS (FPOA, PFNA, PFHxS, PFOS) exceed planetary boundary for chemical pollution (Cousins et al. 2022)



Source: Rockstrom et al. 2009

Developing the Science: Computational Exposure

Recognition

- Exposure science is a complex endeavor that spans chemical, physical, biological, environmental, and social sciences
- The high-throughput need of computation exposure science greatly accentuates the complexity
- Data & models interdependent / highly integrated (NAS, ?)
- Modeling provides the only practical means to achieve

Defining characteristics

- Predictive
- Rapid
- High-throughput
- Results in closure of knowledge/time gap supporting risk management decisions

Part of larger research effort known as NAMs (Wambaugh et al.)

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The integration of advances in chemistry, computer science, mathematics, statistics, and social and behavioral sciences with new and efficient models and data collection methods to reliably and effectively forecast real-world exposures to natural and anthropogenic chemicals in the environment (Egeghy et al., 2016.)

Computational Exposure Research Elements

- Chemical Curation
- Data Development
 - Data curation of public sources
 - Non-targeted Analysis (NTA) methods
- Modeling
- Cross-Cutting
 - Uncertainty
 - Confidence
 - Access

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Chemical Curation

- Defining characteristics
 - Most comprehensive accounting of anthropogenic chemical landscape, i.e., 1.2 M chemicals
 - Chemical ID, structure, and meta data highly quality assured
 - Accessibility for computational, regulatory, public use
- Foundational resource serving to integrate and enable exposure elements as well as linkages to hazard and risk
- Future plans
 - Continued expansion to include polymers, mixtures, and ill-defined substances
 - Continued expansion based on non-targeted analysis discovery



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

Research Example: Curation of Chemicals in Biosolids



- Clarity of pollutants is relevant to Clean Water Act
- Important implications for human exposure & risk
- Replaces standalone biennial reports
- Provides context for interpreting risk
- List includes 726 chemicals / concentrations for 484

Richman et al. 2022

Data Development

- Exposure continuum provides framework
- Consistent with NAS guidance for organization, useability, and access
- Includes advanced
 - Informatics, data-mining, machine learning
 - Dta infrastructure for collection, organizing, a integration
- Receptor oriented / near field data especially valuable
- Exposure Databases developed
 - ChemExpoDB, CPDat, MMDB, and CvTdb
- Future research to address occupational settings, chemicals in consumer articles

S Increasing Complexity	ource
Se	ctor of Use
F	unction
Product category	Industry
Specific product	Specific proces
Quantitative concentrations in products	Quantitative volu used/stored
Near-field	
Far-field	



Example Data Development Research Effort

www.nature.com/scientificdata

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. Dionisio¹, Katherine Phillips¹, Paul S. Price¹, Christopher M. Grulke², Antony Williams², Derya Biryol^{1,3}, Tao Hong⁴ & Kristin K. Isaacs¹

Dionisio et al. Sci Data 5:180125 (2018).

Non-Targeted Analysis (NTA)

- Identifies chemicals unknow (emerging) and without standards
- Application source to dose
 - Source: household (Phillips et al, 2018)

& recycled products (Lowe et al., 2021)

- Environmental: house dust (Rager et al., 2016)
- & water filters (Newton et al., 2018)
- Dose: blood (Phillips et al., in prep) & placenta (Rager et al., 2020)
- Research focused on obstacles to broad adoption
 - Methods development
 - Workflows
 - Web resources
 - Enhancing transparency & reproducibility
 - Building communities of practice



Analytical Instruments





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Comp. Tools & Workflows



Chemical Database



Example NTA Research Demonstration



Tentatively Identified Chemicals

Analysis of Brita filter extracts via

Single surrogate selected and applied to all identified analytes

 Concentration estimates can be above or below true value.

Prediction intervals used to bound concentration estimates.

 95% prediction intervals shown; Can use 99%, 99.9%, etc.

Tentatively identified compounds ranked by upper-bound estimates.

Upper-bound estimates compared to level-of-interest to set priorities.

Modeling

- Ultimate application and integration of computational exposure elements
- Approach is Systematic Empirical Evaluation of Models (SEEM); NHANES biomonitoring key
- Uncertainty quantified and balanced with data inputs / model parametrization
- Exposure estimated for ten/hundreds of thousands chemicals – mostly data poor
- Toxicokinetics modeling is a key consideration allowing linkage between exposure estimates and in vitro bioactivity data

Mechanistic description of the built environment and exposure processes, including geospatial and temporal variability



Administered Equivalent Dose or



Ring *et al*. (2017)

Chemicals Monitored by CDC NHANES

Example Research



Standardized Database of Traditional Observations Across All Available Chemicals Open-Source Analysis Toolkit

- Exposure pathway(s), median intake rate, and credible interval for each of 687,359 chemicals with structures available from the CompTox Chemicals Dashboard are estimated (Ring et al. 2017)
 - 30% low probability for exposure via any of the four pathways
 - 95% confidence that the median intake rate is below 1 μg/kg BW/day for 474,572 compounds

Evaluate Model Performance and Refine NAMs

Estimate Uncertainty

ervations

SdO

aditional

Calibrate models

Apply calibration and estimated uncertainty to chemicals without traditional data

Available NAMs and Descriptors

Mechanistic / Statistical / Machine Learning Models for Prediction New Approach Methodologies and Chemical Structure-Derived Descriptors

Cross-Cutting

- Ensure methods and approaches produce results:
 - Accessible
 - Transparent
 - Reproducible
 - Inform health-protective risk assessment
 - Uncertainty & variability captured
 - Garners confidence

Need Image

Summary

- Computational exposure new approach methods critical to:
 - Protect public health & environment •
 - Keep pace with chemicals in commerce lacksquare
 - Protect habitable planet •
- Integrated elements to computational exposure
 - Chemical curation
 - Data development / non-targeted analysis •
 - Modeling lacksquare
 - Build confidence
- Delivering
 - Rapid exposure estimates at scale of chemicals in commerce
 - Data and model estimates that are transparent, accessible, • quantified uncertainty/variability
 - Integrated workflow with hazard for high throughput risk • estimation

Need Image

QUESTIONS / DISCUSSION

References

- Rockström J, Steffen W, Noone K, Persson A, Chapin FS 3rd, Lambin EF, Lenton TM, Scheffer M, Folke C, Schellnhuber HJ, Nykvist B, de Wit CA, Hughes T, van der Leeuw S, Rodhe H, Sörlin S, Snyder PK, Costanza R, Svedin U, Falkenmark M, Karlberg L, Corell RW, Fabry VJ, Hansen J, Walker B, Liverman D, Richardson K, Crutzen P, Foley JA. A safe operating space for humanity. Nature. 2009 Sep 24;461(7263):472-5. doi: 10.1038/461472a. PMID: 19779433.
- Cousins IT, Johansson JH, Salter ME, Sha B, Scheringer M. Outside the Safe Operating Space of a New Planetary Boundary for Per- and Polyfluoroalkyl Substances (PFAS). Environ Sci • Technol. 2022 Aug 16;56(16):11172-11179. doi: 10.1021/acs.est.2c02765. Epub 2022 Aug 2. PMID: 35916421; PMCID: PMC9387091.
- Persson L, Carney Almroth BM, Collins CD, Cornell S, de Wit CA, Diamond ML, Fantke P, Hassellöv M, MacLeod M, Ryberg MW, Søgaard Jørgensen P, Villarrubia-Gómez P, Wang Z, • Hauschild MZ. Outside the Safe Operating Space of the Planetary Boundary for Novel Entities. Environ Sci Technol. 2022 Feb 1;56(3):1510-1521. doi: 10.1021/acs.est.1c04158. Epub 2022 Jan 18. PMID: 35038861; PMCID: PMC8811958.
- Richman, T., Arnold, E. & Williams, A.J. Curation of a list of chemicals in biosolids from EPA National Sewage Sludge Surveys & Biennial Review Reports. Sci Data 9, 180 (2022). • https://doi.org/10.1038/s41597-022-01267-9
- Phillips, K. A., (2018). Suspect screening analysis of chemicals in consumer products. Environmental science & technology, 52(5), 3125-3135. ٠
- Lowe, Charles N., et al. "Chemical Characterization of Recycled Consumer Products Using Suspect Screening Analysis." Environmental science & technology 55.16 (2021): 11375-11387.
- Rager, Julia E., et al. "Review of the environmental prenatal exposome and its relationship to maternal and fetal health." Reproductive Toxicology 98 (2020): 1-12.
- ing, C. L., et al. (2018). Consensus modeling of median chemical intake for the US population based on predictions of exposure pathways. Environmental science & technology, 53(2), 719-732.
- Newton, Seth R., et al. "Suspect screening and non-targeted analysis of drinking water using point-of-use filters." Environmental pollution 234 (2018): 297-306. ٠