Defining the Cutting - Edge to the U.S. EPA ’s Computational Exposure Science

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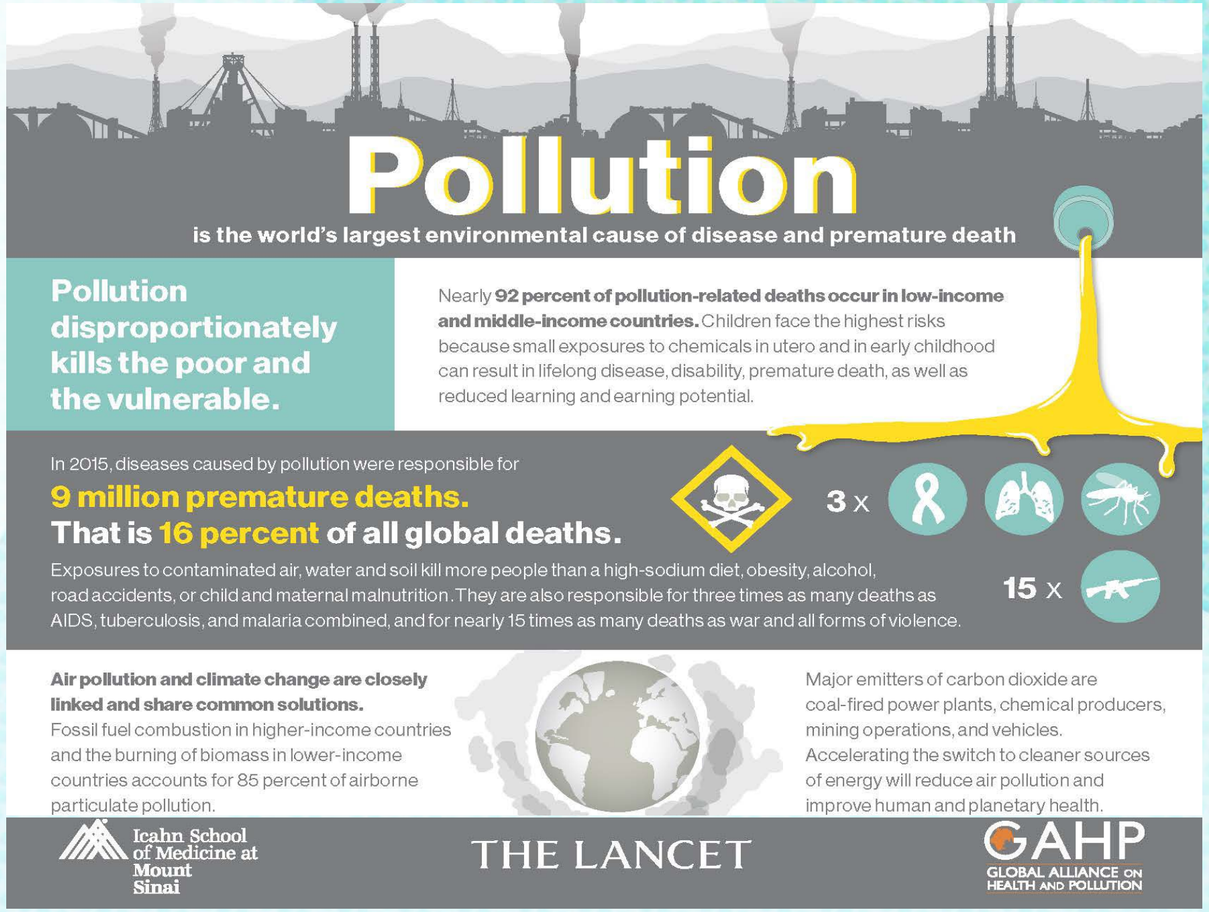
Motivation: Chemical Pollution is an Important Threat to Public Health

- Pollution is known to be a leading public health threat
- A large proportion of the environment-attributed 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



Source: Landrigan et al. 2017

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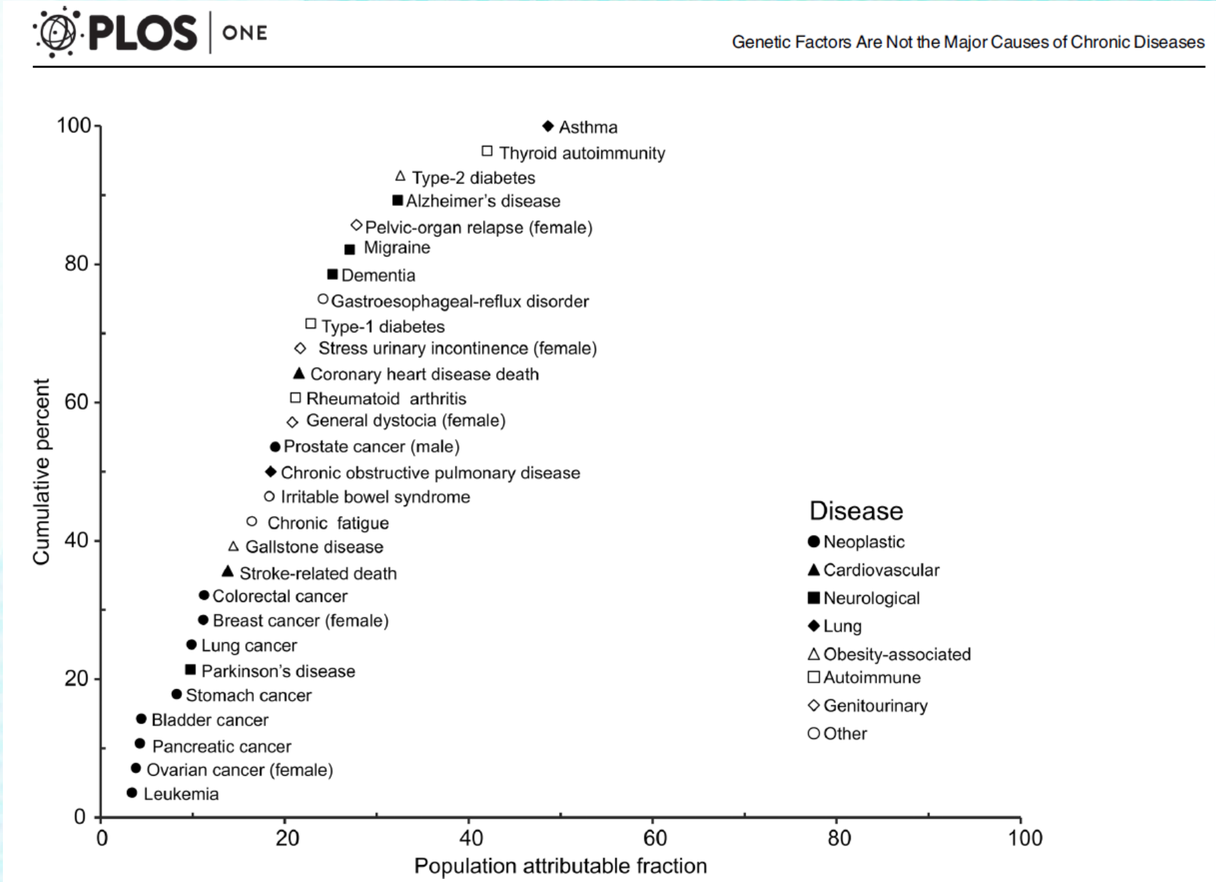

Fig 1. Population attributable fractions (PAFs) for 28 disease phenotypes estimated from studies of monozygotic twins. Sources of data and statistics are summarized in Table 2.

Source: Rappaport, 2016

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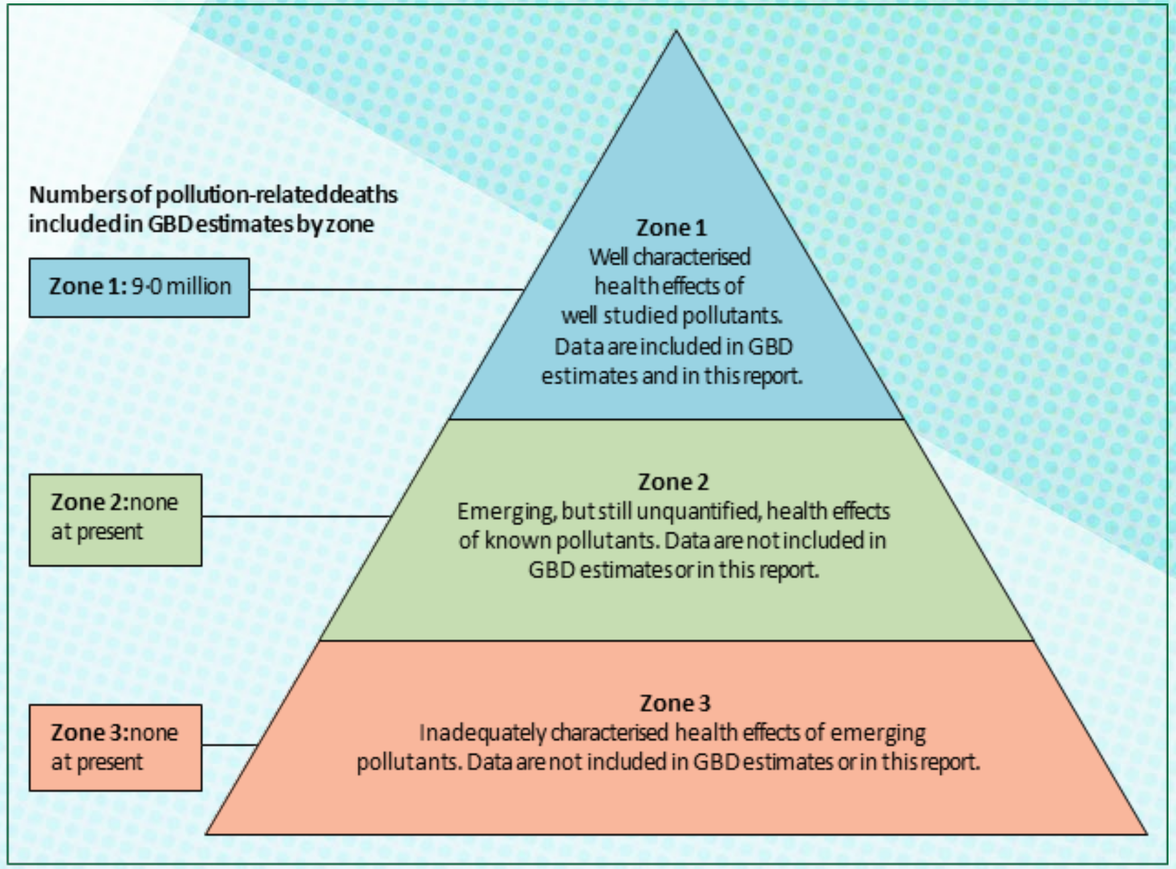


Figure 3: The pollutome

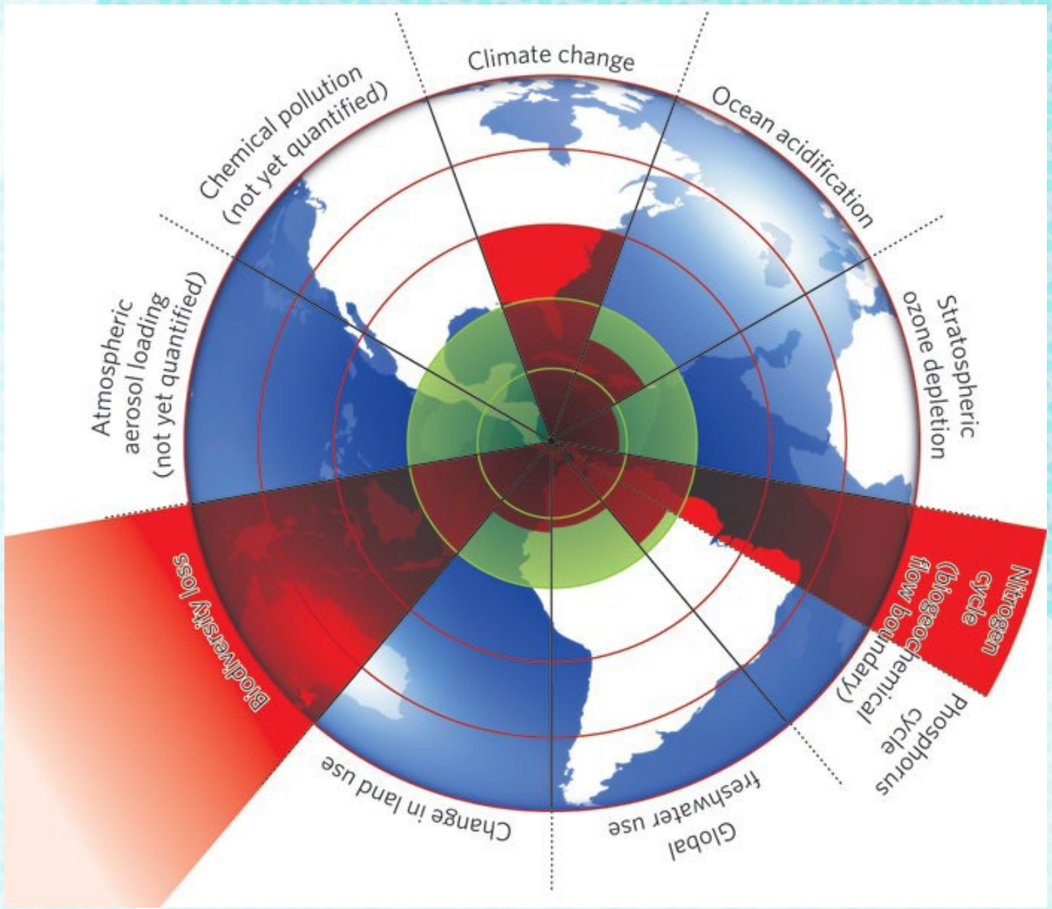
Source: Landrigan et al., 2017

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 (https://comptox.epa.gov/dashboard/chemical_lists/CPDA)
  - 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

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

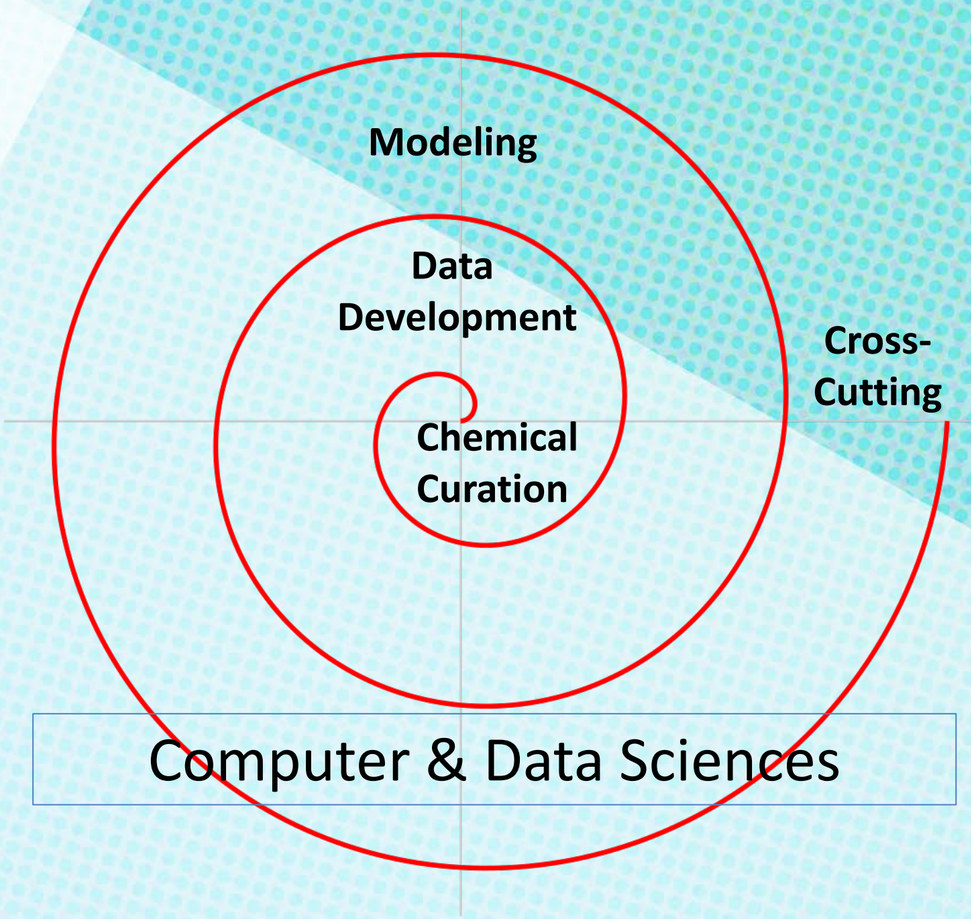
- Predictive
- Rapid
- High-throughput
- Results in closure of knowledge/time gap supporting risk management decisions

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

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.)

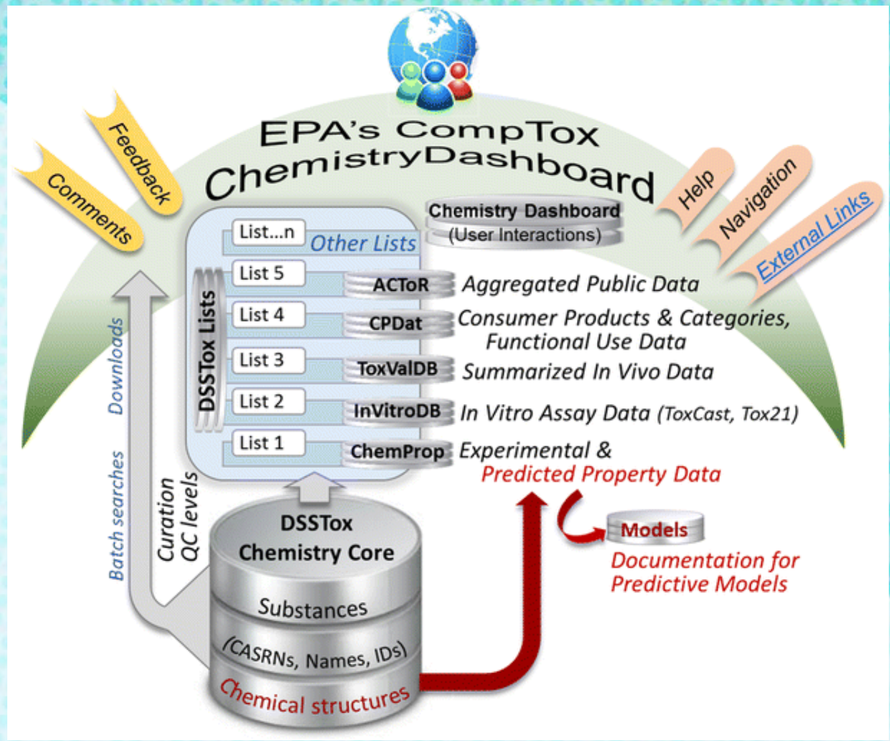
Computational Exposure Research Elements

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



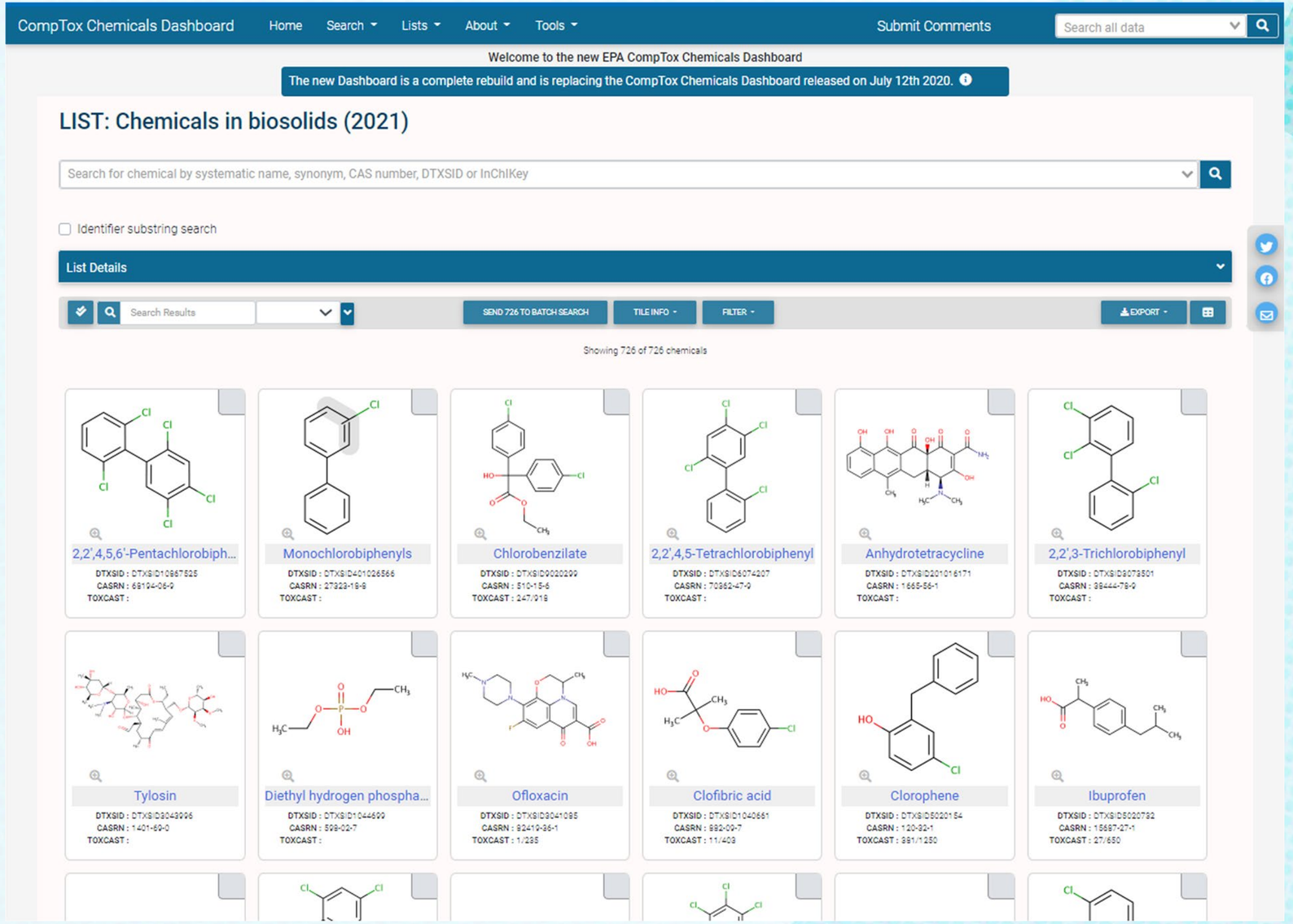
Chemical Curation

- 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

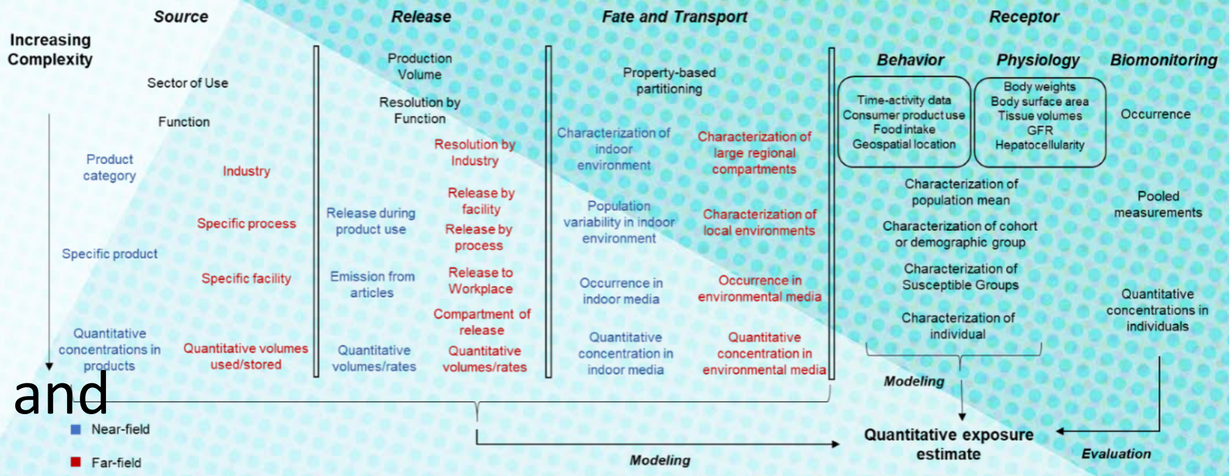


- Clarity of pollutants is relevant to Clean Water Act
- Important implications for human exposure & risk
- Replaces standalone biennial reports
- Provides context for interpreting risk
- List includes 726 chemicals / concentrations for 484

Richman et al. 2022

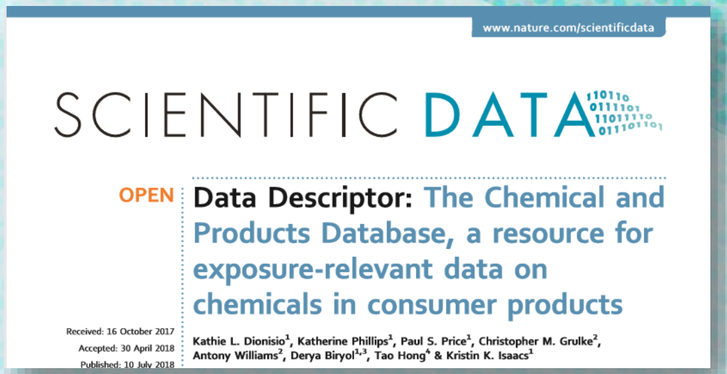
Data Development

- 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, and 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



#ISES2022LIBSON

Example Data Development Research Effort



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

Comp. Tools & Workflows

FOR IDENT

Xcms Online

MetFrag

Chemical Database

https://comptox.epa.gov/

BP4NTA
BENCHMARKING AND PUBLICATIONS FOR NON-TARGETED ANALYSIS

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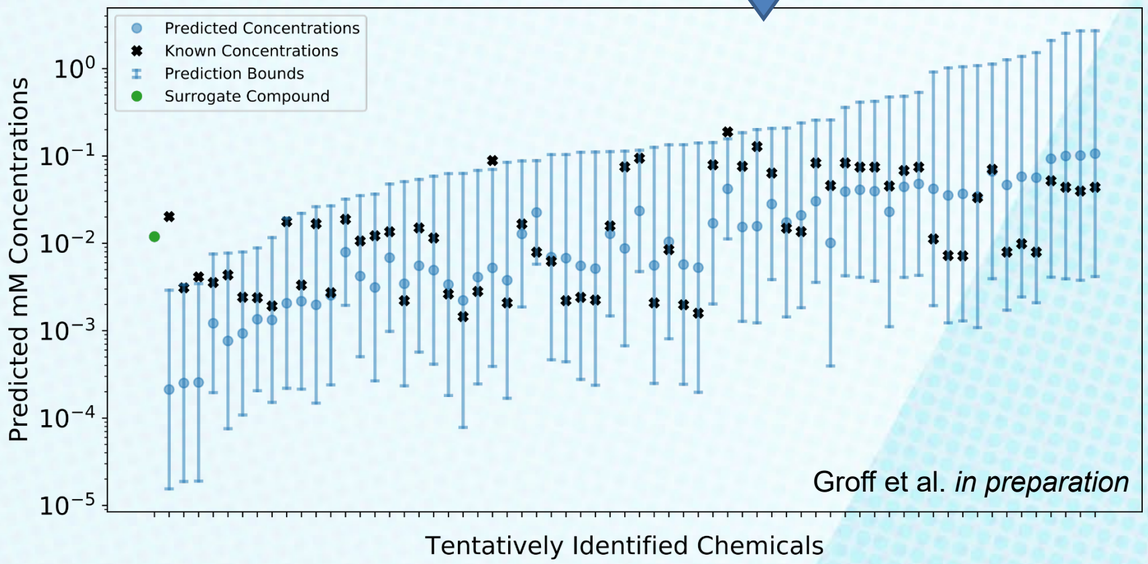
Example NTA Research Demonstration

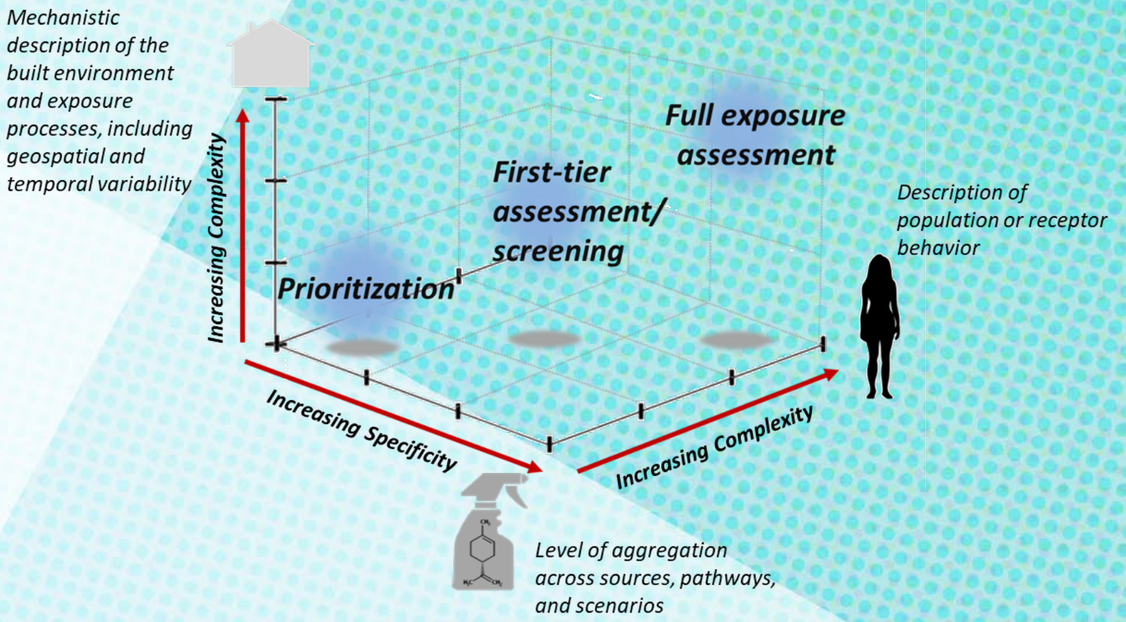
qNTA Proof-of-Concept

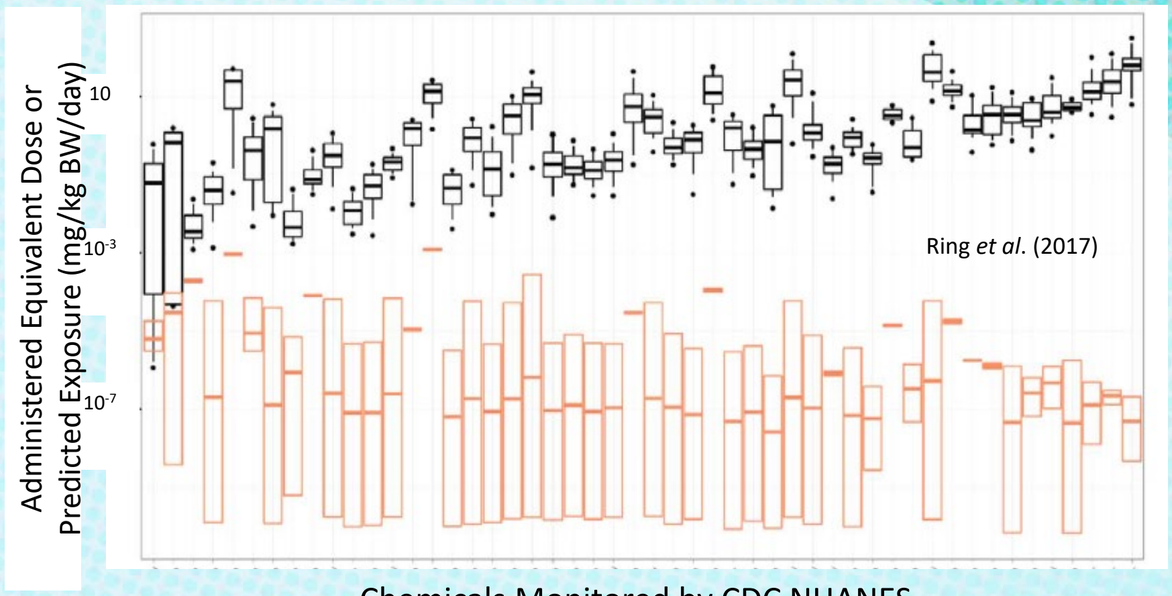


- Analysis of Brita filter extracts via GC-HRMS.
- Single surrogate selected and applied to all identified analytes
- Concentration estimates can be above or below true value.
- Prediction intervals used to bound concentration estimates.
- 95% prediction intervals shown; Can use 99%, 99.9%, etc.
- Tentatively identified compounds ranked by upper-bound estimates.
- Upper-bound estimates compared to level-of-interest to set priorities.

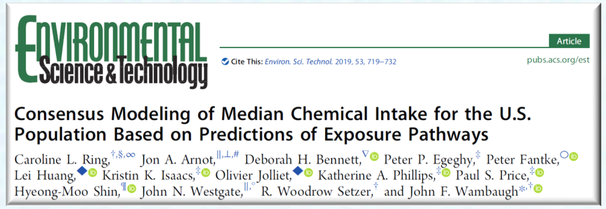
Modeling

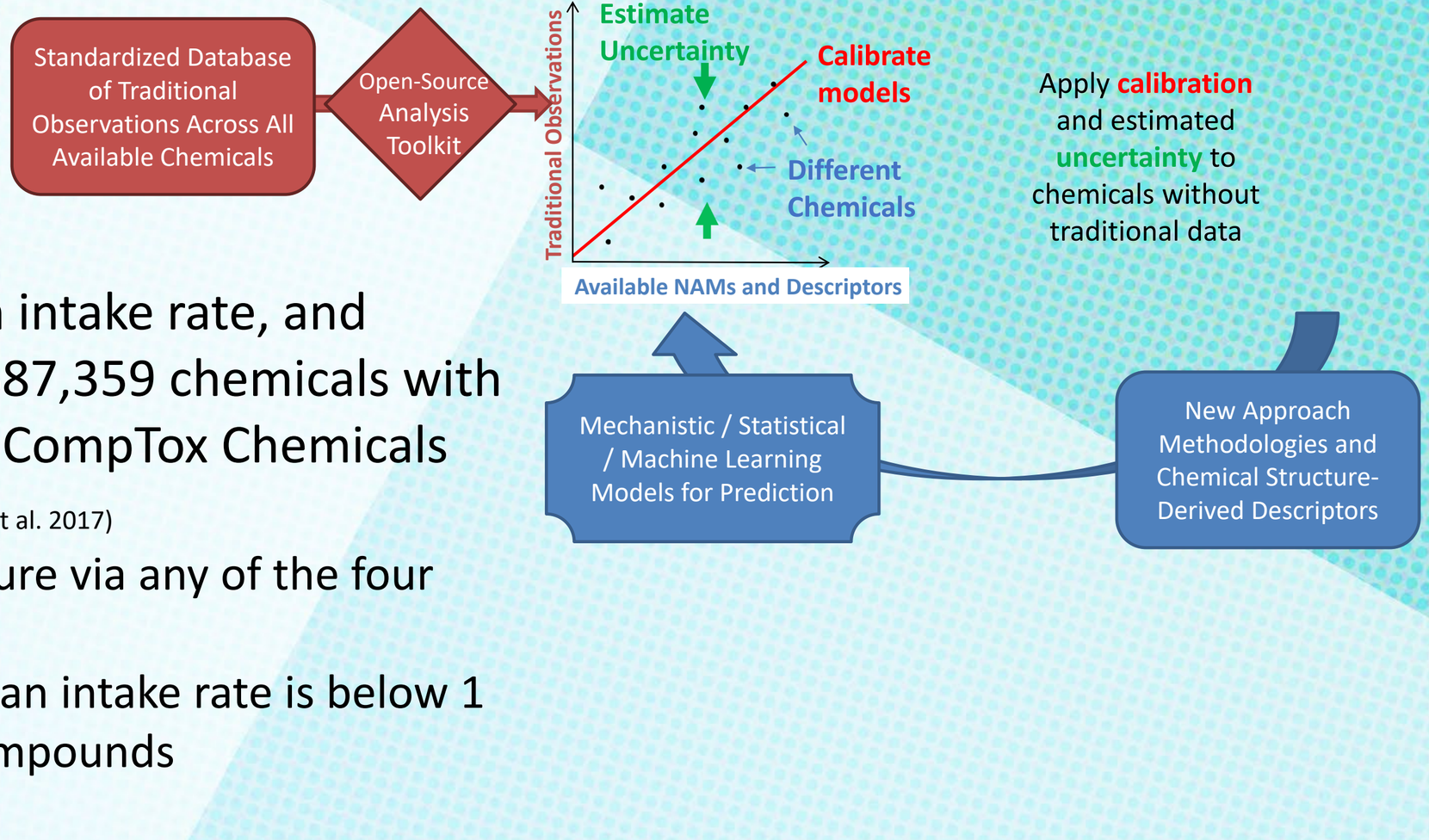
- Ultimate application and integration of computational exposure elements
- Approach is Systematic Empirical Evaluation of Models (SEEM); NHANES biomonitoring key
- Uncertainty quantified and balanced with data inputs / model parametrization
- Exposure estimated for ten/hundreds of thousands chemicals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





Example Research





- 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

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
  - Protect habitable planet
- Integrated elements to computational exposure
  - Chemical curation
  - Data development / non-targeted analysis
  - Modeling
  - 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

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QUESTIONS / DISCUSSION

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