United States
Environmental Protection
Agency

The Science of Exposure Assessment

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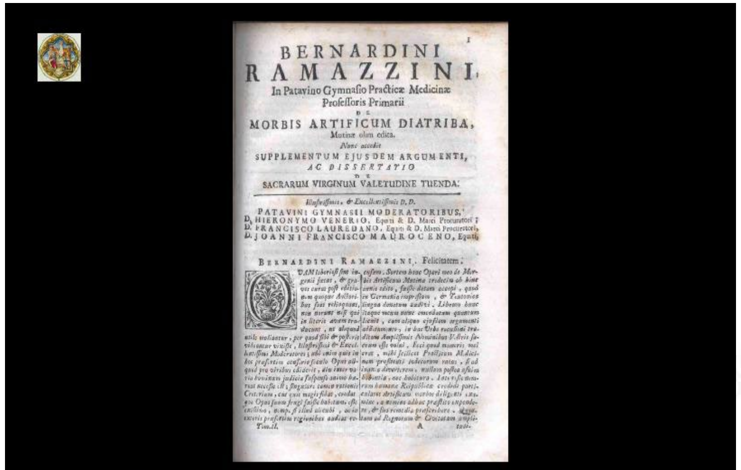
Dayton, OH

United States Environmental Protection Agency

Outline

- A view of historical evolution
- Responding to evolving complex environmental health problems
- Public health stakes
- Computational exposure science at the cutting edge

Exposure Science’s Historical Context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RAMAZZINI,
In Patavino Gymnasio Practicæ Medicinæ
Professoris Primarii
DE
MORBIS ARTIFICUM DIATRIBA,
Mutinæ olim edita.
Nunc accedit
SUPPLEMENTUM EJUSDEM ARGUMENTI,
AC DISSERTATIO
DE
SACRARUM VIRGINUM VALETUDINE TUENDA.

PATAVINI GYMNASII MODERATORIBUS,
D. HIERONYMO VENERIO, Equiti & D. Marci Procuratori;
D. FRANCISCO LAUREDANO, Equiti & D. Marci Procuratori,
D. JOANNI FRANCISCO MAUROCENO, Equiti,

BERNARDINI RAMAZZINI, Felicitatem.

Pagina iniziale del “De Morbis Artificum Diatriba”
In: Opera Omnia, Paulum et Isaacum Vaillant, Londra, 1739

Bernardino Ramazzini, 1633 - 1714

De Morbis Artificum Diatriba, 1700 (The Diseases of Workers) – the first comprehensive book on industrial medicine establishing occupation and disease links

Alice Hamilton (1869 – 1970)

- First major champion of occupational health in the United States
- Pioneer of occupational health, safety and industrial hygiene.
- Developed the specialized field of industrial hygiene in the USA
- Discovered more than seventy industrial processes where workers suffered lead exposure/poisoning

Percival Pott – 1761

- Noted high incidence of scrotal cancers in chimney sweeps
- Linked cancer to soot
- One of the first recorded connections between occupational exposures and cancer.
- Lead to Chimney Sweepers Act of 1788

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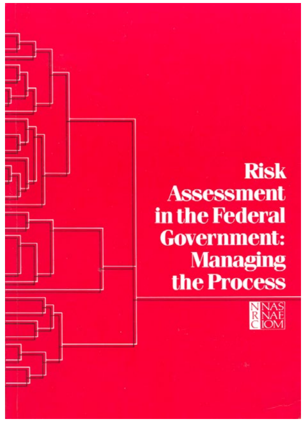
Exposure Science Branches from Industrial Hygiene



- 1983/91 -- NAS Reports

- 1979 – 85 TEAM Observational Studies

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[1]

LANCE A. WALLACE

RD-680 U.S. Environmental Protection Agency, 401 M Street, SW, Washington, D.C. 20460

AND

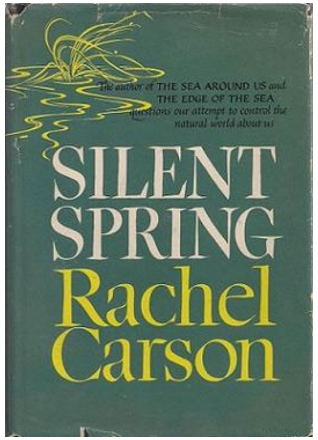
EDO D. PELLIZZARI, TYLER D. HARTWELL, CHARLES SPARACINO, ROY WHITMORE, LINDA SHELDON, HARVEY ZELON, AND REBECCA PERRITT

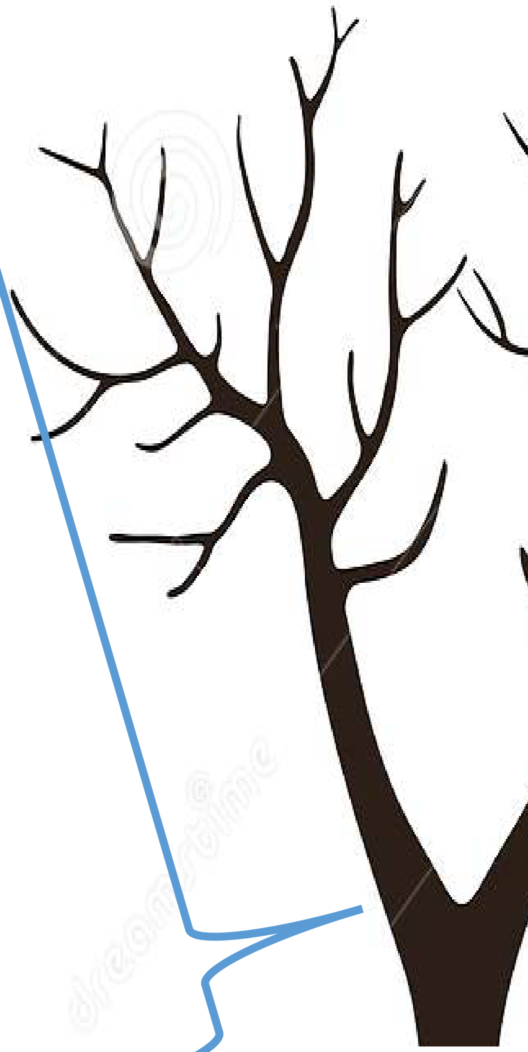
Research Triangle Institute, Research Triangle Park, North Carolina 27709

Received July 25, 1986

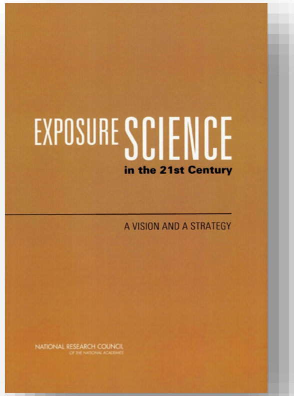
- 1970 -- EPA created

- 1962 -- Silent Spring published





Becoming a Distinct Science



- NAS 2012 Exposure Science in the 21st Century
- 2005 – Exposome Introduced

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

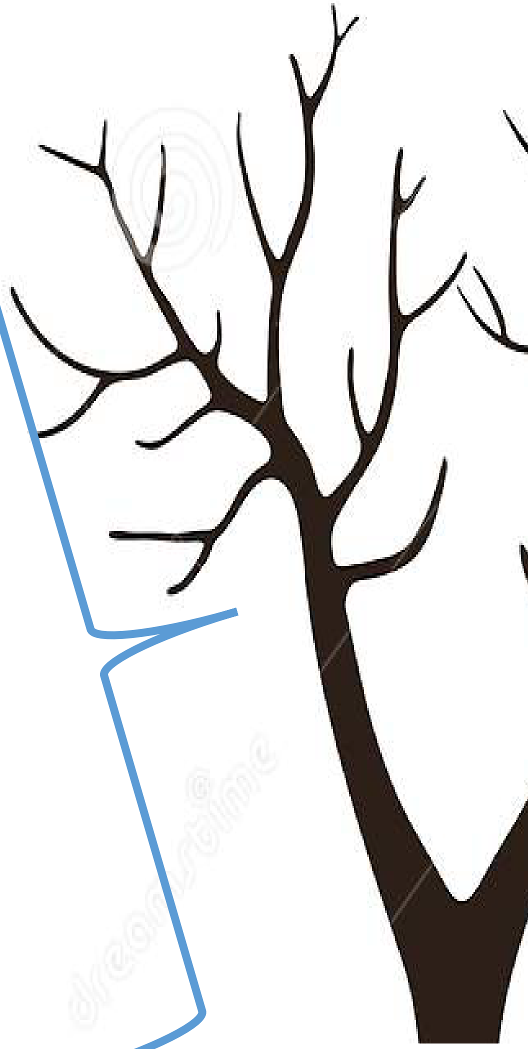
Complementing the Genome with an "Exposome": The Outstanding Challenge of Environmental Exposure Measurement in Molecular Epidemiology

Christopher Paul Wild

Cancer Epidemiol Biomarkers Prev 2005;14:1847-1850.

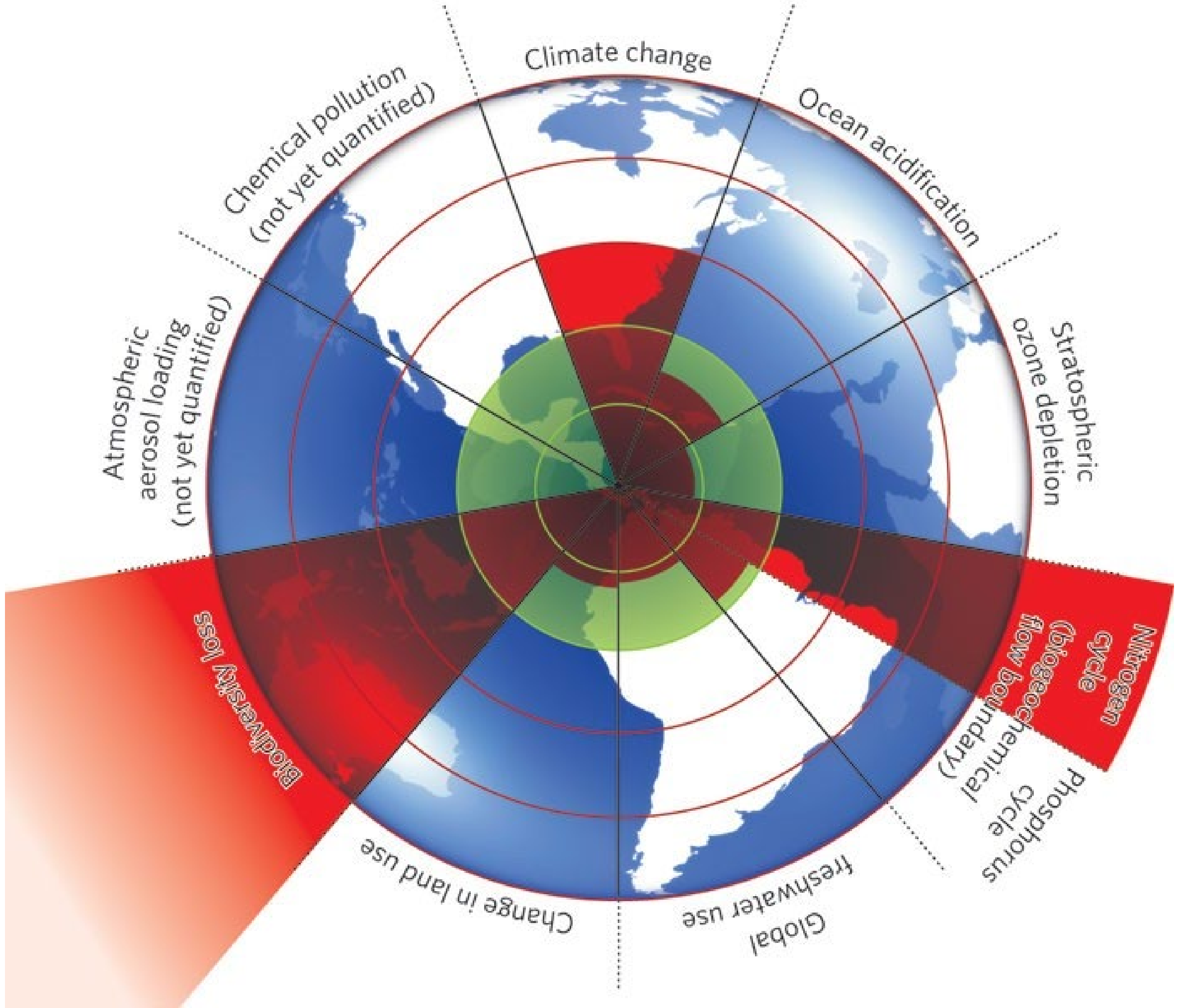
- 1990 – ISEA/ISES Founded

INTERNATIONAL SOCIETY OF ISES EXPOSURE SCIENCE



Growing Demand on Exposure Science to Help Address Expanding and Wicked Environmental Heath Challenges

- Climate change
- Population pressure on ecosystem services
- Environmental justice
- Urbanization
- Natural resource depletion
- Loss of biodiversity
- Chemical contaminants
- Habitable planet
- Infectious disease pandemics

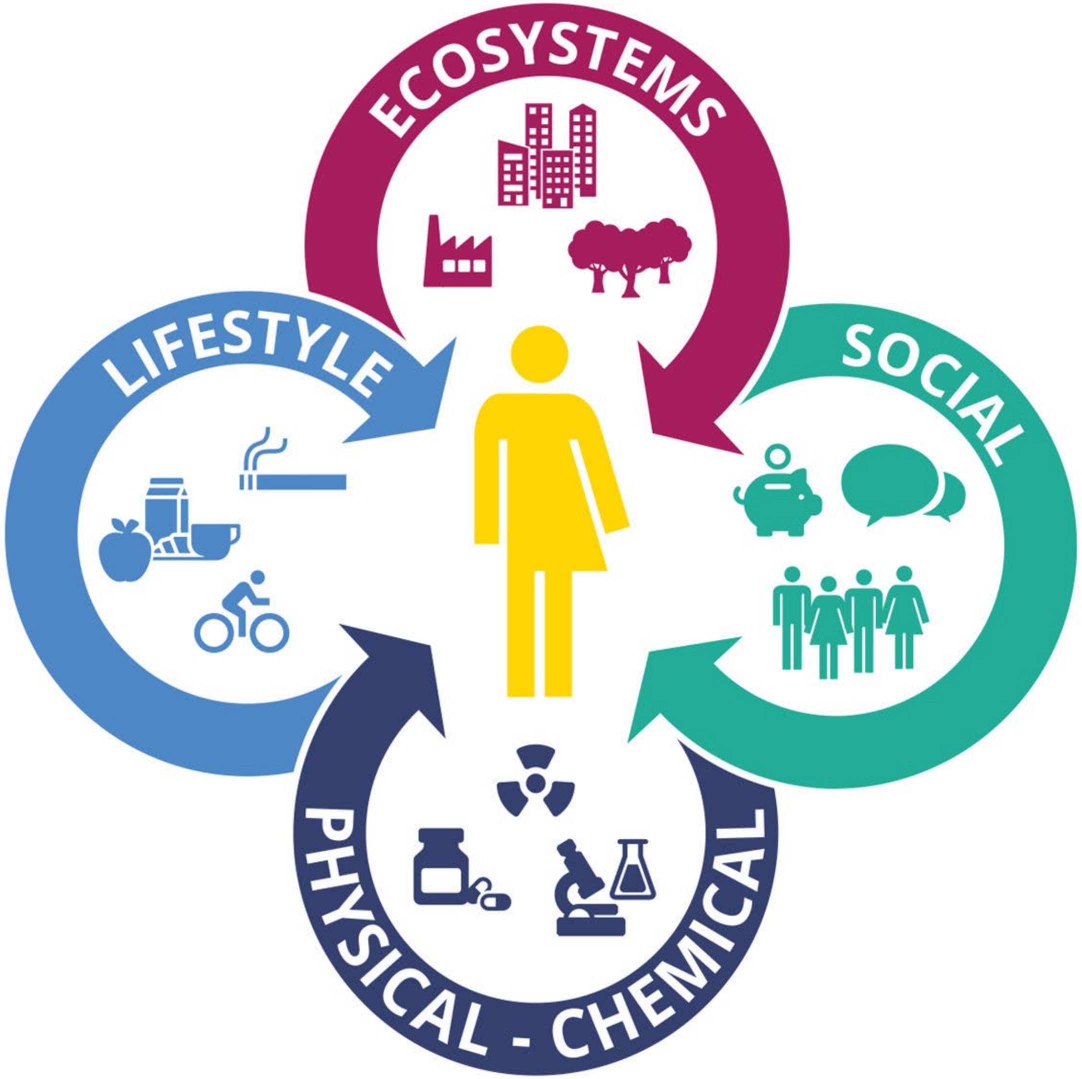


Source: Rockstrom et al., 2009

Exposure Science's Expanding Scope/Complexity

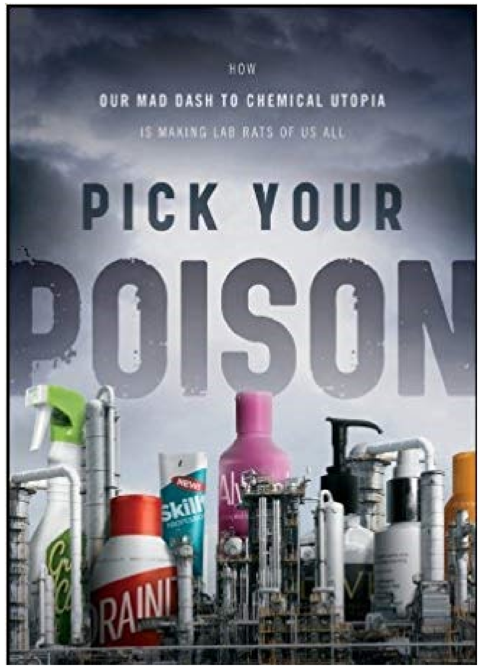
<u>Integral Sciences</u>

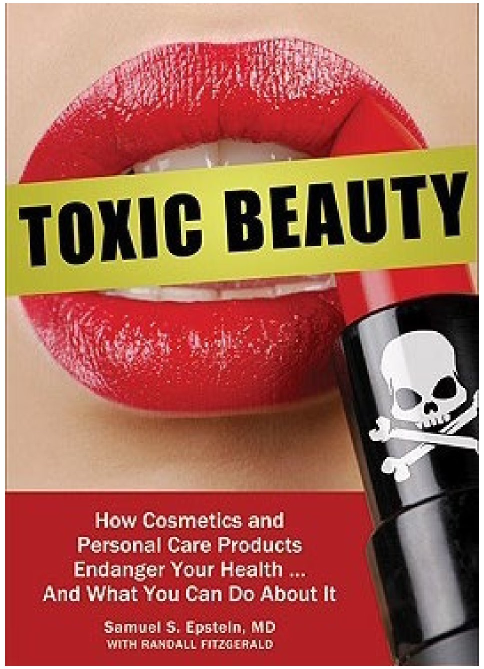
- Biological Sciences
- Ecological Sciences
- Social Sciences
- Chemistry
- Data Sciences
- Personalized Medicine
- Exposomics
- One Health
- Systems Science

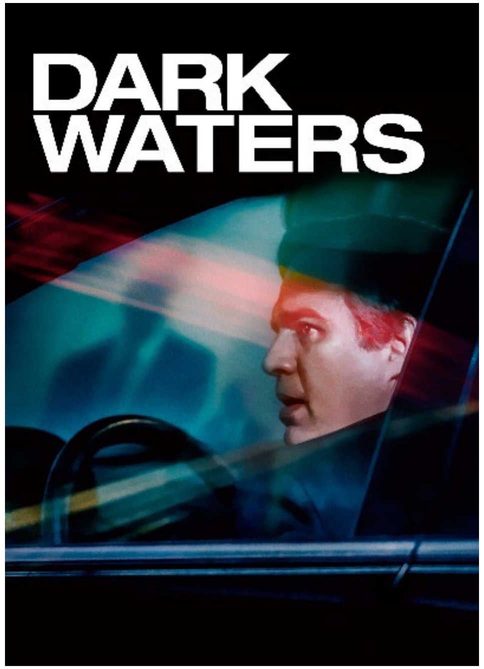


Source: Vermeulen et al., Science 2020

Case Example of Exposure Science and the Challenge of Chemical Exposure





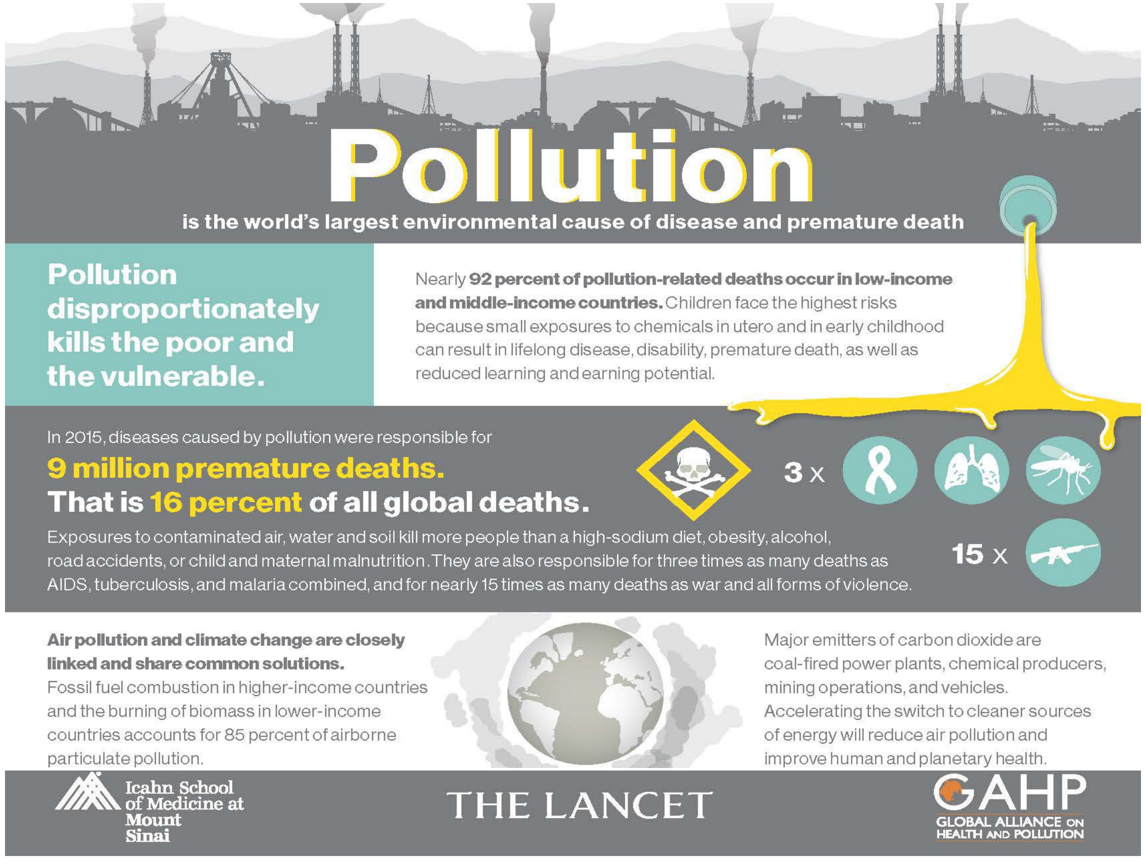


Computational Exposure Science Colleagues

Peter P. Egeghy
Ann M. Richard
Jon Sobus
Elin M. Ulrich
Kristin Isaacs
John Wambaugh
Caroline Ring
Risa R. Sayre
Antony J. Williams
Russell S. Thomas

Challenge: Chemical Pollution and Public Health

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



Source: Landrigan et al., 2017

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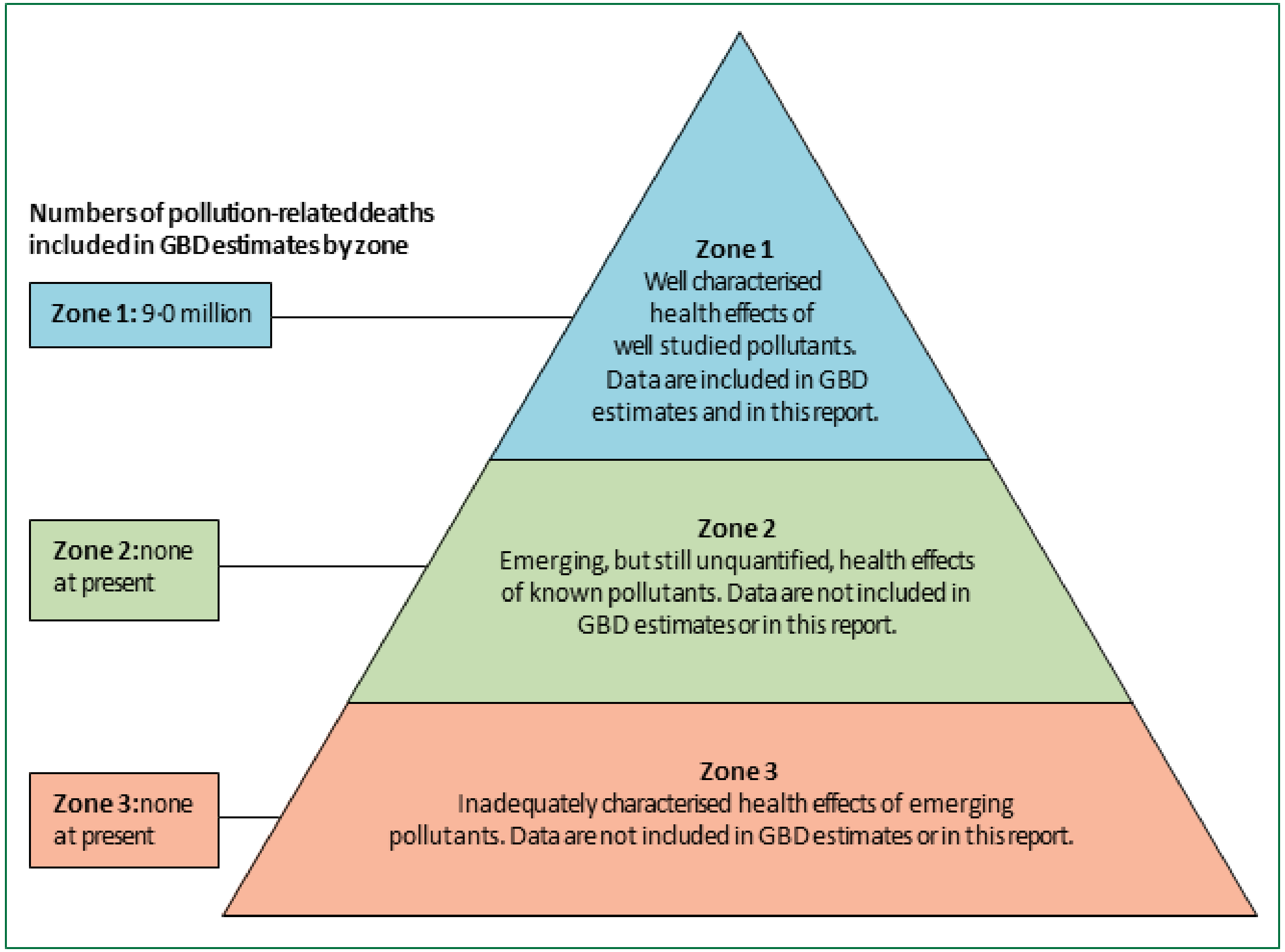

Figure 3: The pollutome

Source: Landrigan et al., 2017

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PLOS ONE — Genetic Factors Are Not the Major Causes of Chronic Diseases

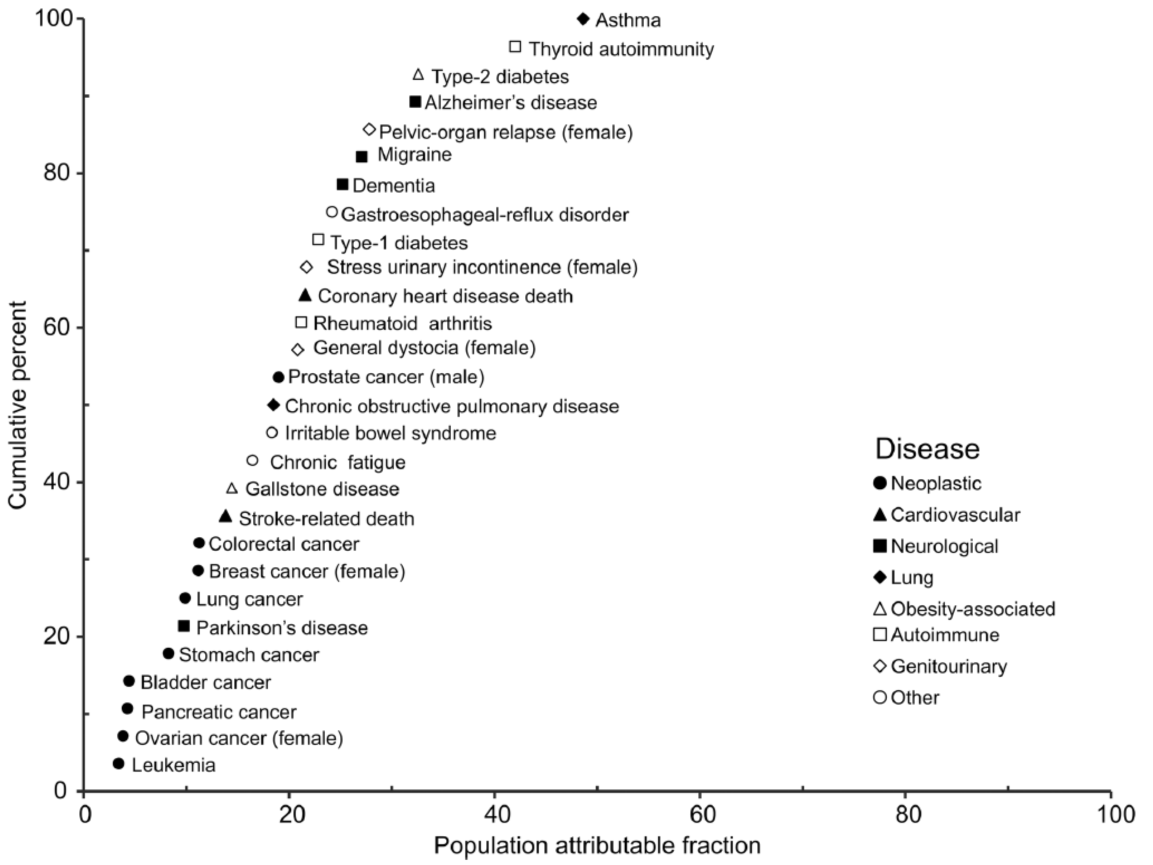

Fig 1. Population attributable fractions (PAFs) for 28 disease phenotypes estimated from studies of monozygotic twins. Sources of data and statistics are summarized in Table 2.

Source: Rappaport, 2016

Challenge: Managing the Enormous Number of Chemicals in Commerce

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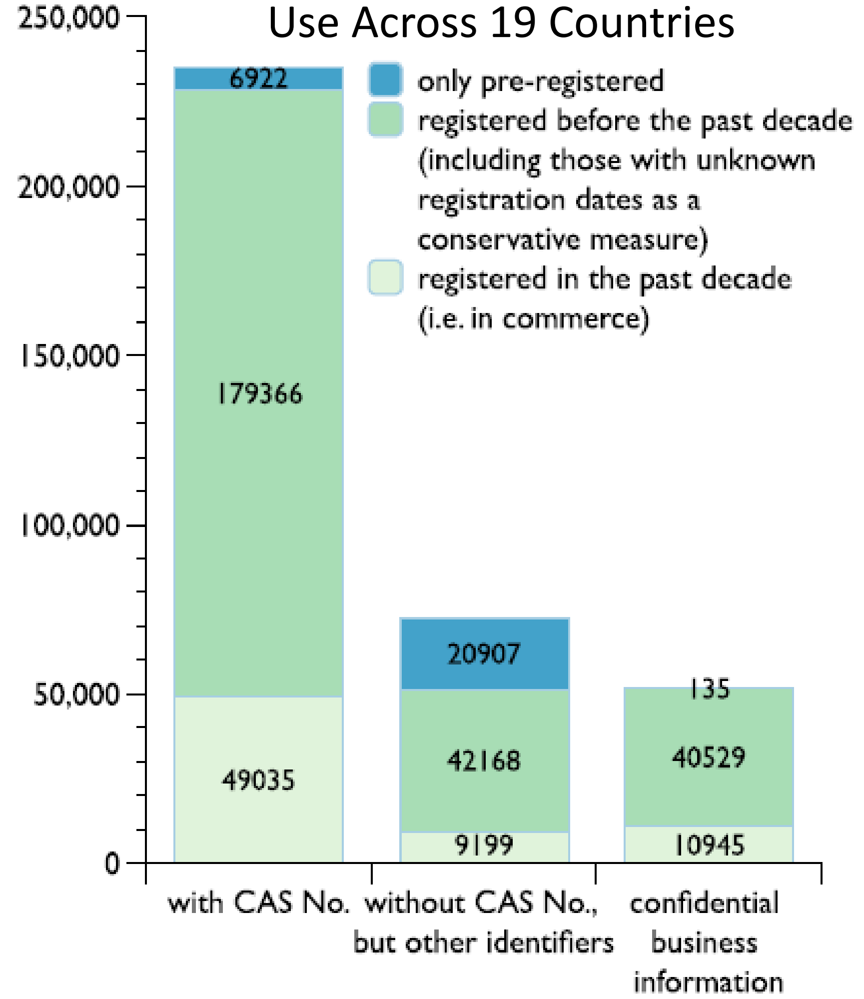
- A large proportion of the environment-attributed disease is of unknown etiology
- Effects likely underestimated
- Exposure and effects are poorly understood
- Chemical production and release to the environment vastly outpaces ability to test and measure
  - 350,000 chemicals and mixtures registered for production and use across 19 countries (Wang et al., 2020)
  - The EPA CompTox Chemicals 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 assessment approaches are needed

Chemicals Registered for Production and Use Across 19 Countries



Source: Wang et al. 2020

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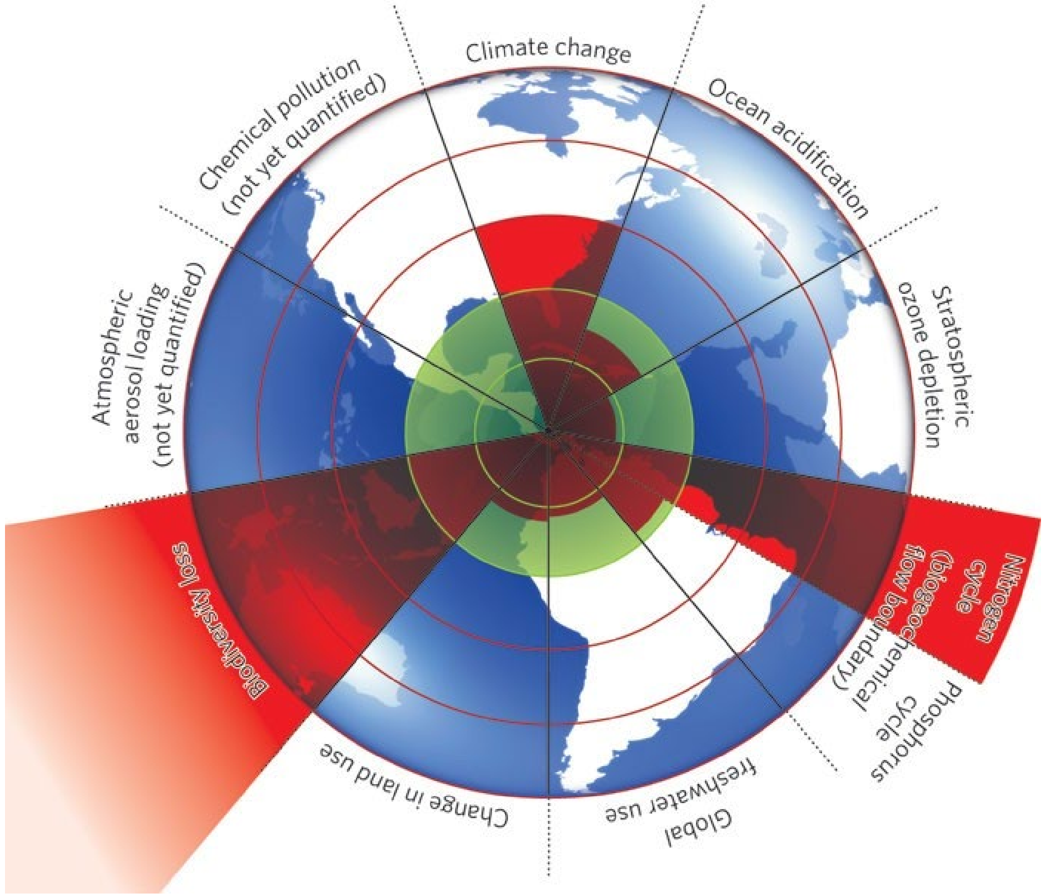
Challenge: Threat to a Habitable Planet

- Need 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)
- Sufficient evidence shows stresses on ecosystem and human health at local to global scales, suggesting that planetary boundary is being transgressed (Diamond et al., 2015)
- Production and releases of novel entities outstrips global capacity for assessment and monitoring (Persson et al., 2022; Cousins et al., 2022)

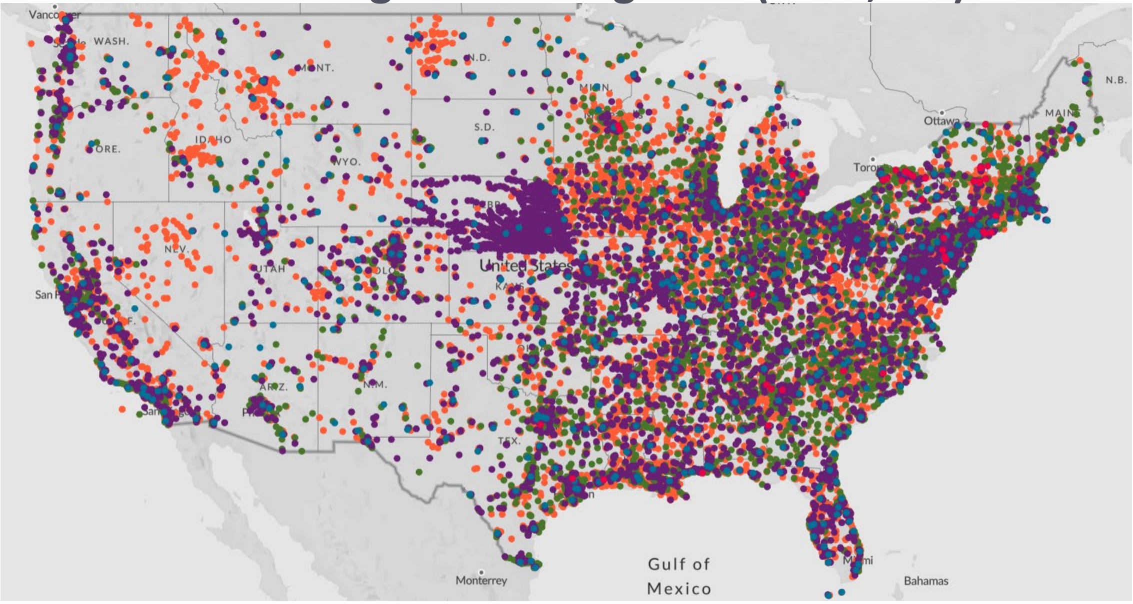


Source: Rockstrom et al., 2009

PFAS A Case-in-Point

- US Mortality Attributed to PFAS Exposure (Wen et al., EHP 2023)
  - Analysis based on NHANES 1999 – 2014; 7 PFAS measured in serum
  - Hazard Ratios for mortality:
    - All-cause -- 1.38 (95% CI: 1.07, 1.80)
    - Heart disease – 1.58 (95% CI: 1.05, 2.51)
    - Cancer – 1.70 (95% CI: 1.08, 2.84)
  - PFOS exposure associated annual mortality
    - 1999 – 2015: ~382,000
    - 2015 – 2018: ~69,000
    - Estimated total deaths >6 million
- Risk to threatened and endangered species
  - 120 unique PFAS found in over 330 species on every continent except Antarctica (Source: EWG; https://www.ewg.org/news-insights/news/2023/02/wildlife-warning-more-330-species-contaminated-forever-chemicals)

Sites known or suspected of making, using or releasing PFAS (n=41,828)



Different colors points represent PFAS known users; suspected users; airports previously required to use AFFF; landfills and waste disposal facilities'; and sewage and waste treatment plants.

Source: https://www.ewg.org/interactive-maps/2021_suspected_industrial_discharges_of_pfas/map/

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Strengthening Exposure Science

- Provide tools for exposure assessment that keep pace with chemicals in commerce including chemicals designated CBI;
- Make assessment dynamic reflecting dynamic changes in manufacturing, use, behavior, etc.;
- Better account for human behaviors and co-exposures; and
- Strengthen toxicokinetic modeling

Vandenberg *et al. Environmental Health* 2023, **21**(Suppl 1):121
https://doi.org/10.1186/s12940-022-00917-0

Environmental Health

REVIEW **Open Access**

Addressing systemic problems with exposure assessments to protect the public's health

Laura N. Vandenberg[1*], Swati D. G. Rayasam[2], Daniel A. Axelrad[3], Deborah H. Bennett[4], Phil Brown[5], Courtney C. Carignan[6], Nicholas Chartres[2], Miriam L. Diamond[7,8], Rashmi Joglekar[9,10], Bhavna Shamasunder[11], Kristin Shrader-Frechette[12,13], Wilma A. Subra[14], Ken Zarker[15^] and Tracey J. Woodruff[2]

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, 2012)
- 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. 2019)

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.)

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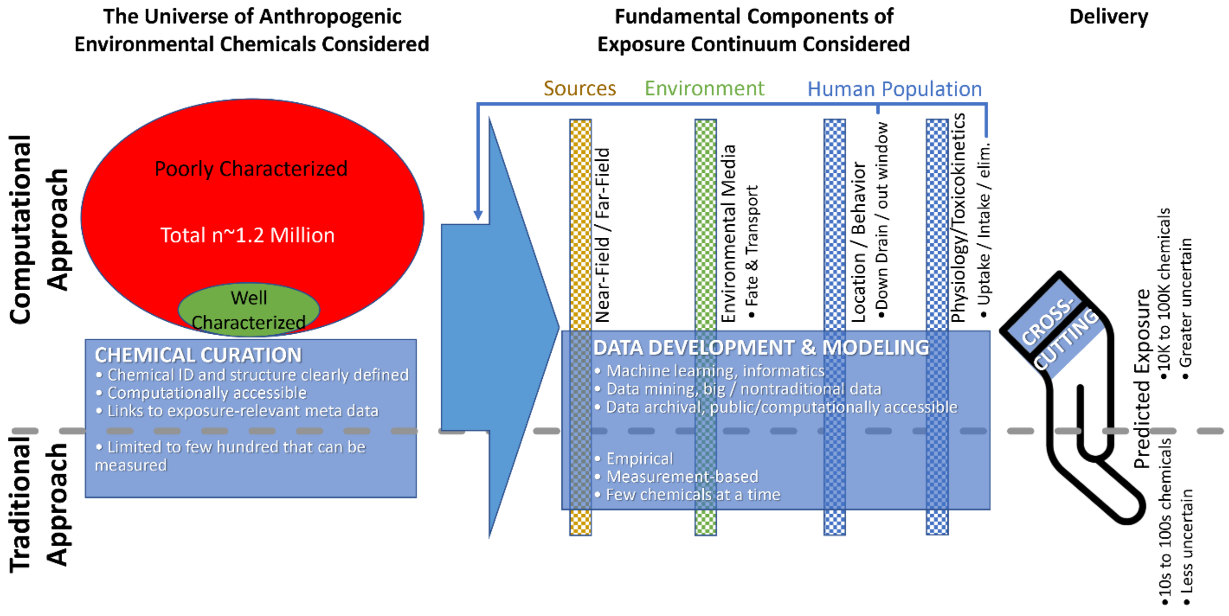
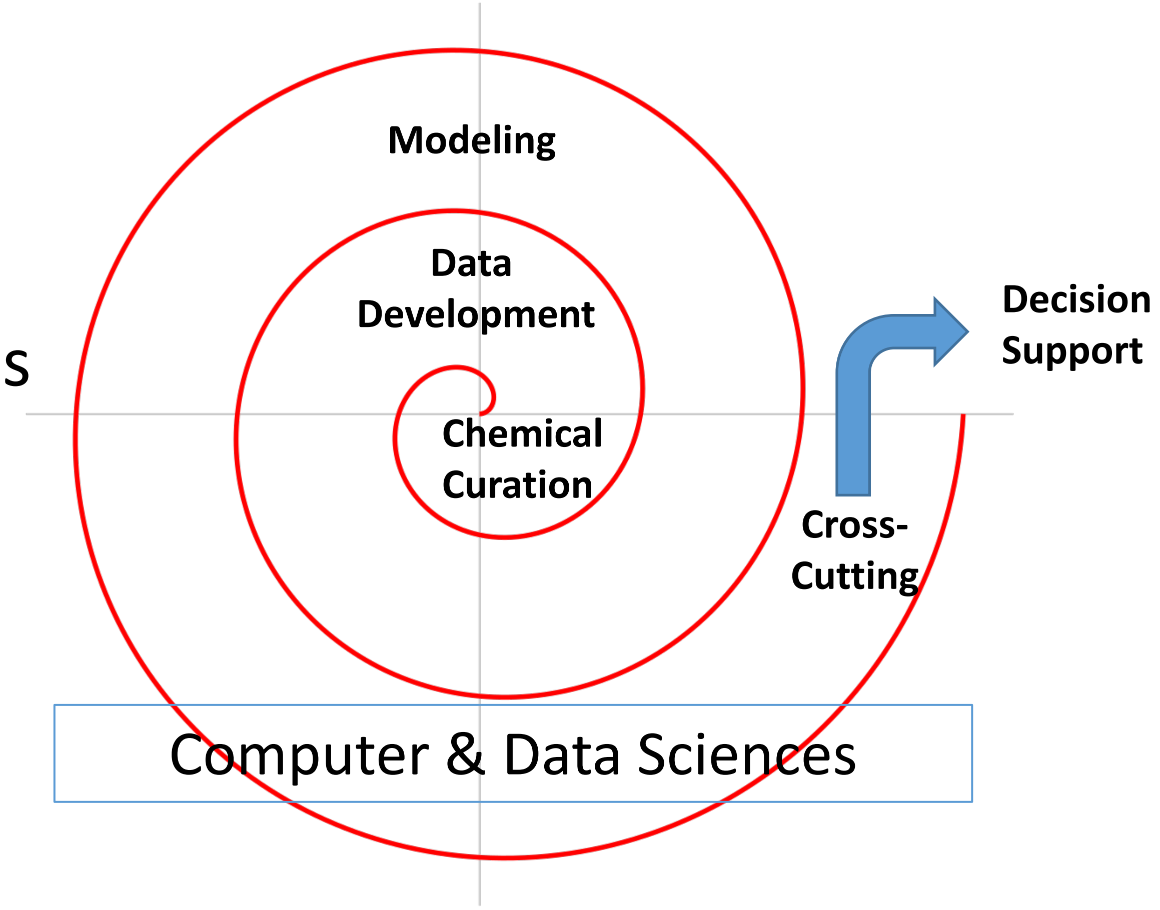


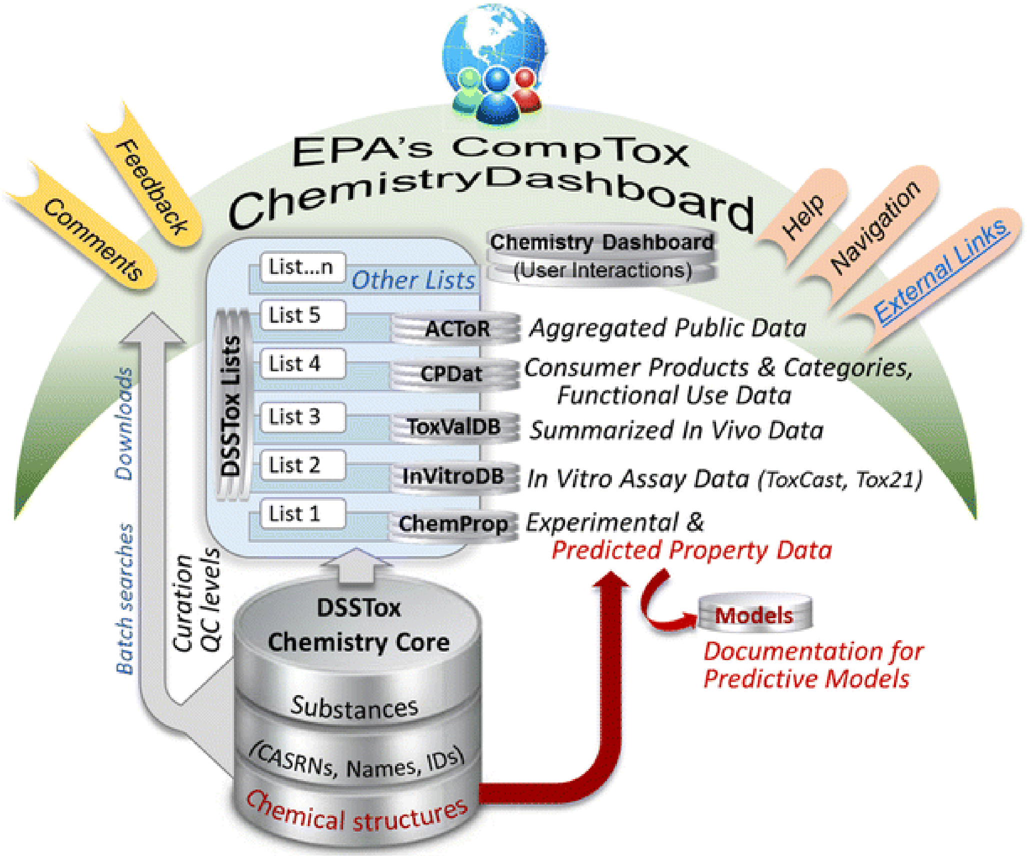
Computational Exposure Research Elements

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



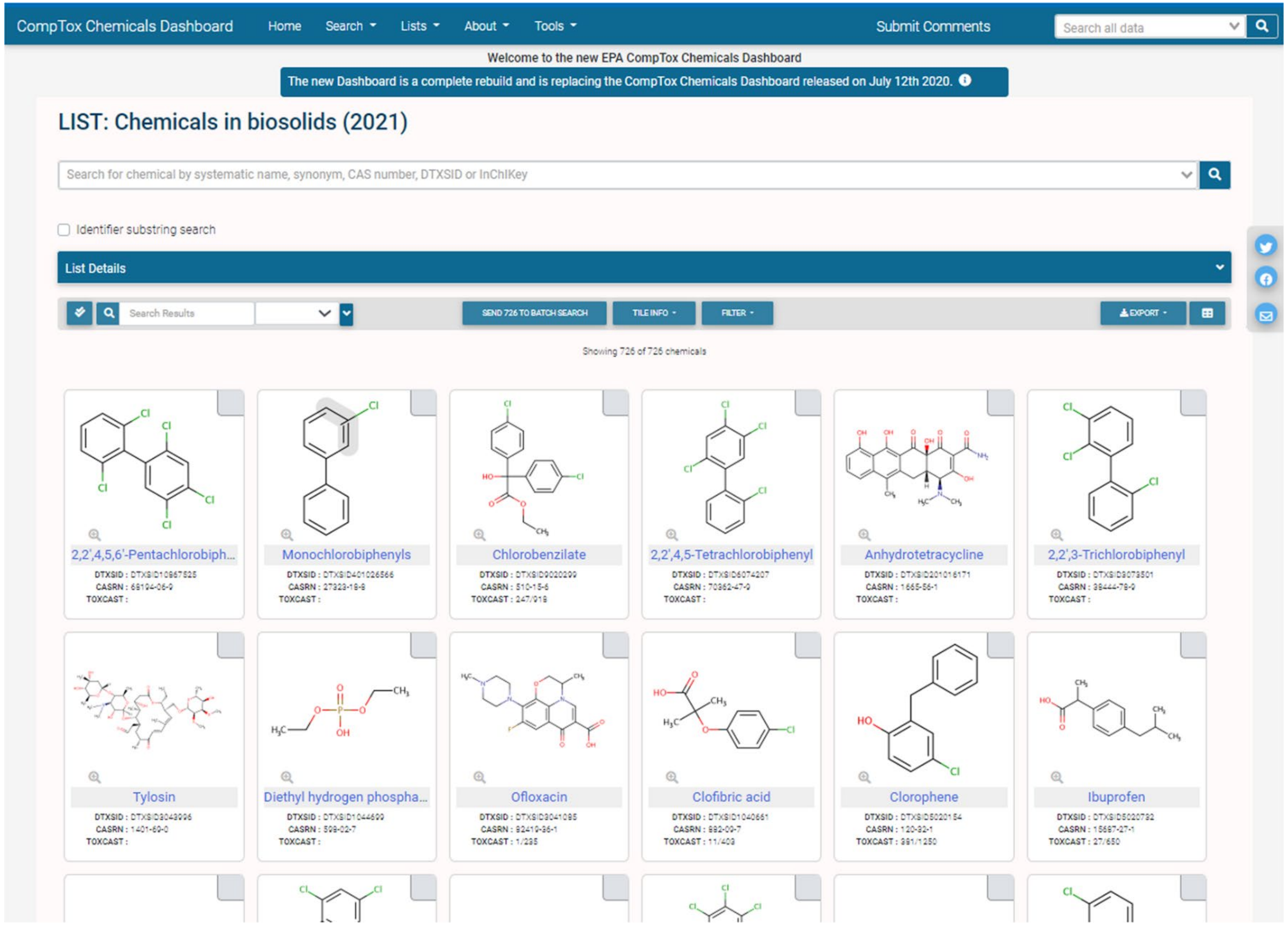
Chemical Curation

- Defining characteristics
  - Most comprehensive accounting of anthropogenic chemical landscape, i.e., 1.2 M chemicals
  - Chemical ID, structure, and meta data rigorously 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 ambiguously-defined substances
  - Continued expansion based on non-targeted analysis discovery



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

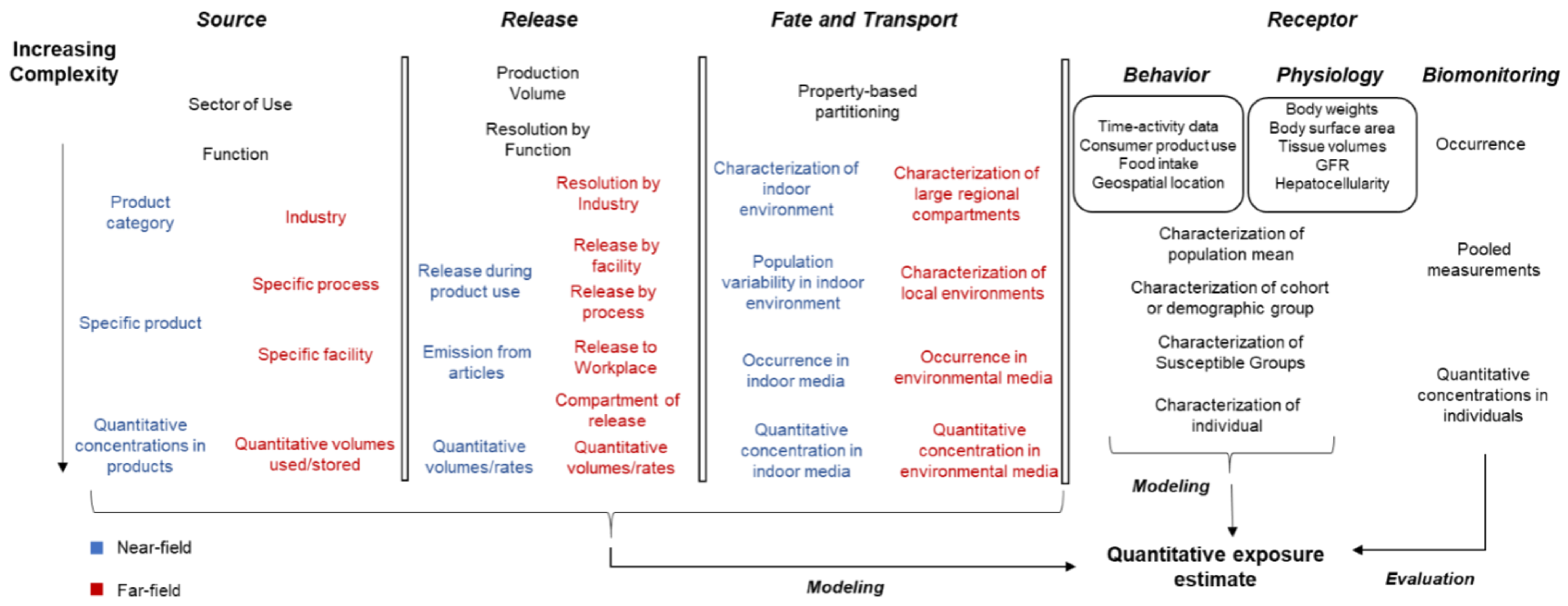
Research Example: Curation of Chemicals in Biosolids



- Clarity of candidate pollutants 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 Framework



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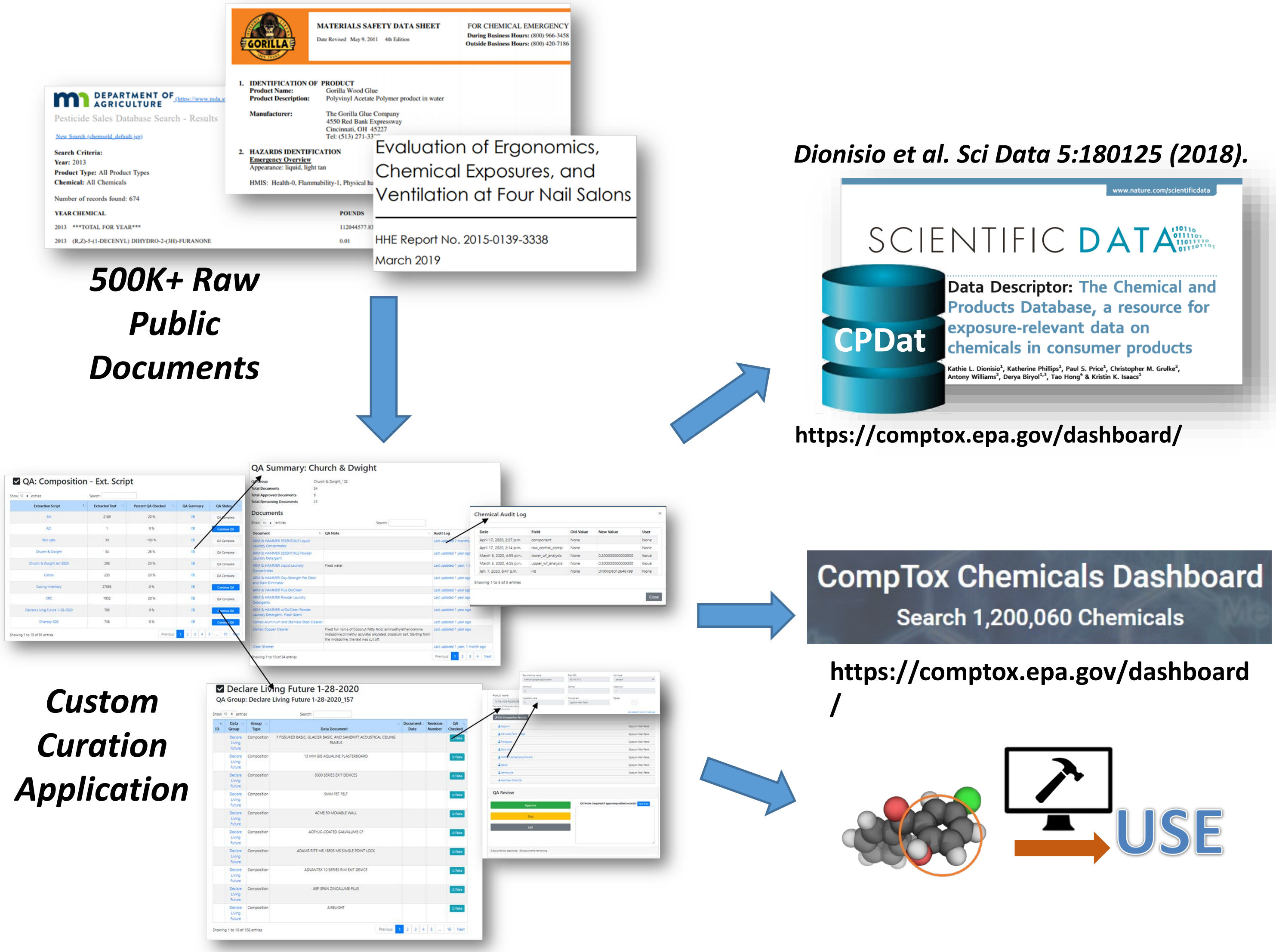
Data Development

- Exposure continuum provides framework
- Consistent with NAS guidance for organization, useability, and access
- Includes advanced
  - Informatics, data-mining, machine learning
  - Data infrastructure for collection, organizing, and integration
- Receptor oriented / near field data especially valuable
- Exposure Databases developed
  - ChemExpoDB , CPDat (Dionisio et al., 2018), MMDB (Isaacs et al., 2022), and CvTdb (Sayre et al., 2020)
- Future research to address occupational settings, chemicals in consumer articles

Example Data Development Research Effort

- Informatics approaches and a custom document management/curation application are being used to obtain and curate chemical use descriptor information from thousands of public documents
- Consumer product ingredient data (composition), functional use information, general chemical use keywords
  - **600K+ products**
  - **>35K unique chemicals**
  - **>45K functional use records (91 unique functions)**
- Extraction and curation of chemical and product data via reproducible script-based methods (including natural language processing) or manual tools
- QA/audit trail tools
- Data released to CompTox Chemicals Dashboard and in bulk as CPDat
- Data also forms basis for Quantitative Structure-Use Relationships (QSURs)



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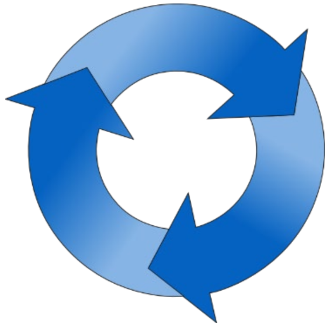
Non-Targeted Analysis (NTA)

- Identifies chemicals without *a priori* knowledge or standards
- Applications → source to dose
  - Source: household (& recycled products
  - Environmental: house dust & water filters
  - Dose: blood & placenta
- Research focused on obstacles to broad adoption (Ulrich et al., 2019)
  - Methods development
  - Workflows
  - Web resources
  - Enhancing transparency & reproducibility
  - Building communities of practice

Analytical Instruments



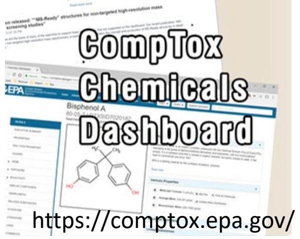
Comp. Tools & Workflows

CFM-ID
Competitive Fragmentation Modeling for Metabolite Identification

XCMS Online

MetFrag

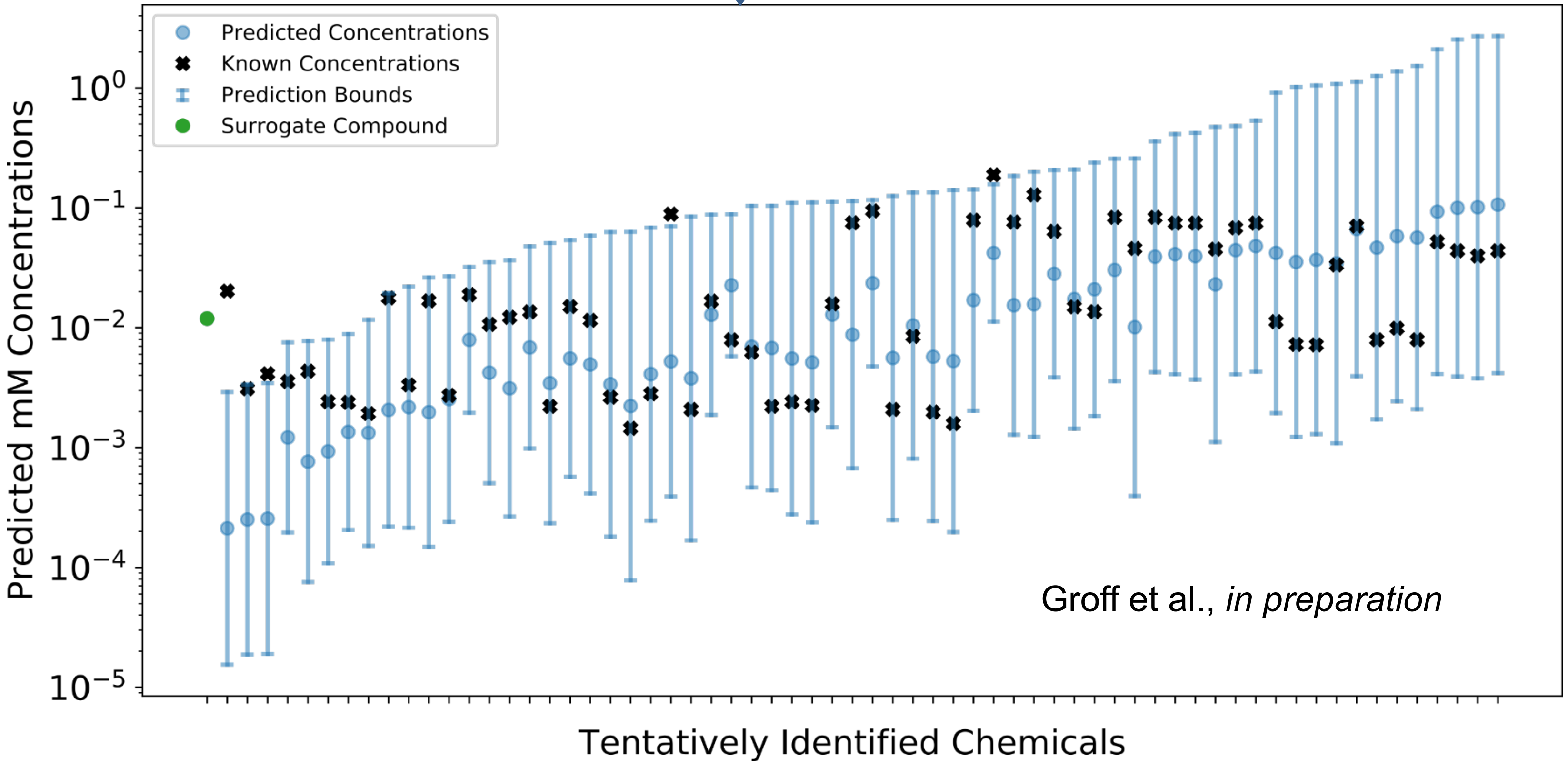
Chemical Database



BP4NTA
BENCHMARKING AND PUBLICATIONS FOR NON-TARGETED ANALYSIS

Example NTA Research

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
- % prediction intervals shown; Can use 95%, 99%, 99.9%, etc.
- Tentatively identified compounds ranked by upper-bound estimates
- Upper-bound estimates compared to level-of-interest to set priorities

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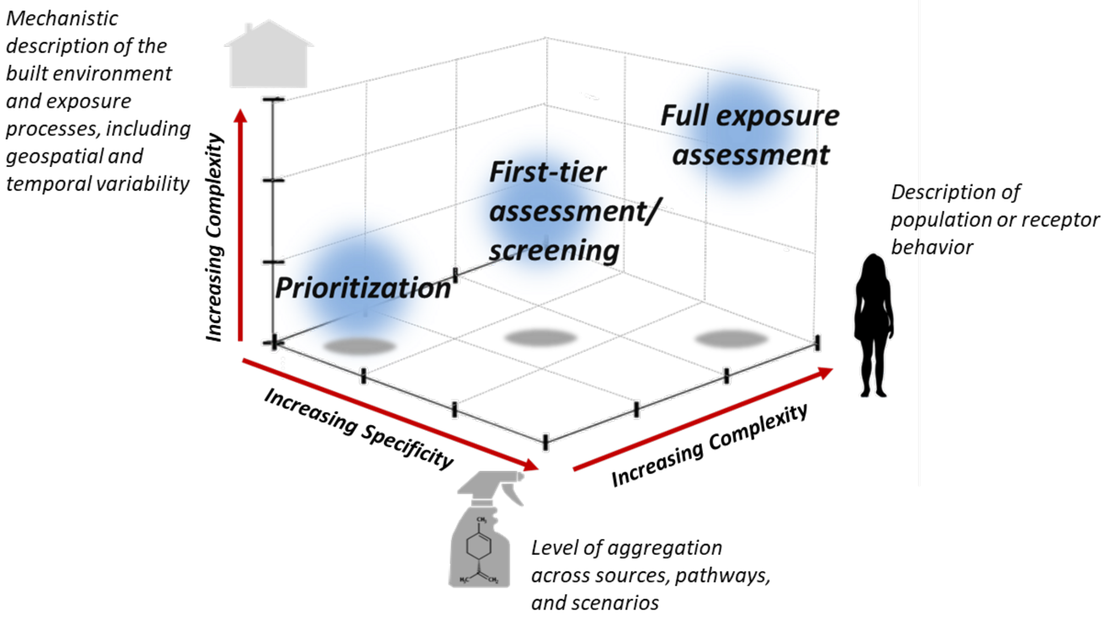
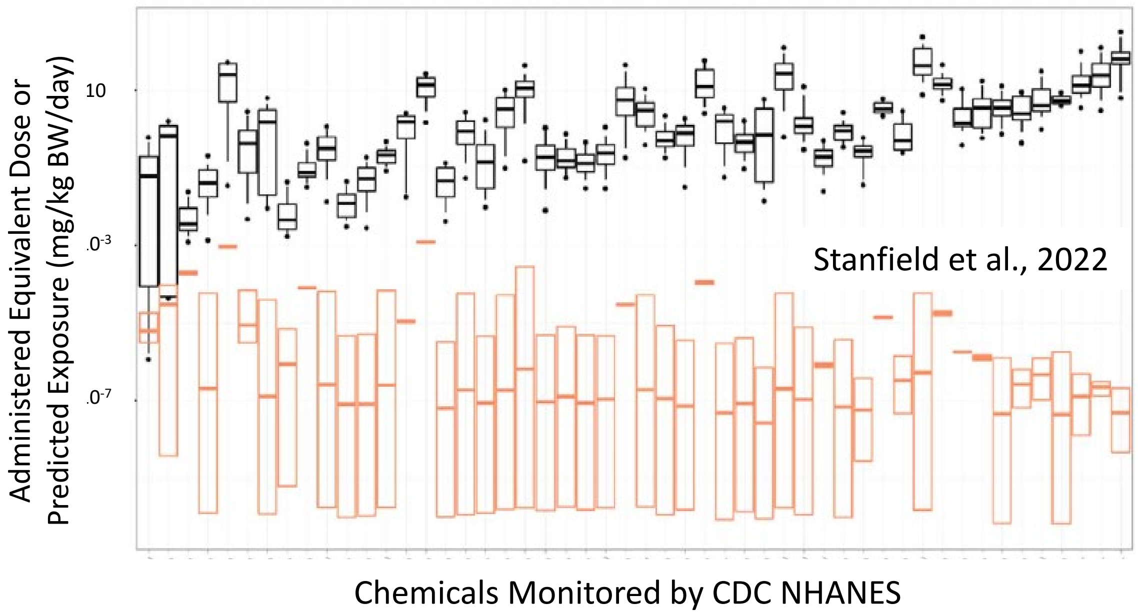
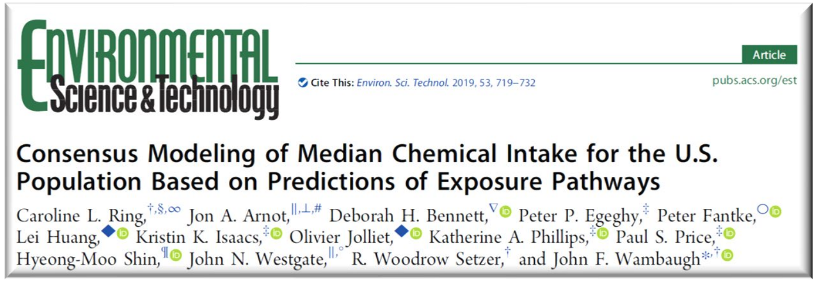
Modeling

- Source-to-receptor exposure modeling is the ultimate application and integration of computational exposure elements
- Systematic Empirical Evaluation of Models (SEEM) is a consensus modeling approach for intake rate (mg/kg/day) (Wambaugh et al., 2013)
- NHANES biomonitoring key: Uncertainty quantified and balanced with data inputs / model parameterization
- Intake rates have been estimated for hundreds of thousands chemicals – mostly data poor
- Complementary toxicokinetics modeling is a key consideration allowing linkage between exposure estimates and *in vitro* bioactivity data (Breen et al., 2021)





Example Research



Environmental Science & Technology

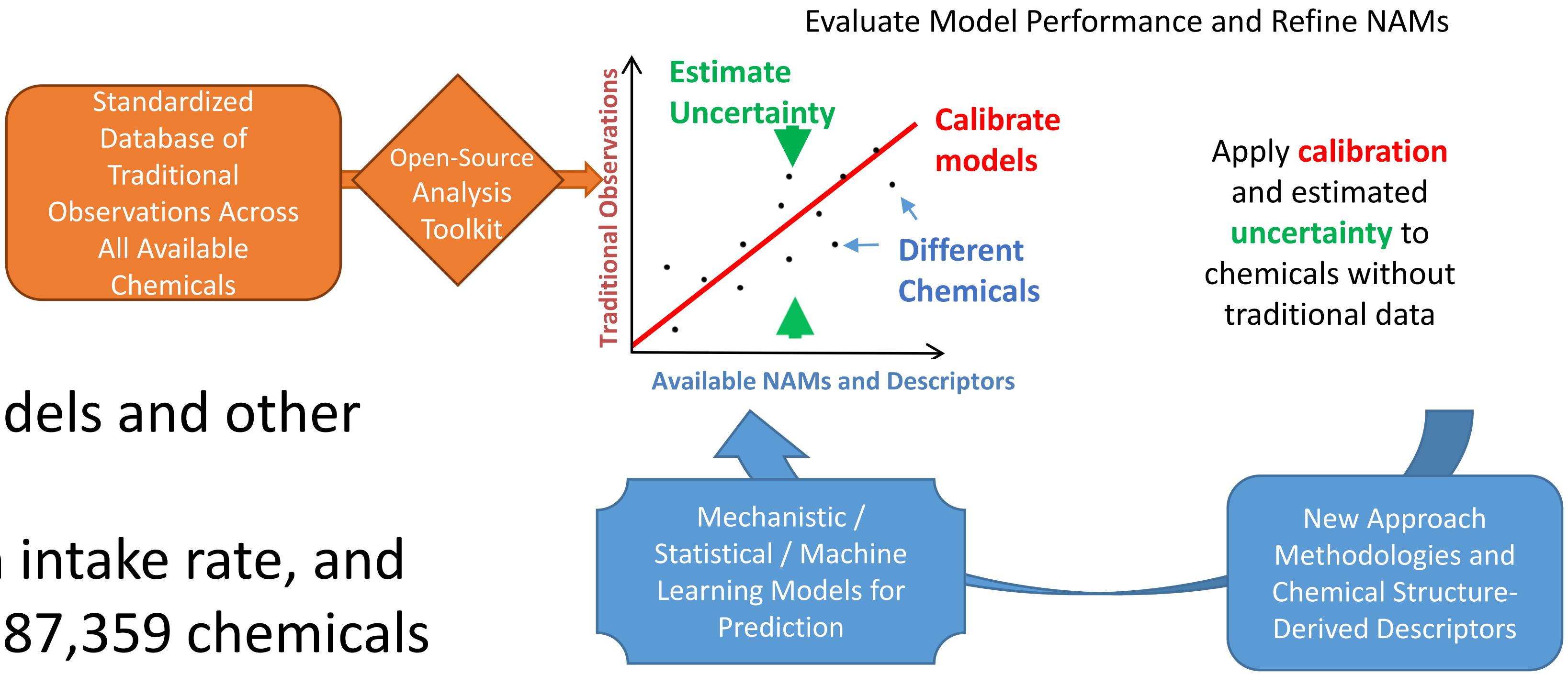
Article

Cite This: Environ. Sci. Technol. 2019, 53, 719−732

pubs.acs.org/est

Consensus Modeling of Median Chemical Intake for the U.S. Population Based on Predictions of Exposure Pathways

Caroline L. Ring,[†,§,∞] Jon A. Arnot,[∥,⊥,#] Deborah H. Bennett,[∇] Peter P. Egeghy,[‡] Peter Fantke,[○] Lei Huang,[◆] Kristin K. Isaacs,[‡] Olivier Jolliet,[◆] Katherine A. Phillips,[‡] Paul S. Price,[‡] Hyeong-Moo Shin,[¶] John N. Westgate,[∥] R. Woodrow Setzer,[†] and John F. Wambaugh[*,†]



- Consensus of 12 different models and other exposure predictors
- 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
    - 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

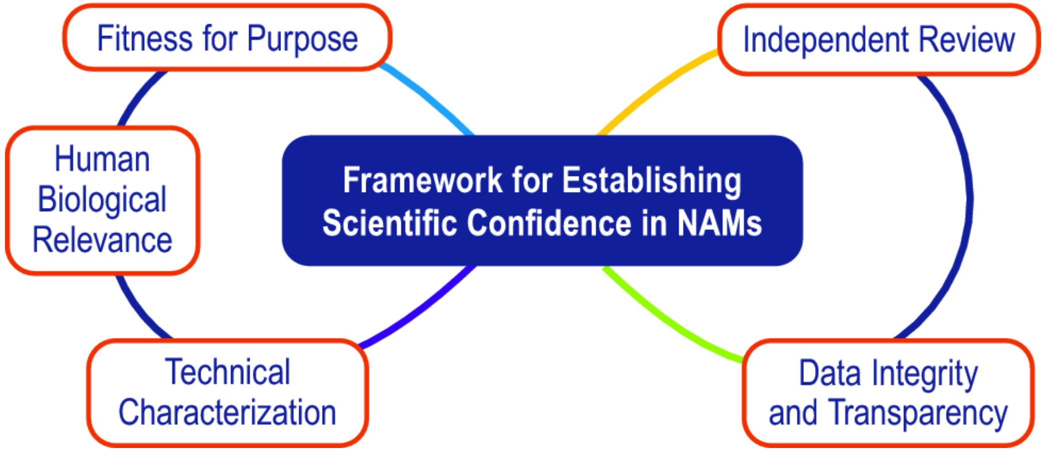
Cross-Cutting

Ensure methods and approaches produce results:

- Accessible
- Fit for purpose
- Effectively communicated
- Transparent
- Reproducible
- Inform health-protective risk assessment
- Uncertainty & variability captured
- Garners confidence

Consistent with NAS (2017) Using 21st Century Science to Improve Risk-Related Evaluations

Analyses should be carried out in transparent and replicable ways to ensure credibility and to enhance review and acceptance of findings for decision-making. Open data access might be critical for ensuring transparency.



Source: van der Zalm et al., 2022

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Summary

- Exposure science is rapidly evolving from its industrial hygiene roots
  - Expanding scientific scope
  - Responding to wicked/complex environmental challenges
- Chemical exposure presented as case example
  - Habitable planet boundary exceeded
  - Number of chemicals in commerce vasty out-paces traditional approaches to assessment
- EPA developing computational exposure science strategies to address challenge
- 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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United States Environmental Protection Agency

Thank you!

QUESTIONS / COMMENTS