



# The Aggregate Exposure Pathway (AEP): An Organizational Framework for Advancing Exposure Science Research and Applications

Justin. G. Teeguarden (Part One: Why)  
Cecilia Tan (Part Two, What and How)

U.S. Environmental Protection Agency

*The views expressed in this presentation are those of the presenter, and do not necessarily reflect the views and policies of the Agency.*



# Why

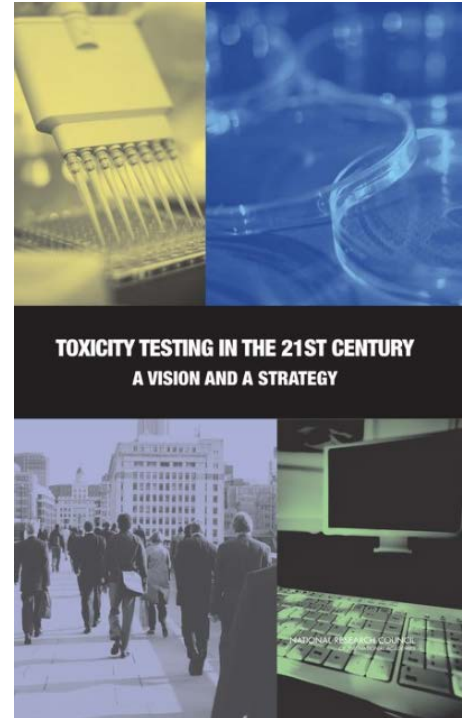
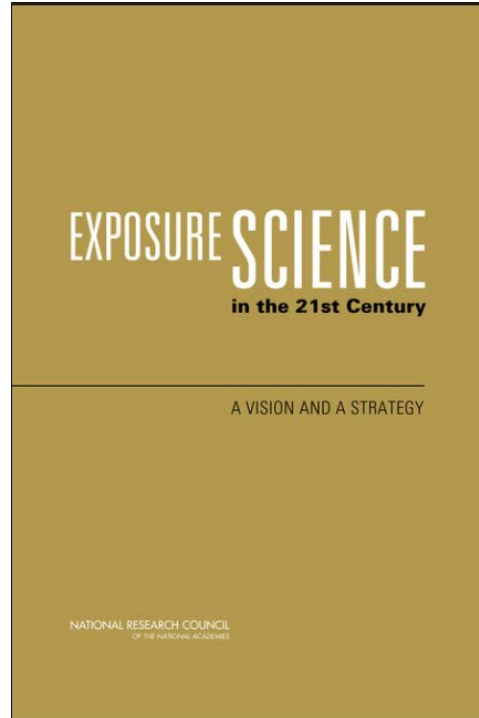
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# Data Acquisition, Integration and Modeling at a Grand Scale

- More comprehensive exposure characterization
- Source to receptor
- **Biokinetic models**
- **Human equivalent exposures**
- **Population exposures**
- **Target site exposures**



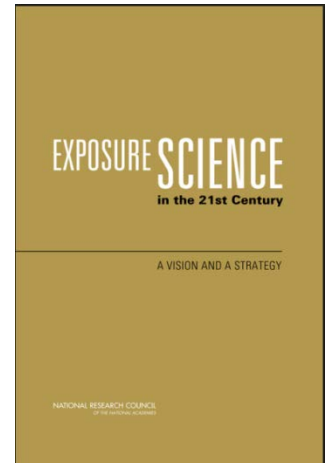
- More comprehensive In vitro hazard assessment
- Pathway based assessment
- **Biokinetic models**
- **Human equivalent exposures**
- **Population exposures**
- **Target tissue exposures**

**ES21: Exposure Science should respond to and influence toxicity testing**  
**New NRC Panel: ES21 and Tox21 for Risk Assessment**

# Exposure Science in the 21<sup>st</sup> Century a Vision and a Strategy

**“EPA and NIEHS asked the NRC to develop a “unifying conceptual framework for the advancement of exposure science.”**

**“...adopt a systems-based approach that, to the extent possible, considers exposures from source to dose and dose to source and considers multiple levels of integration.”**



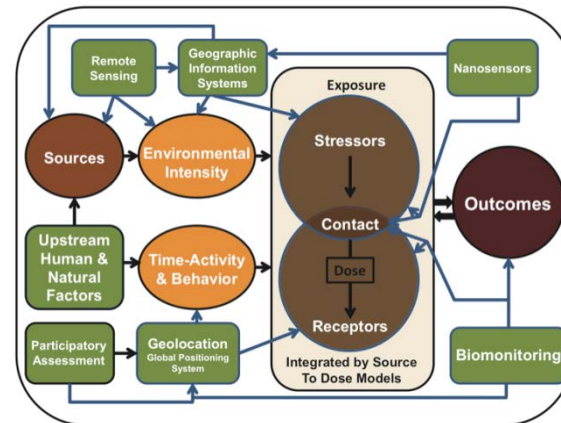
# Biological Networks Produce Toxicological Outcomes: Mechanistic Thinking has Impacted all Aspects of Toxicology

- Mechanism of action, mode of action (MOA), adverse outcome pathway (AOP) are all representations of an overarching organizational framework for toxicology.

- Influences
  - Investigative toxicology
  - Design of high throughput tests, whole animal studies, establishment of transgenic animal models and cell systems. Interpretation of data. Data gaps
  - QSAR and pathway modeling
  - Risk assessment and hazard assessment (FDA, EPA)
  - Database development and chemical classification

# Exposure Networks Produce Exposure Outcomes: Less Completely Embraced

- Conceptual site models, fate and transport models, and the AEP are all representations of an overarching organizational framework for exposure science



- Influences
  - Site assessment
  - Fate and transport models (environmental, biokinetic)
  - Aggregate and cumulative exposure assessment

## Why do We Need a “Framework”

- Major growth in exposure science will produce more data on more chemicals, for an expanding list of matrices and sources and an emphasis of prediction and exposure-based decision making
  - How do we combine these data? How do we organize these data? How do we make it accessible?
  - How do we handle the deep complexity of exposure networks?
  - How do we relate exposures across systems? From sites to cells?
  - Careful planning of experiments and modeling is required for prediction
  - How do we most effectively work across domains (Tox, Epi and Exposure)?

# The Aggregate Exposure Pathway Concept



Capturing the complex nature of human and ecological exposure to stressors is a major challenge for environmental health decision making.

The Aggregate Exposure Pathway (AEP) concept offers an intuitive framework to organize exposure data, setting the stage for more meaningful collection and use of exposure data.

The AEP is a flexible, data-driven framework to organize exposure data for supporting and extending a number of current and emerging uses for these data including exposure based decision making, prediction, and risk assessment

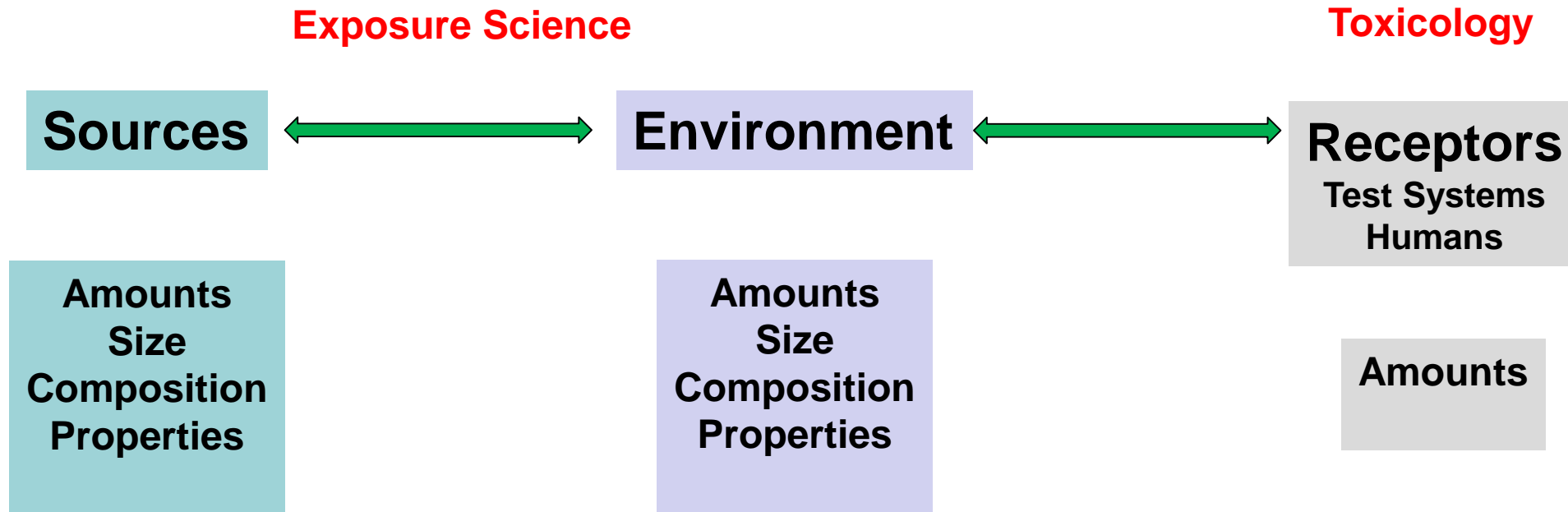
Teeguarden, Tan, et al. (2016) *Completing the Link between Exposure Science and Toxicology for Improved Environmental Health Decision Making: The Aggregate Exposure Pathway Framework*. Environ Sci Technol, 50(9): 4579-4892.

## **The AEP Framework is NOT**

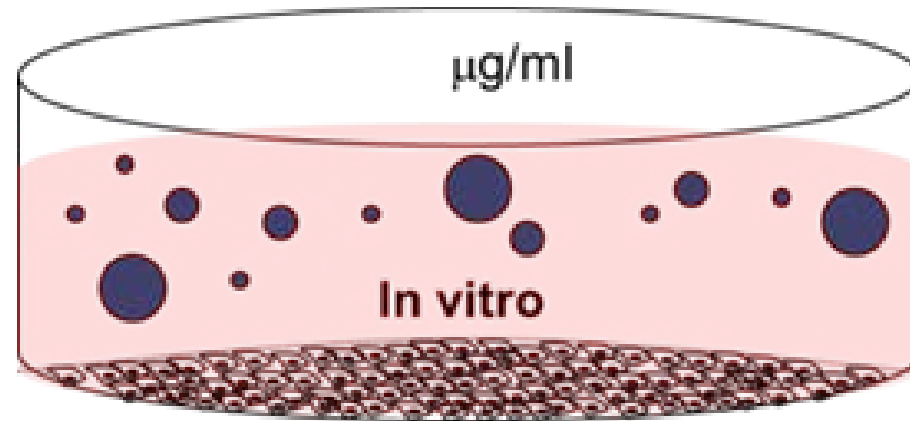
- A replacement for existing exposure models
- A rigid organizational framework
- A requirement to work across the source to target site exposure continuum
- A database

# Nanotoxicology:

## An Emerging Science Starts without an Exposure Framework

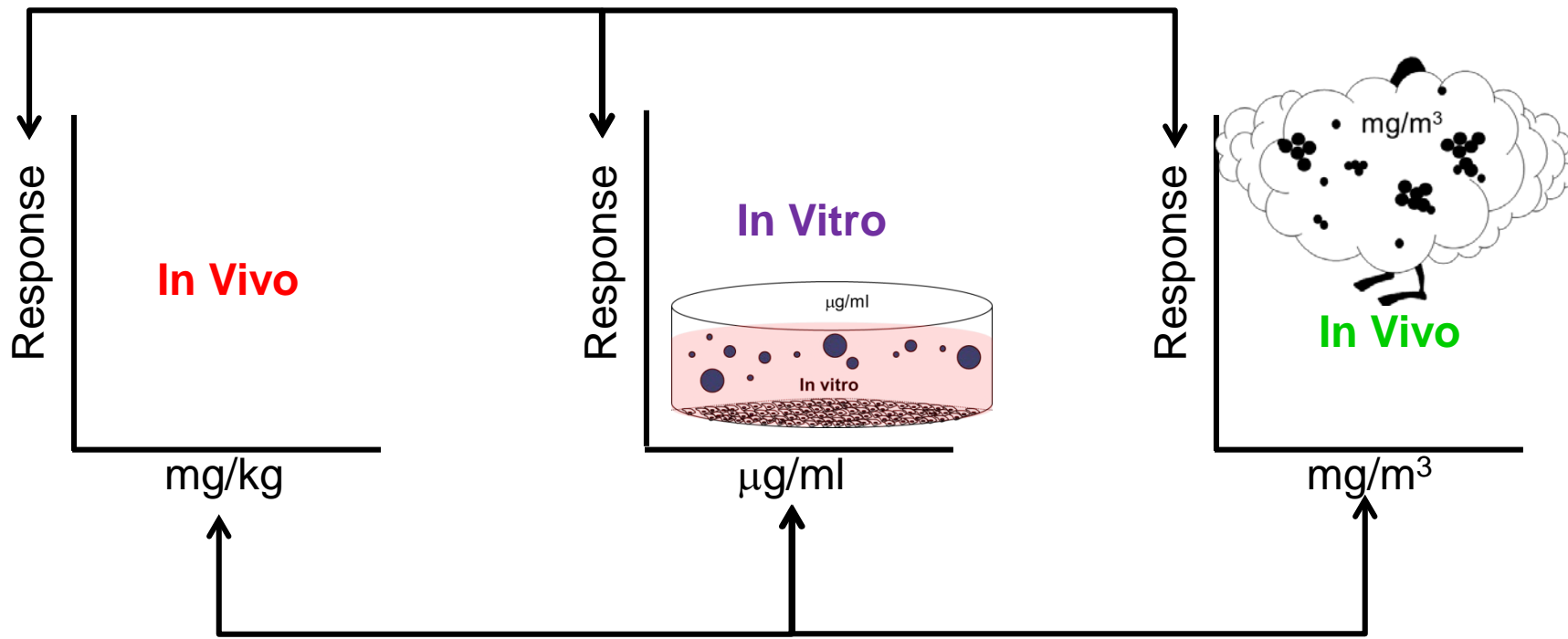


# Tests Systems 2005-2015: Exposure=Concentration



# Incompatible Exposure Estimates

How Do the Biological Responses Compare?

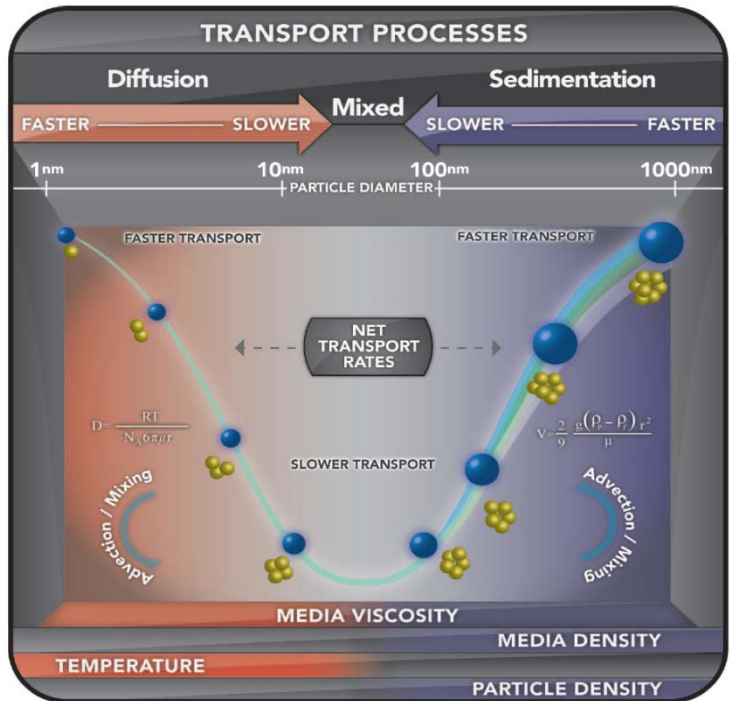


How Do the Exposures Compare?

EPA STAR Grant: We don't believe anything important happens to particles in vitro

Toxicology Literature, 2000-2015: nominal media concentrations only

# One Basis for Understanding the Fundamentals of Nanomaterial Dosimetry



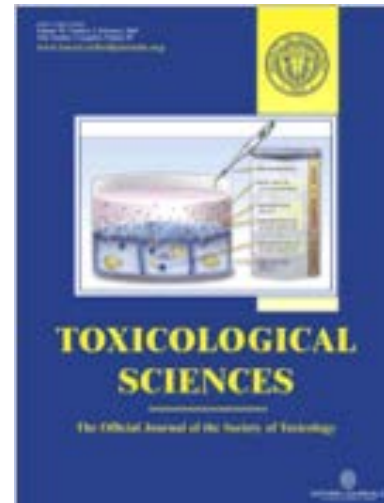
## REVIEW

### Particokinetics *In Vitro*: Dosimetry Considerations for *In Vitro* Nanoparticle Toxicity Assessments

Justin G. Teeguarden,<sup>1</sup> Paul M. Hinderliter, Galya Orr, Brian D. Thrall, and Joel G. Pounds

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## RESEARCH

## Open Access

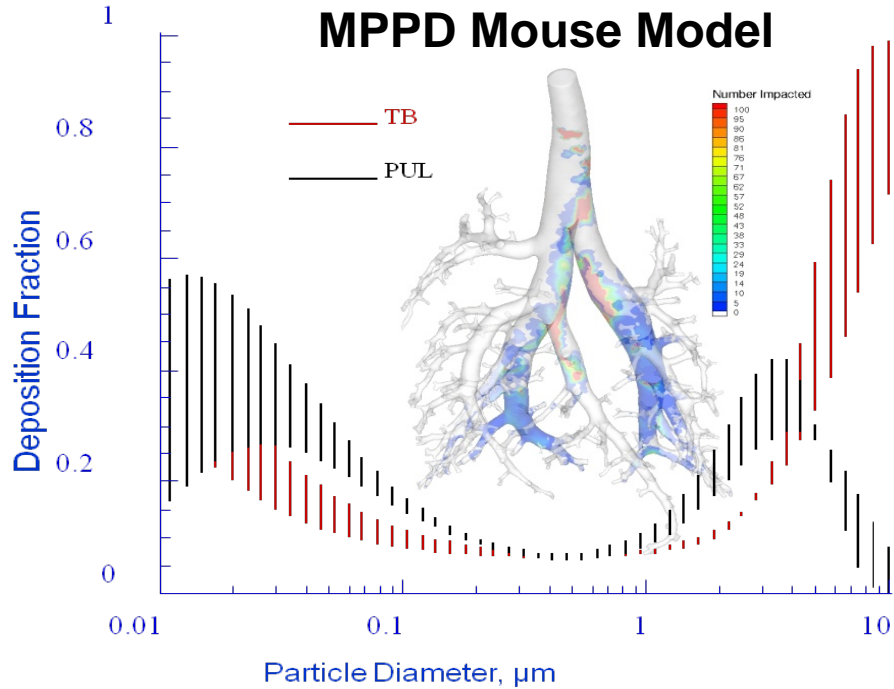
### ISDD: A computational model of particle sedimentation, diffusion and target cell dosimetry for *in vitro* toxicity studies

Paul M Hinderliter<sup>1</sup>, Kevin R Minard<sup>1,3</sup>, Galya Orr<sup>2,3</sup>, William B Chrisler<sup>1</sup>, Brian D Thrall<sup>1,3</sup>, Joel G Pounds<sup>1</sup>, Justin G Teeguarden<sup>1,3\*</sup>

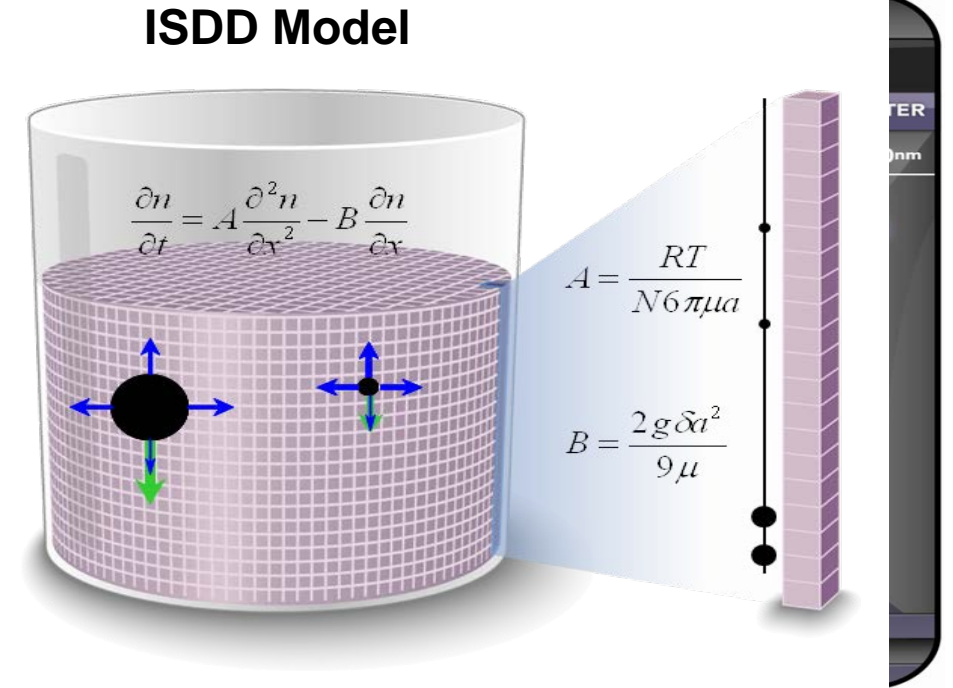


*Publicly Operated by Battelle Since 1965*

# Framework and Tools for Rapid Translation Exposures across Test Systems and Humans



How Do We Relate These?



MPPD Model

Particle # or Surface Area/Cell

ISDD Model



# Occupational Exposure Limits for Metal Oxides from the In Vitro UCLA Toxicity Library

Teeguarden et al. *Particle and Fibre Toxicology* 2014, **11**:46  
<http://www.particleandfibretoxicology.com/content/11/1/46>



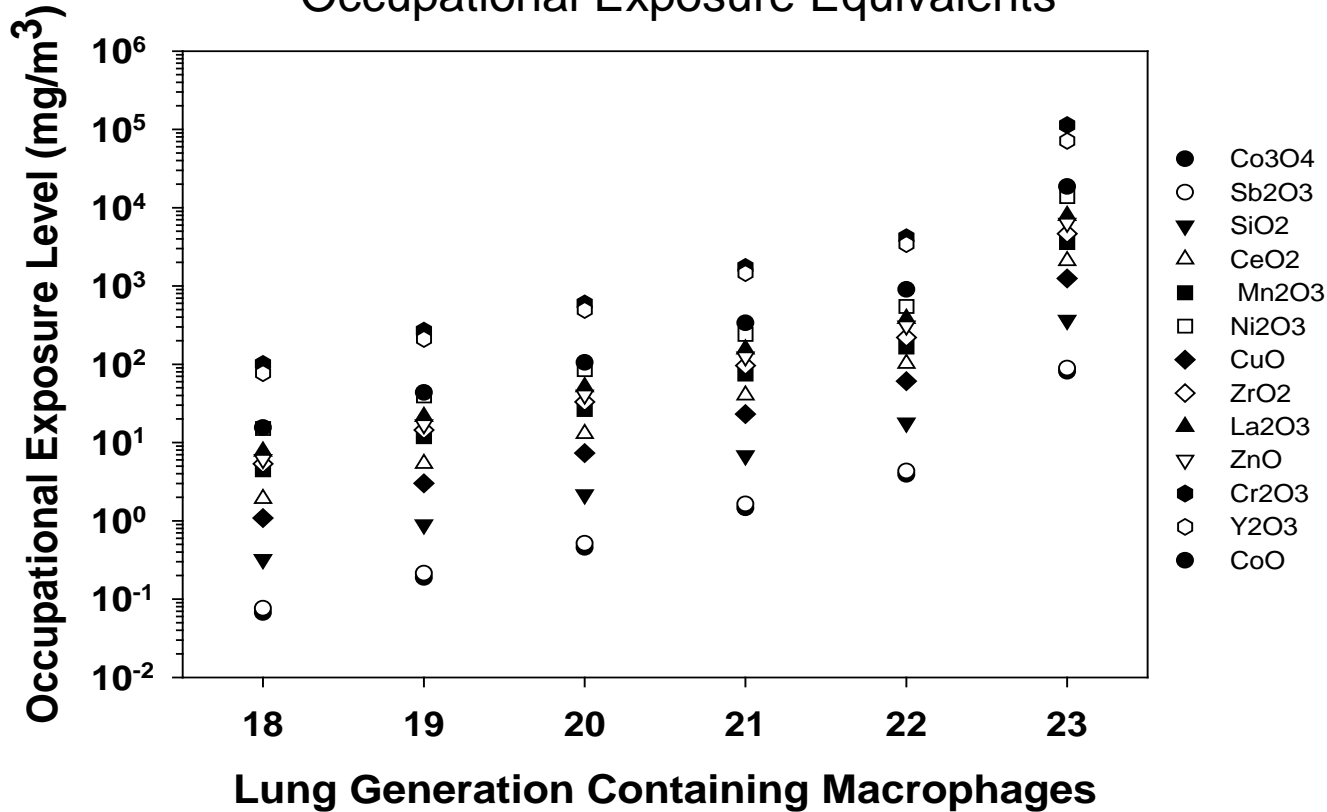
RESEARCH

Open Access

Comparative iron oxide nanoparticle cellular dosimetry and response in mice by the inhalation and liquid cell culture exposure routes

Justin G Teeguarden<sup>1\*</sup>, Vladimir B Mikheev<sup>2</sup>, Kevin R Minard<sup>1</sup>, William C Forsythe<sup>2</sup>, Wei Wang<sup>3</sup>, Gaurav Sharma<sup>2</sup>, Norman Karin<sup>4</sup>, Susan C Tilton<sup>1</sup>, Katrina M Waters<sup>1</sup>, Bahman Asgharian<sup>5</sup>, Owen R Price<sup>5</sup>, Joel G Pounds<sup>1</sup> and Brian D Thrall<sup>1</sup>

Occupational Exposure Equivalents



## Hazard Ranking

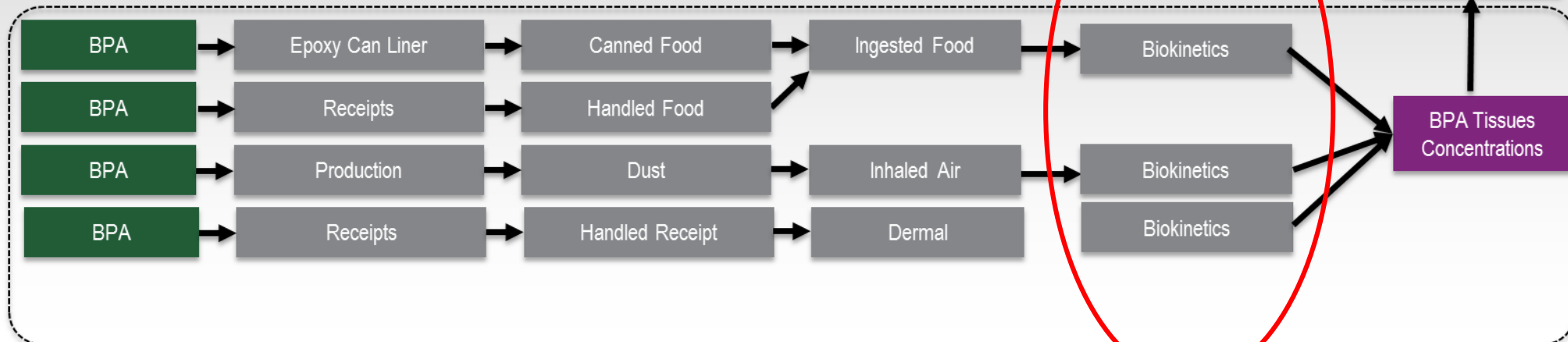
Particle	In Vitro Ranking	Human OEL Ranking
Co <sub>3</sub> O <sub>4</sub>	10	1
Sb <sub>2</sub> O <sub>3</sub>	4	2
SiO <sub>2</sub>	1	3
CeO <sub>2</sub>	12	5
Mn <sub>2</sub> O <sub>3</sub>	7	6
Ni <sub>2</sub> O <sub>3</sub>	6	7
CuO	2	4
ZrO <sub>2</sub>	3	7
La <sub>2</sub> O <sub>3</sub>	13	9
ZnO	5	8
Cr <sub>2</sub> O <sub>3</sub>	9	13
Y <sub>2</sub> O <sub>3</sub>	11	12
CoO	8	11

# Bisphenol A

## An Old Science Continues without an Exposure Framework

Toxicity Testing: Extensive  
Epidemiology: Extensive  
Biomonitoring: Extensive  
External Exposure Assessment: Extensive

Without Biokinetics:  
No linkages across  
Exposure domains



# AEP-AOP Linkage for a Critical Public Health Issue

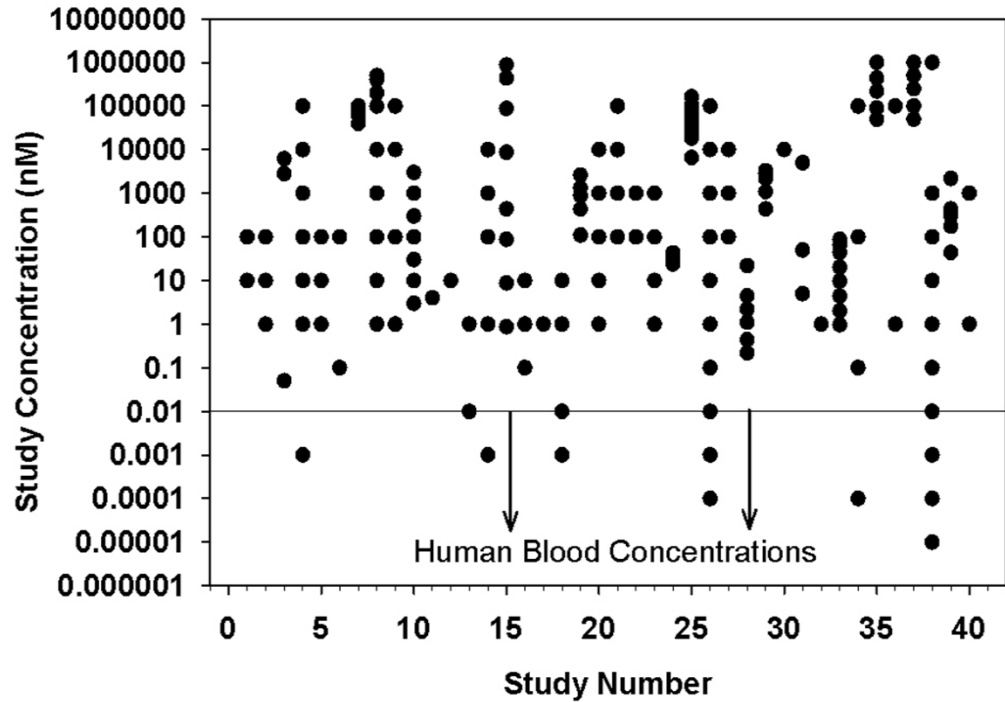
## Organizing the BPA Exposure Narrative and Translating Exposures Across the Source to Outcome Continuum:

### ► Approach

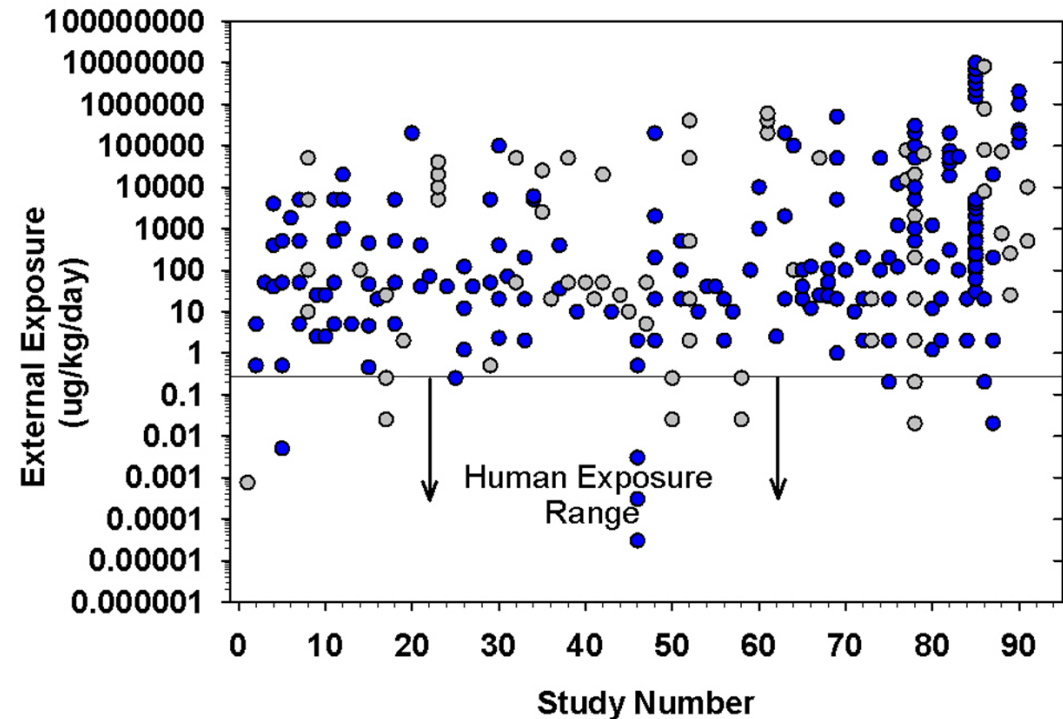
- Characterized and modeled in vitro processes influencing cellular exposures
- Characterized biokinetics in humans (oral, sublingual, dermal)
- Assemble aggregate BPA exposure data across pathways
- Compared serum BPA concentrations at human aggregate exposure levels to in vitro concentrations reported to cause effects
- Calculated receptor occupancy for 5 estrogen receptor sub-types.

# Few BPA “Low-Dose” Studies have been Conducted in the Range of Human Exposure

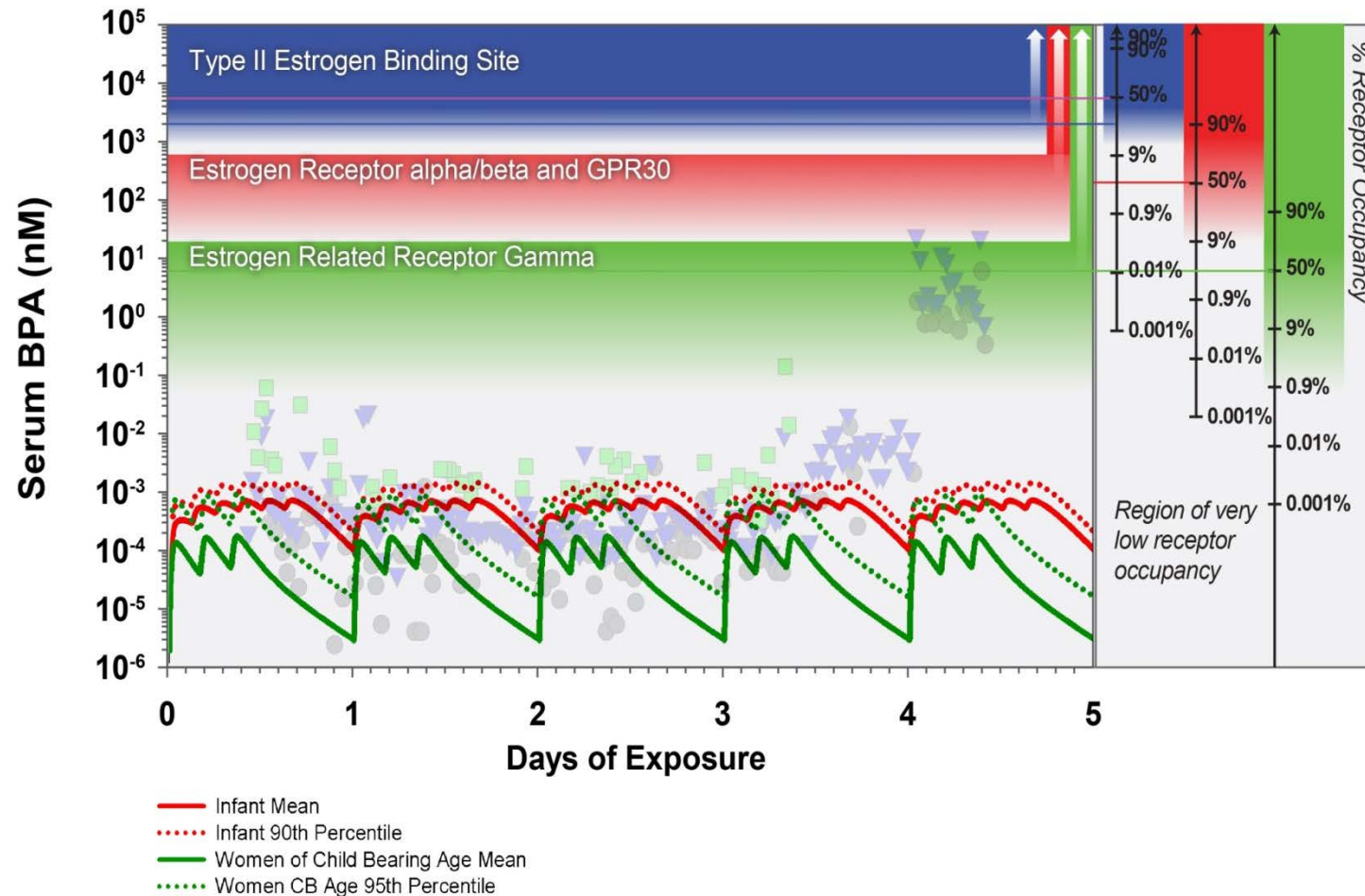
## In Vitro



## In Vivo



# Receptor Occupancy of Less than 0.001 % in Infants and Women of Child Bearing Age



# Some Conclusions

- For Nanoparticles and BPA, organization of the “network” of exposures, and the quantitative data on kinetics with human biomonitoring data required for integration and modeling benefited from a systems based approach like the AEP
- If there was broader acceptance and application of an organizational framework, earlier, the data generated would have had greater impacts on public health protection.
- Where will risk assessment be if we face this challenge for the next 1000 chemicals?
- The AEP framework embraces existing frameworks and looks to expand their use across more than one community
  - Conceptual Site Models, Fate and transport models.
- Positioning our respective communities, exposure and toxicology, to make the maximum use of emerging exposure data will require broader adoption and utilization of an organizational framework for exposure science



# What and How

Cecilia Tan, PhD, MBA  
U.S. Environmental Protection Agency

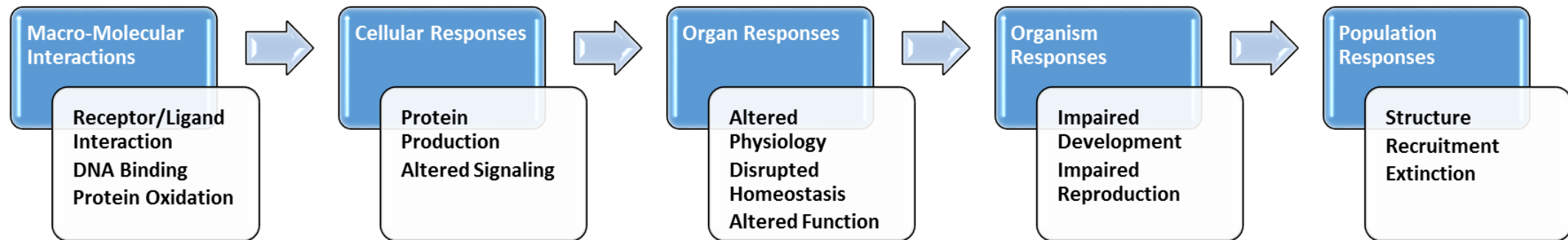
## What is an AEP?

- The AEP is a flexible, data-driven framework for organizing exposure data
- The AEP may begin and end at any environmental or biological level appropriate for the needs of the users
- An AEP framework facilitates information exchange and model interoperability by providing a common terminology

## **How do we adapt a successful framework?**

- The Adverse Outcome Pathway (AOP) framework has been successful in the organization of toxicology information
- The AEP provides a similar framework for facilitating the organization of exposure information
- The AEP framework can be used separate from or as a complement to the AOP framework

## Two components of an AOP



- **Key Events (KEs)**
  - Change in biological state
  - Measurable and essential for progression
  - **Molecular Initiating Event (MIE)**: Initial point of chemical interaction
  - **Adverse Outcome (AO)**: Adverse outcome of regulatory significance
- **Key Event Relationships (KERs)**
  - Connections between two KEs
  - Critical for assembling evidence in support of the AOP

## Two components of an AEP: (1) Key Exposure State (KES)



- A KES defines the state of a stressor in space and time
- Two specialized KESs: **Source** and **Target Site Exposure (TSE)**

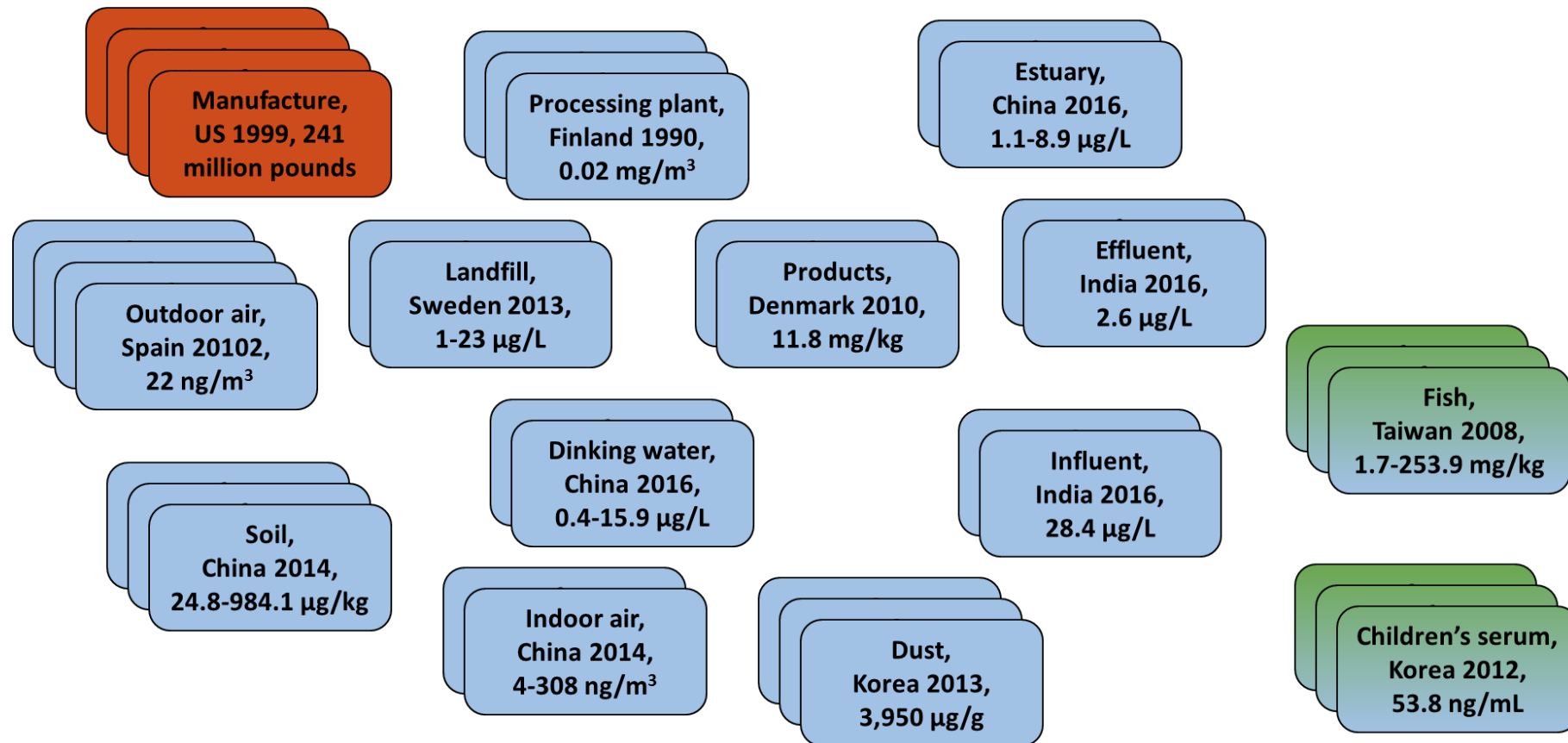
## Two components of an AEP: (1) Key Exposure State (KES)

- KES is data-driven and represents a unique state for a specific stressor
- Source and TSE are considered present in the AEP even when data are not available
  - Source is defined as the state of a stressor at its origin
  - TSE is defined as the state of a stressor at a site of action
  - Following a stressor from its source to a TSE is not required when developing and applying an AEP

## **An example of bis(2-ethylhexyl) phthalate (DEHP)**

- 138 references obtained from numerous sources (e.g., PubMed, ScienceDirect)
- Keywords searched: DEHP and its synonym(s), along with environmental media and biological media
- Approximately 200 KESs were summarized for ~12 types of media (e.g., surface water, air, dust, consumer products, municipal waste)
- Approximately 80 man-hours spent conducting literature search and summarizing results

# An example of DEHP

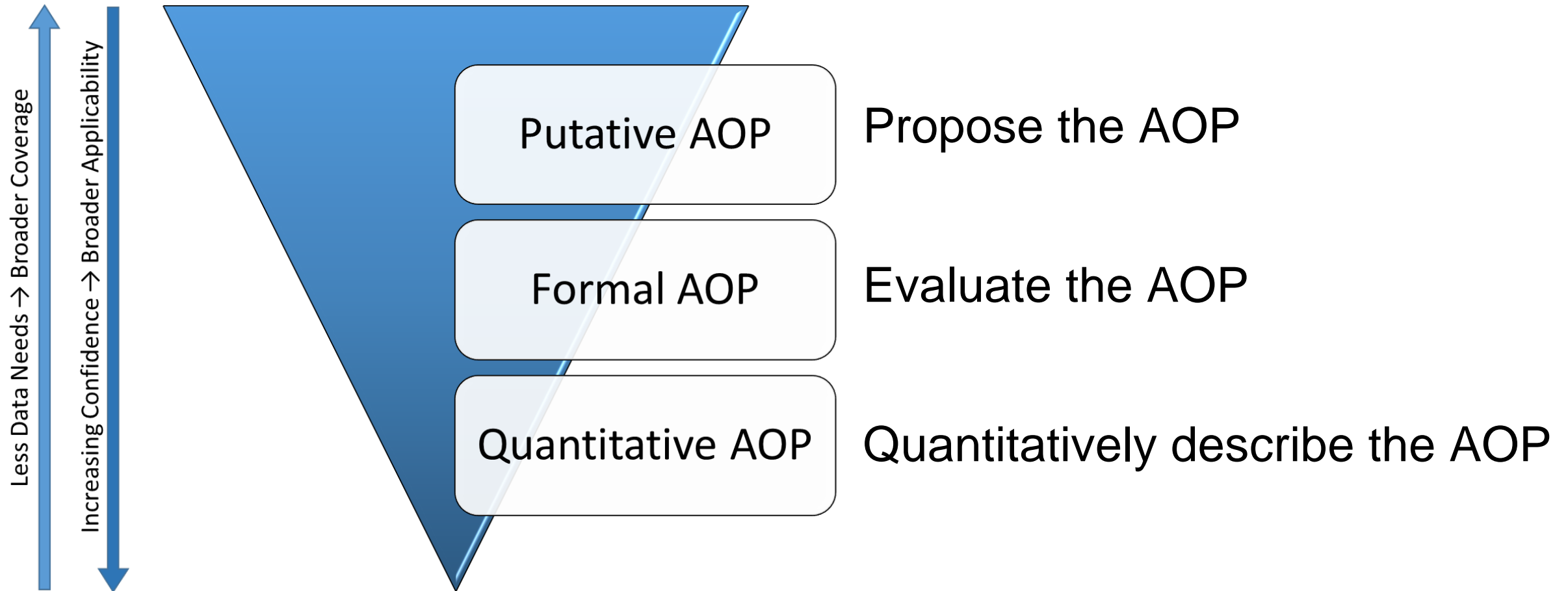


## **Two components of an AEP:**

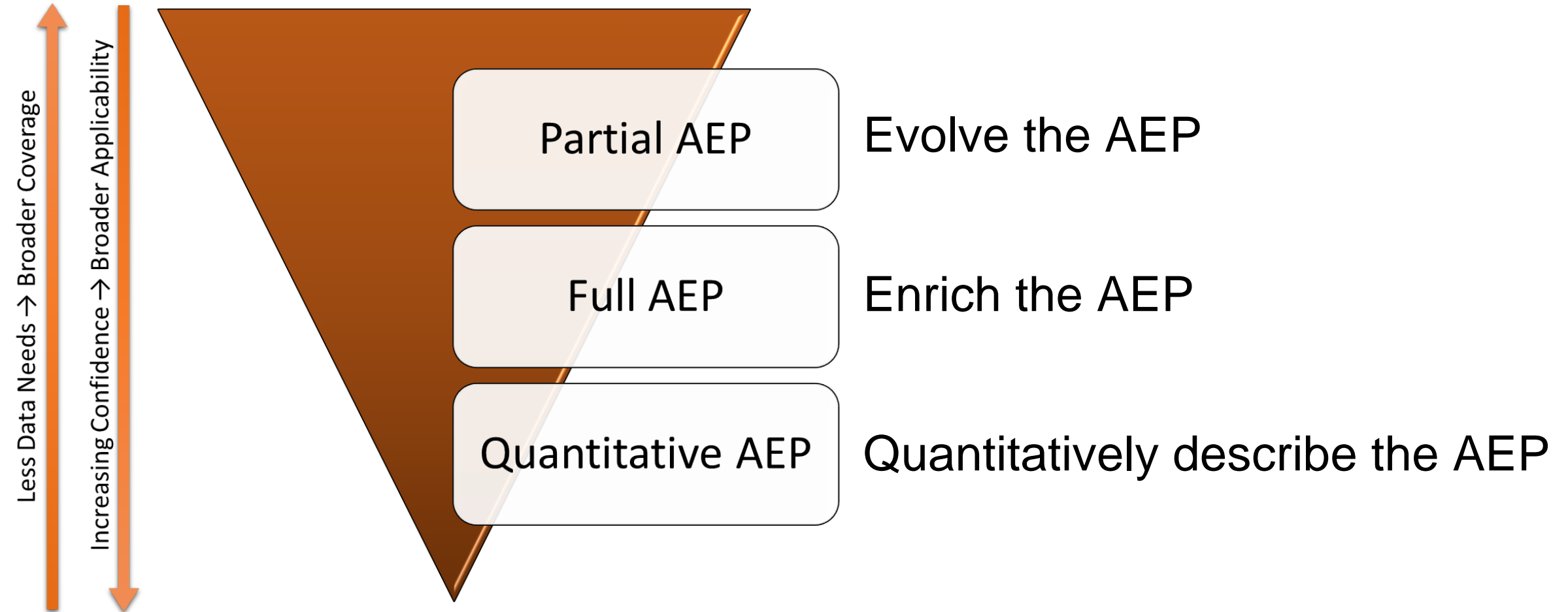
### **(2) Key Transitional Relationship (KTR)**

- A KTR connects two KESs to describe one of the two key processes:
- A key transport relationship describes a process that controls the transport of a stressor between two media types contained within an AEP (e.g., air to dust)
- A key transformation relationship describes a process that controls the transformation of one stressor to another across two AEPs (e.g., parent to metabolite)

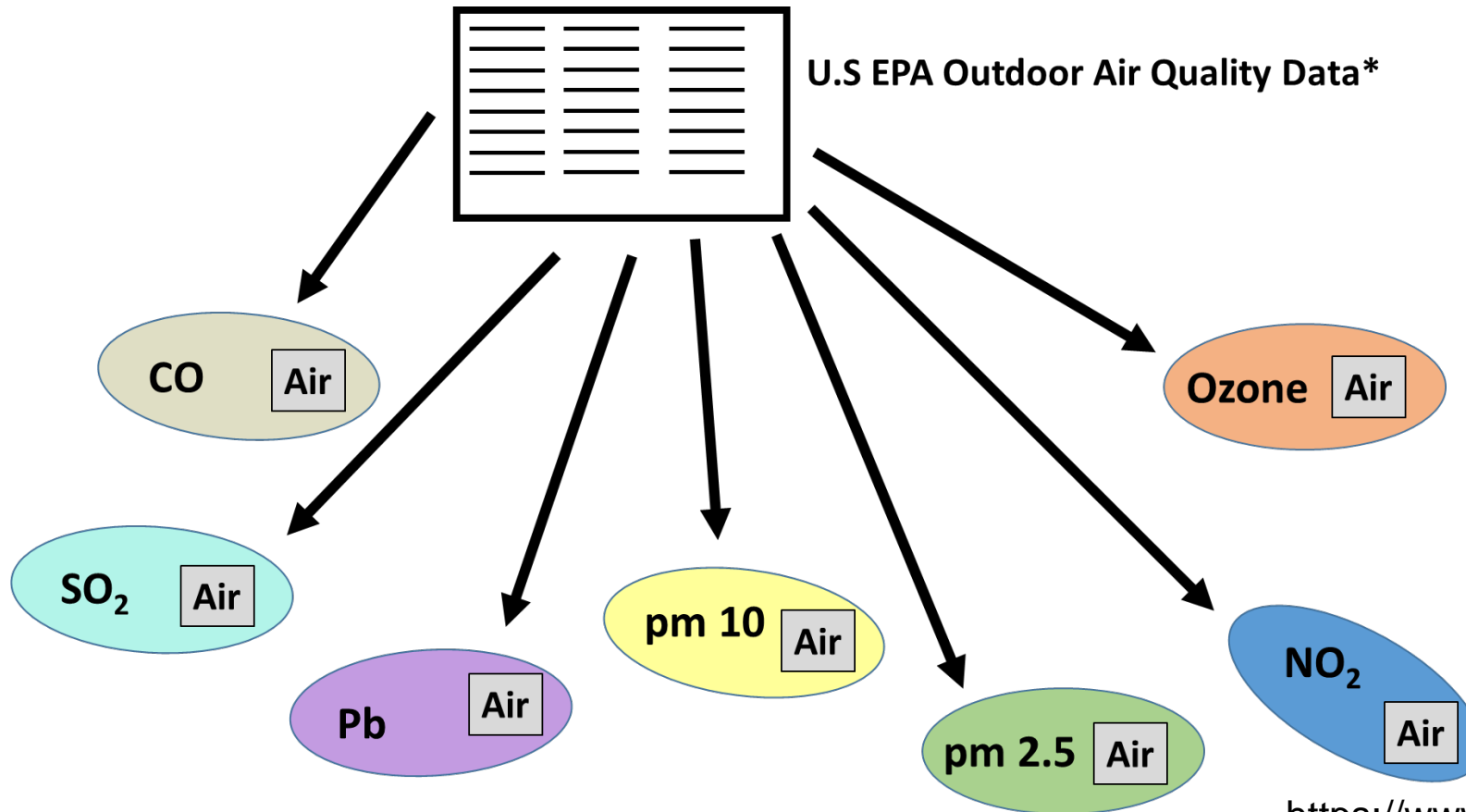
# Overlapping phases of AOP development



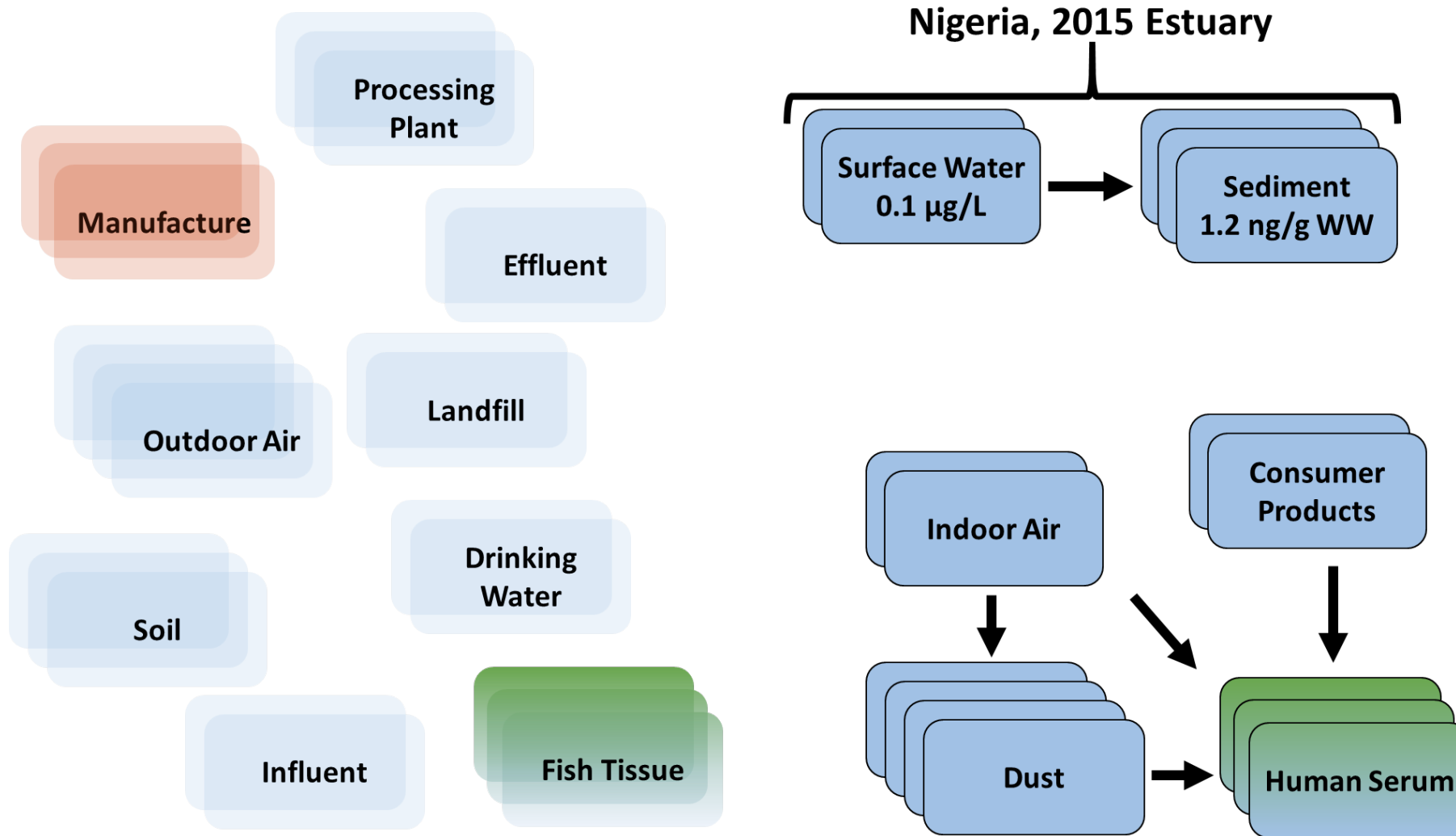
# Overlapping phases of AEP development



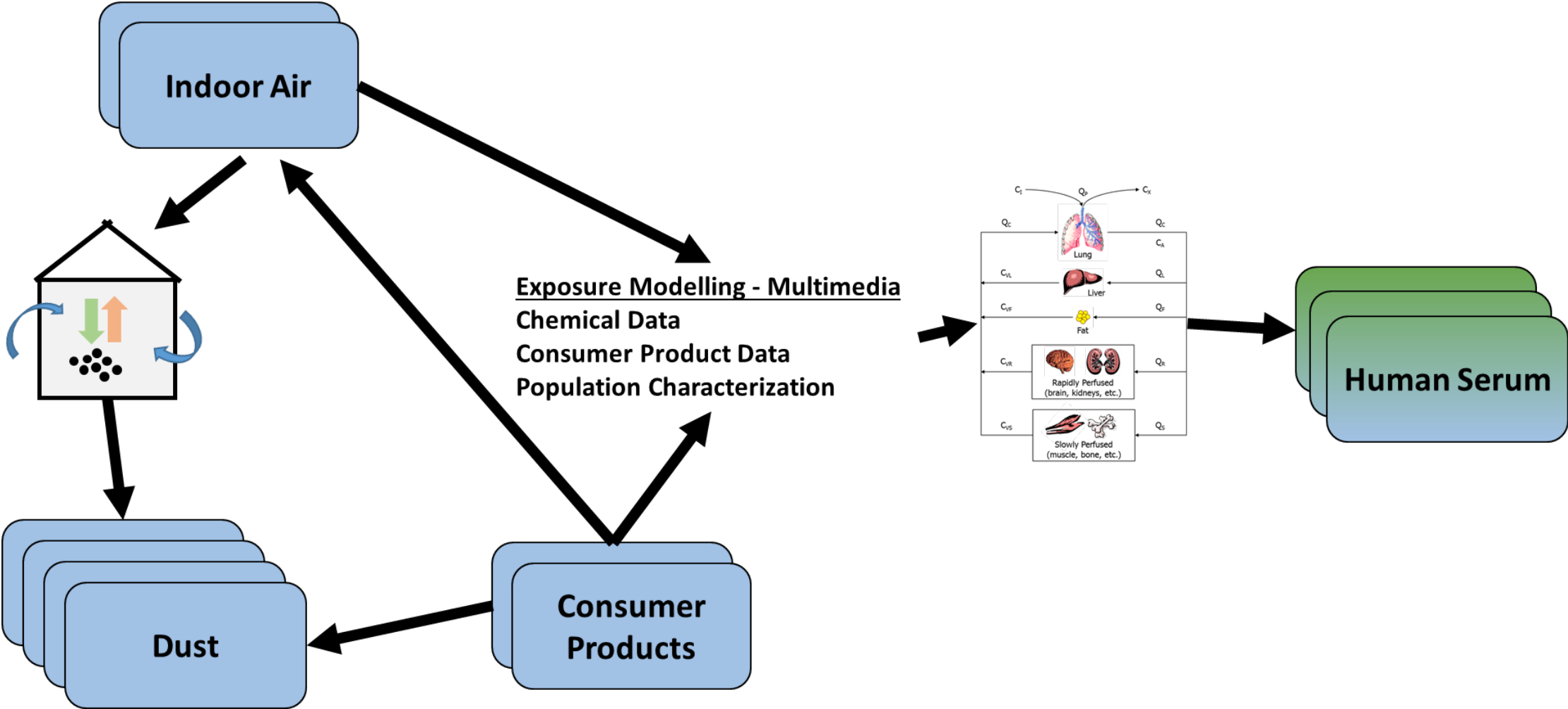
# A monitoring study may contribute to multiple AEPs



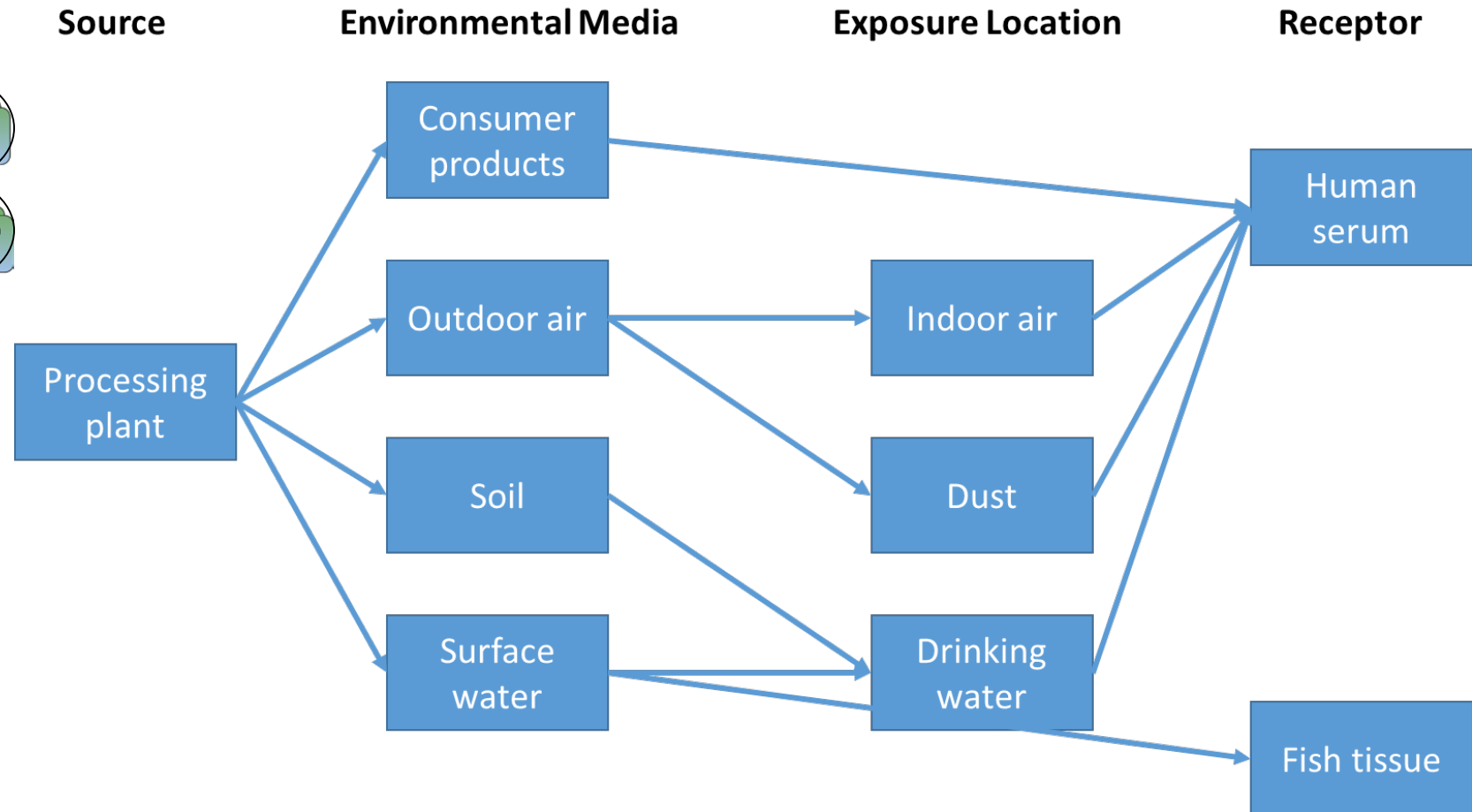
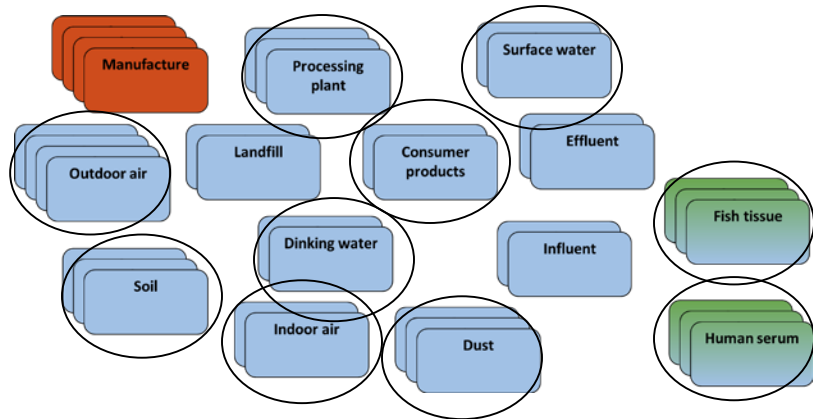
# Partial AEP



# The role of predictive modeling: QAEP



# Applying the AEP to construct a conceptual site model



# Comparing AEPs and CSMs

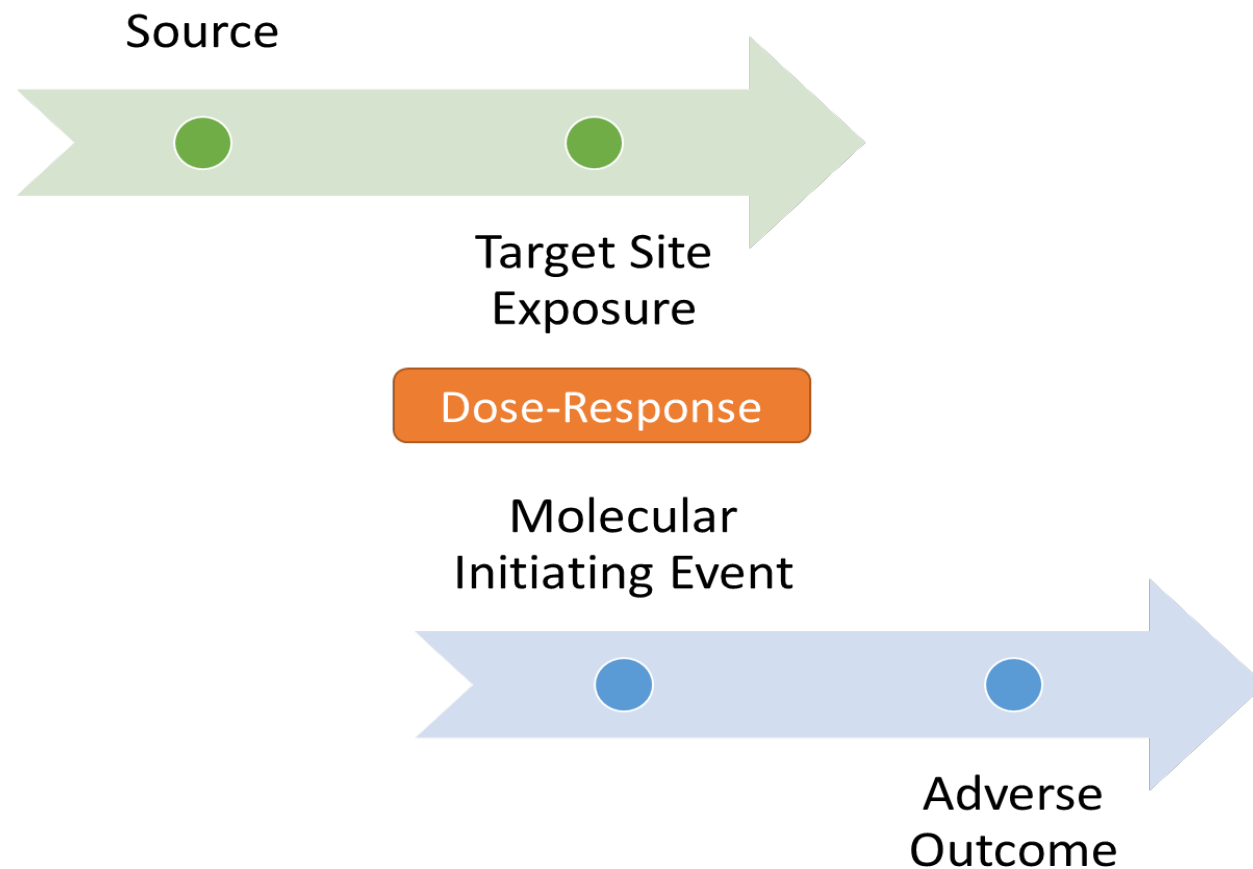
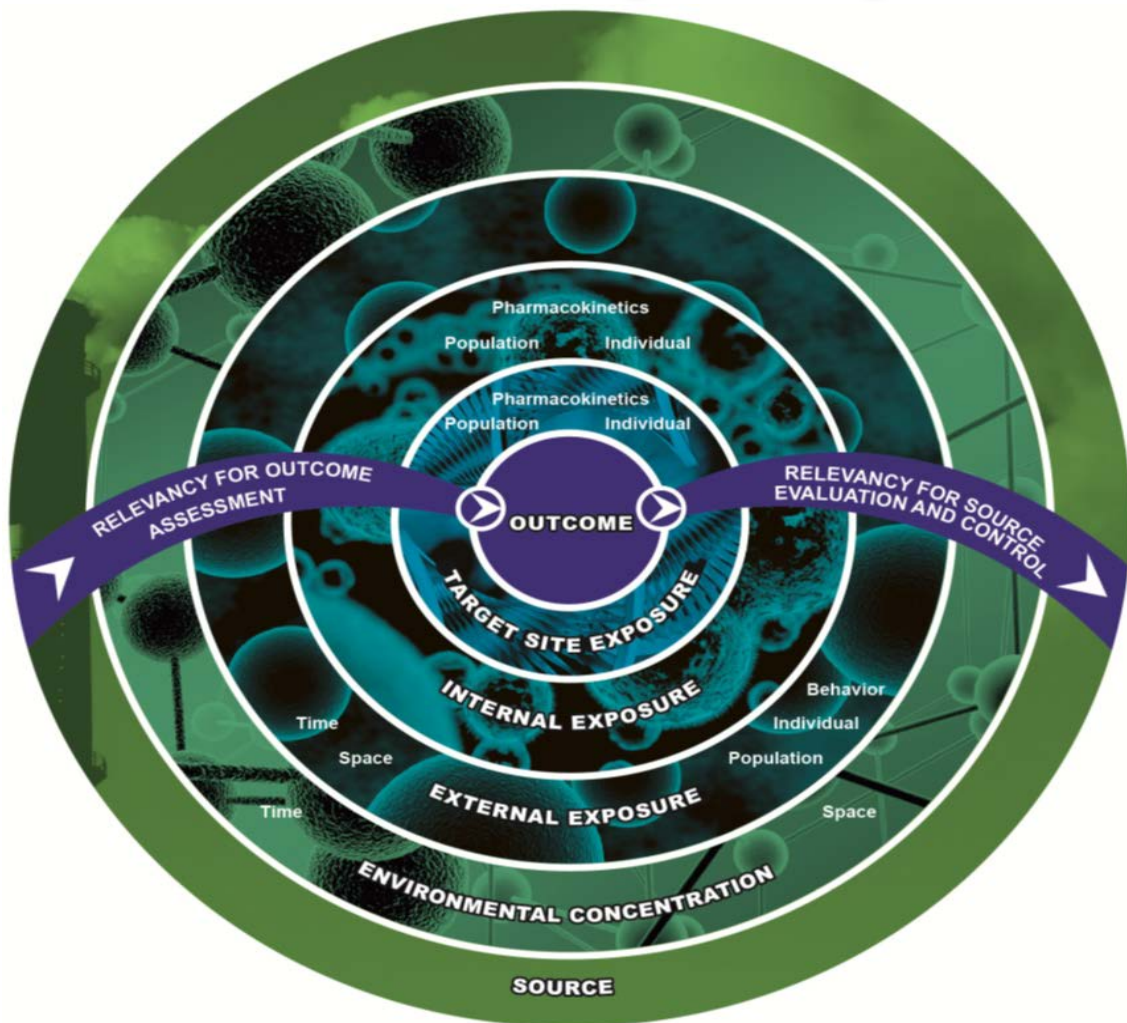
## AEPs

- Data-driven
- Strives for complete exposure information
- Can extend from source to internal exposure
- Can link to AOP
- Amenable to crowd-sourcing

## CSMs

- Abstract
- Fit-for-purpose summary of exposure information
- Generally excludes internal exposure information
- Supports source mitigation
- Individual efforts

# Integrating AEP and AOP frameworks



## Conclusions

- Advancements in technology, biomonitoring, and model development have resulted in a large influx of new data and predictions
- There is a need for assembling the various pieces of exposure information into a holistic perspective to inform the current state of knowledge for a stressor
- Success will require cooperation across multiple organizations dedicated to developing guidances on best practices, outreaching, and training
- An information exchange platform is necessary for sharing and reporting information across a wide variety of sectors

# Acknowledgment

- Stephen Edwards (EPA)
- Jeremy Leonard (EPA)
- Peter Egeghy (EPA)