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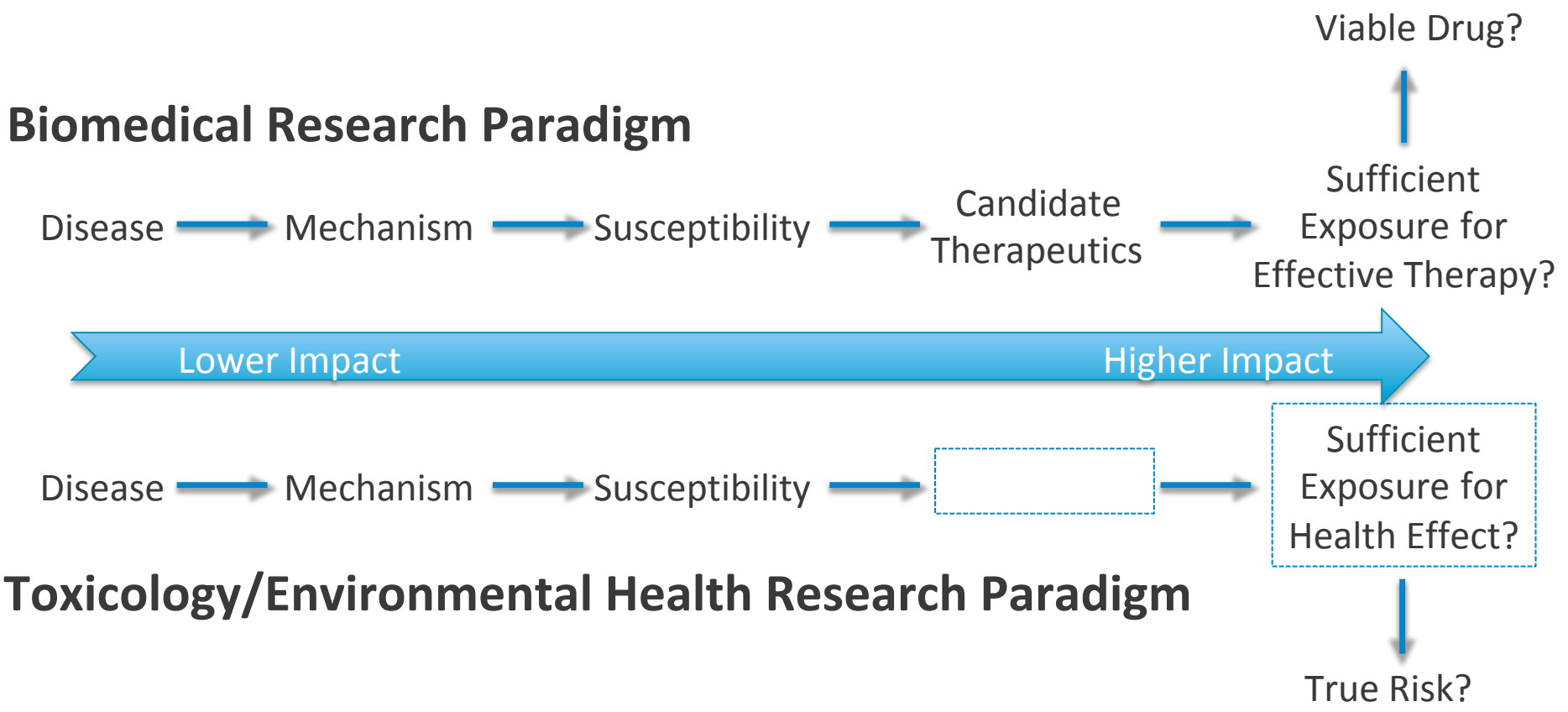
Contrasting Research Paradigms



Is Exposure Science used Effectively As a Bridge between Toxicology and Epidemiology?

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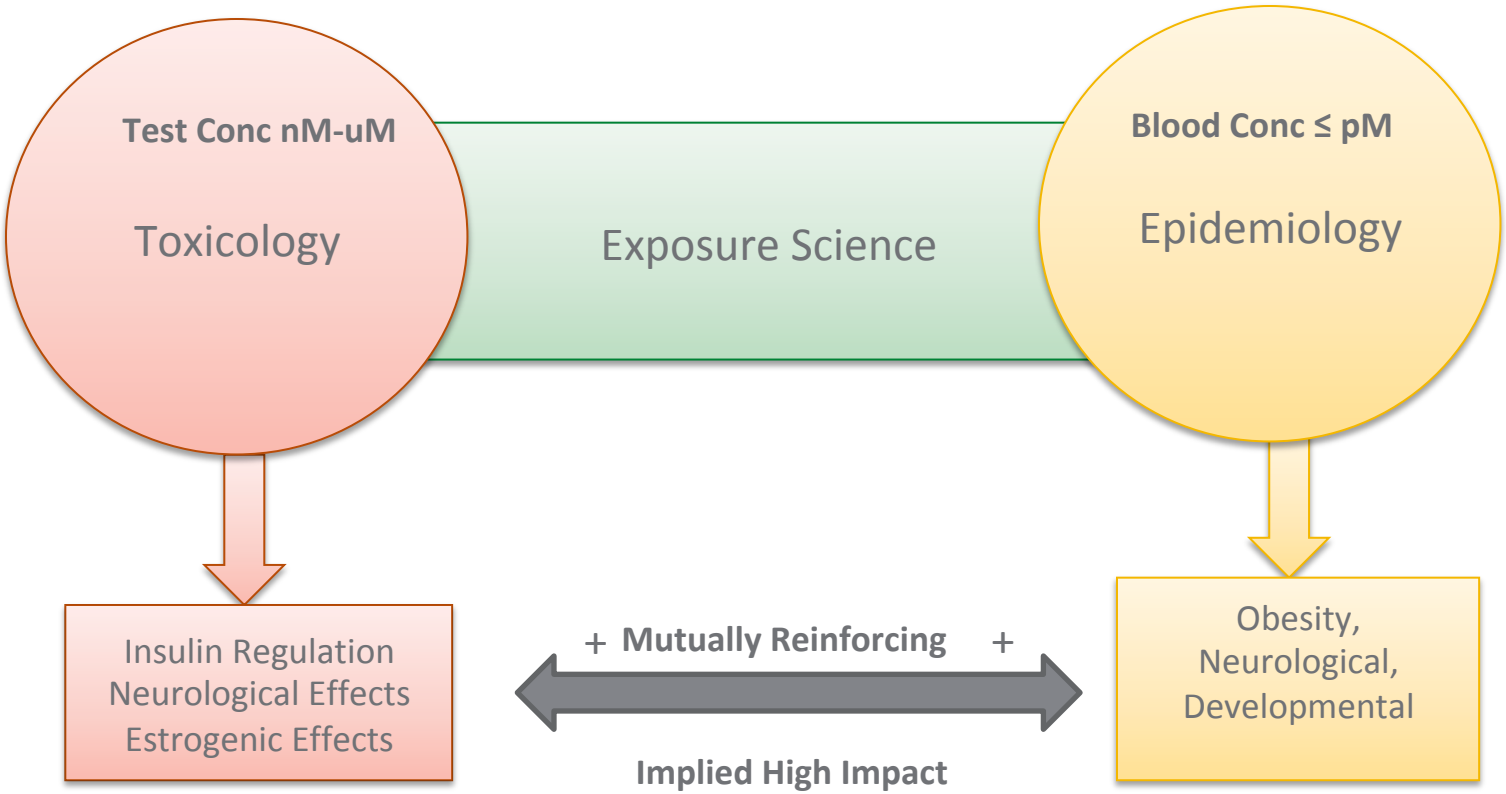
Are these diseases addressable with exposure intervention?



Has the Focus on Biological Effects Left Essential Exposure Questions Unaddressed?

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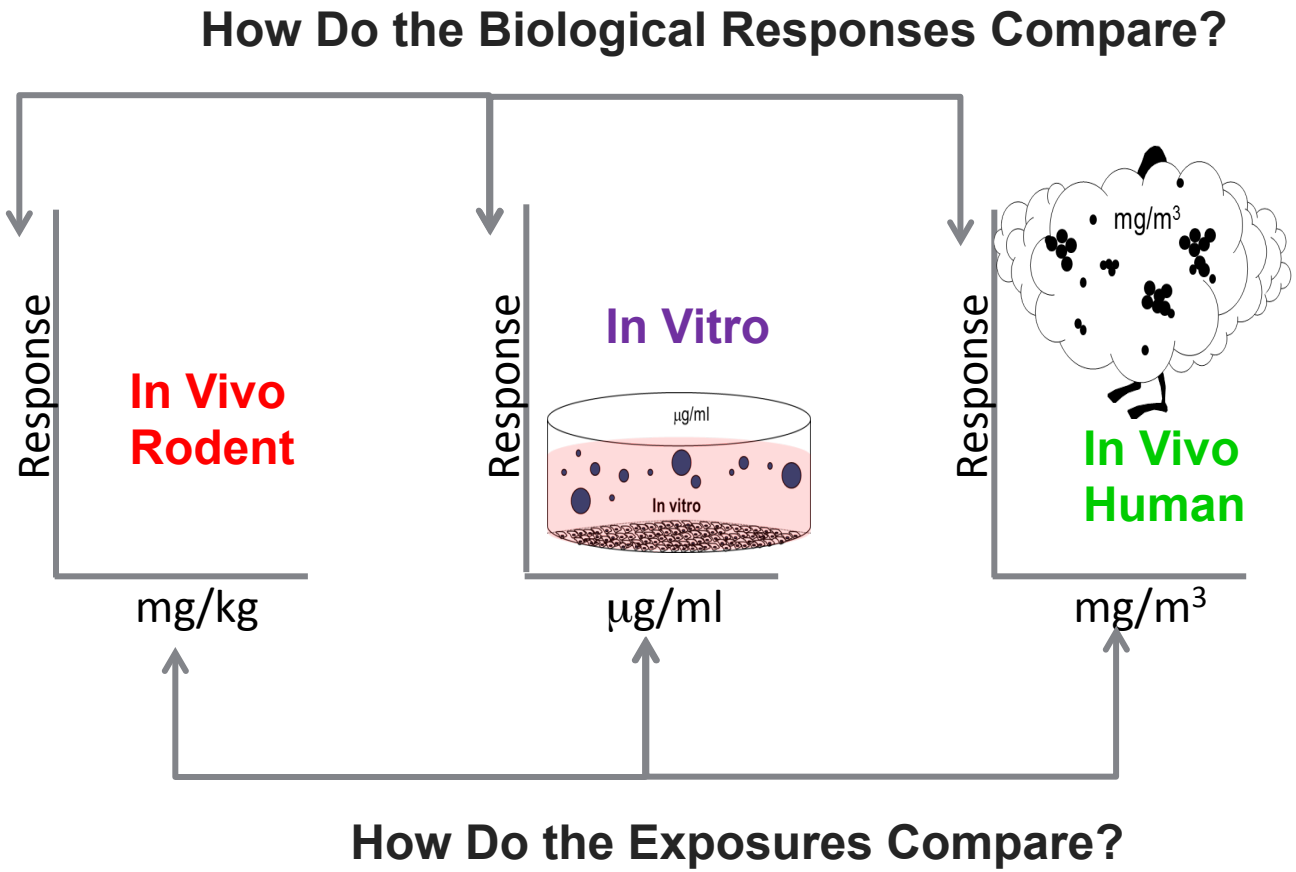
The preponderance of funded scientific "art" supports discovery of faster, richer, deeper, more specific, more sensitive assays for biological response.

- How do test system exposures relate to real-world exposures?
  - Composition, magnitude, frequency, duration, location (target site)
- How does exposure impact the relevance of hazards we identify?
  - Environmental/human exposures vs. higher exposures (not low or high!)
  - Is the biology different or the same?
- How do we relate exposures across test systems?
  - Animal models, tissue models, cell-based models, cell-free systems

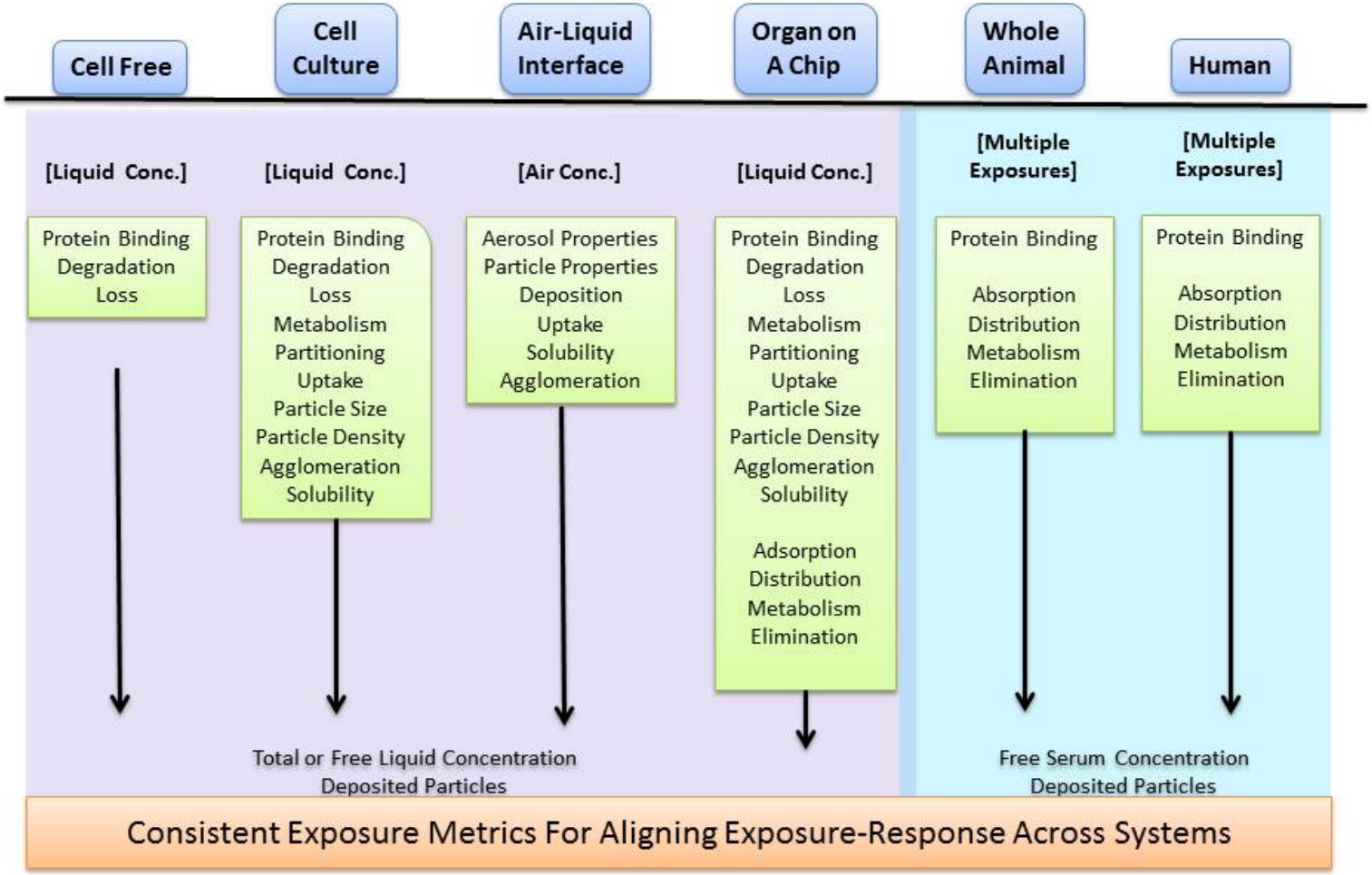
Exposure Translation: Relevant Exposures? Relevant Biology? How would we Know?



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

Toxicology Literature, 2000-2015: nominal media concentrations only

Exposure Should be Understood Across All Test Systems and Populations of Concern



If studies are conducted outside the range of human exposure, is the studied biology relevant to disease induction?

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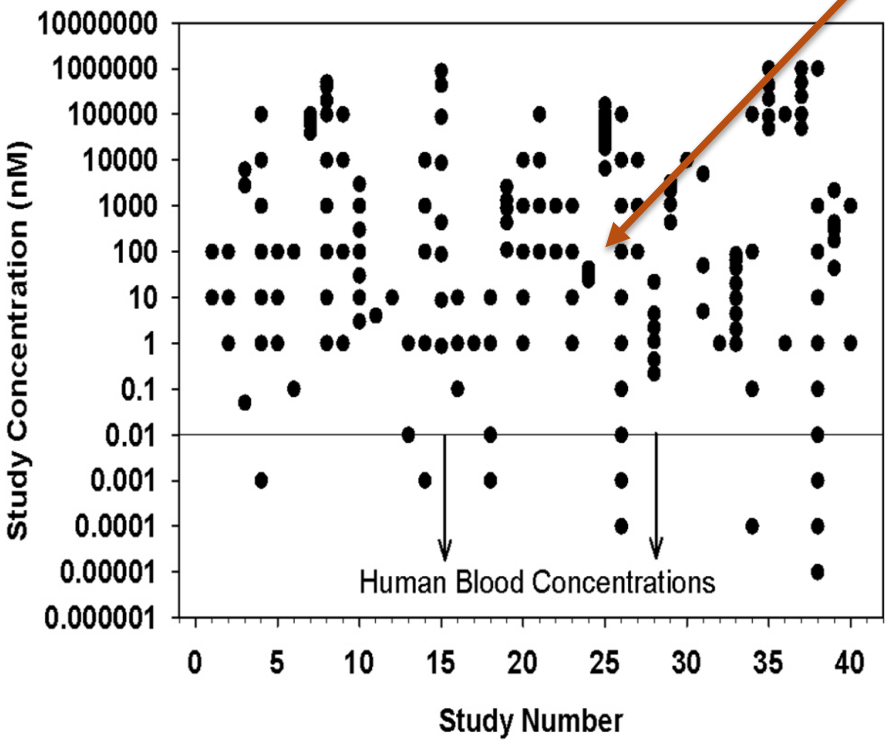
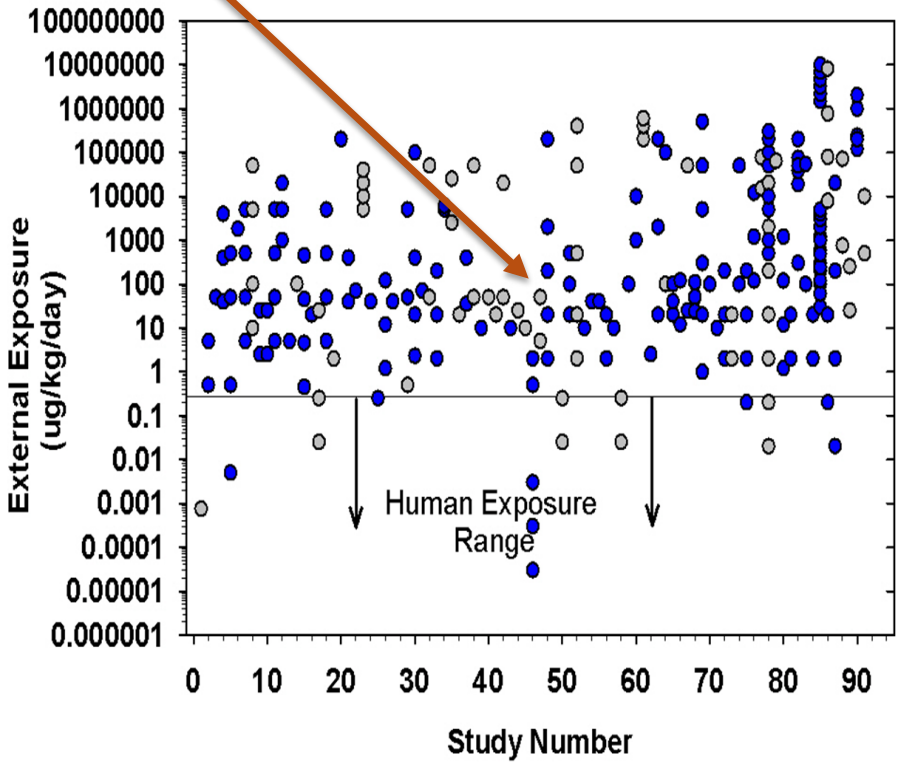
Studies to Define Mechanism
Studies to Define Hazard/Disease

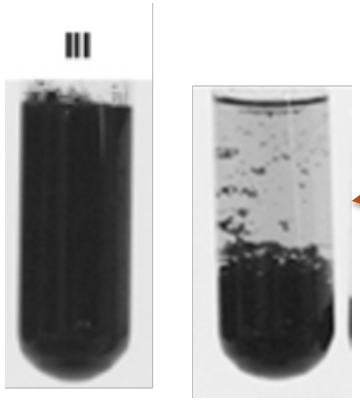
In Vitro



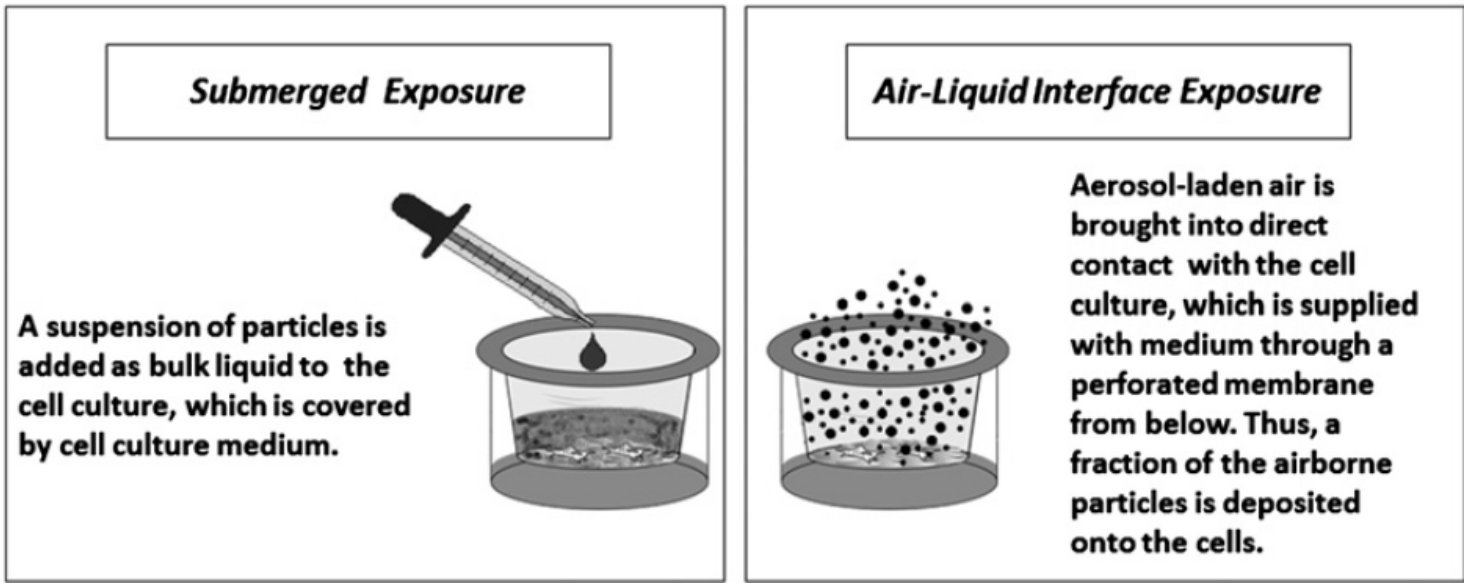
In Vivo



Nanotoxicology: Heroic Particle Exposures In Vitro



Why would these particles be more toxic?



A Contrast in the Penetrance of Mechanistic and Exposure Frameworks in Environmental Health Training and Research

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

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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

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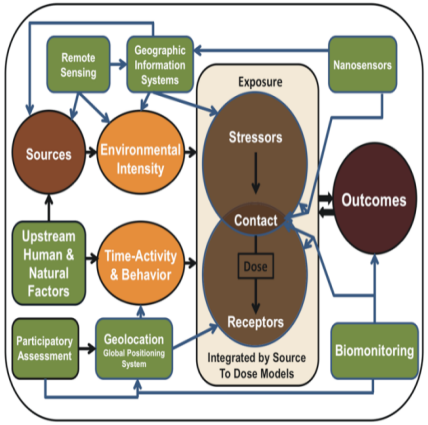
Conceptual site models, fate and transport models, and the AEP are all representations of an overarching organizational framework for exposure science



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

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.

Organizing Exposure data for Toxicology

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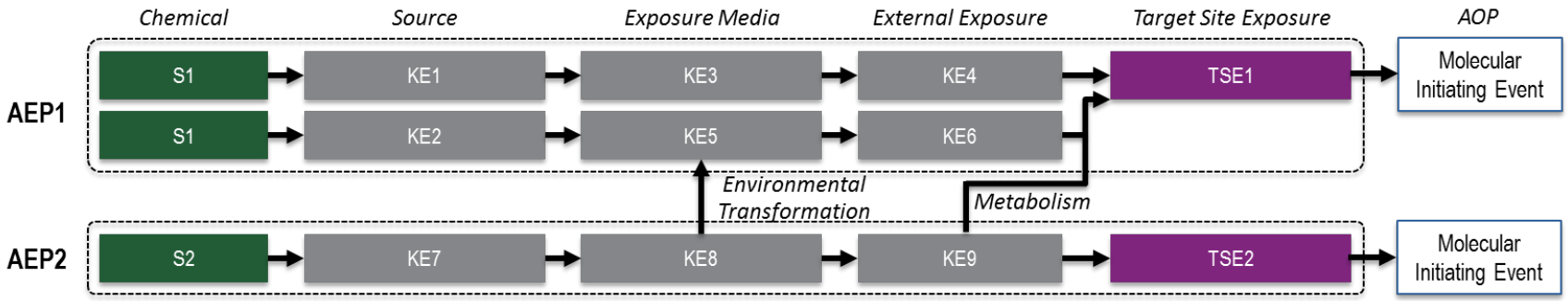
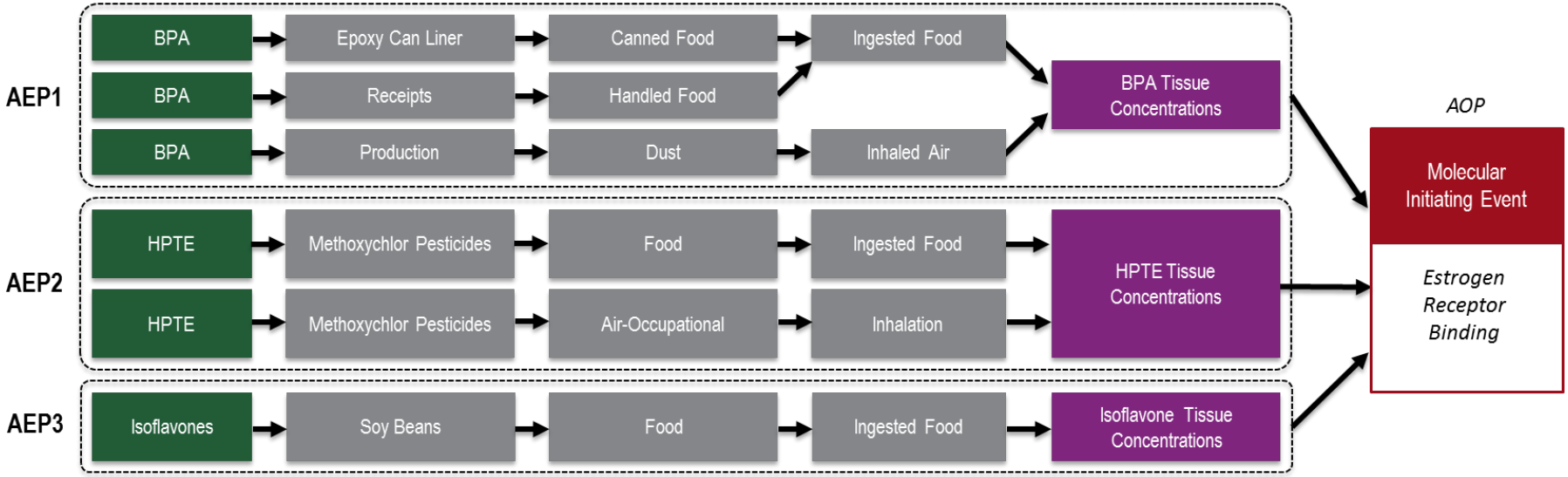
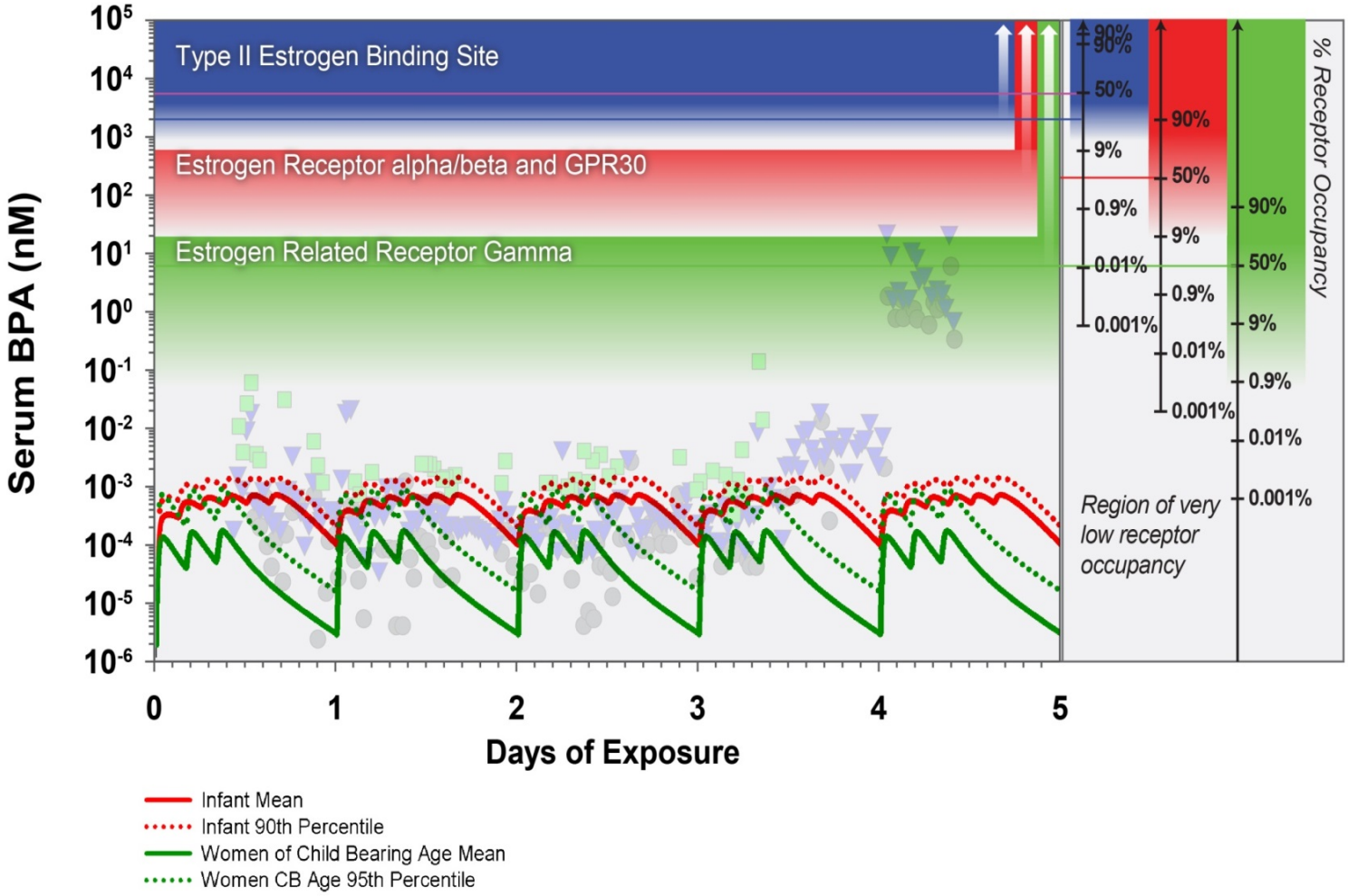
A: Conceptual AEP Framework



B: Interacting AEP Networks for Natural and Synthetic Dietary Estrogens



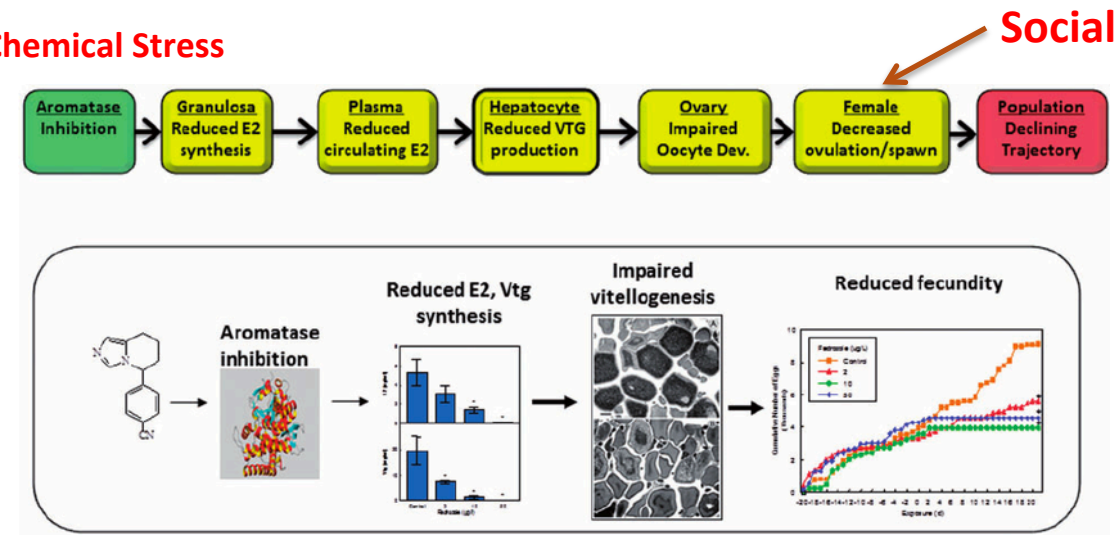
The AEP-AOP Linkage: Receptor Occupancy of Less than 0.001 % in Infants and Women of Child Bearing Age

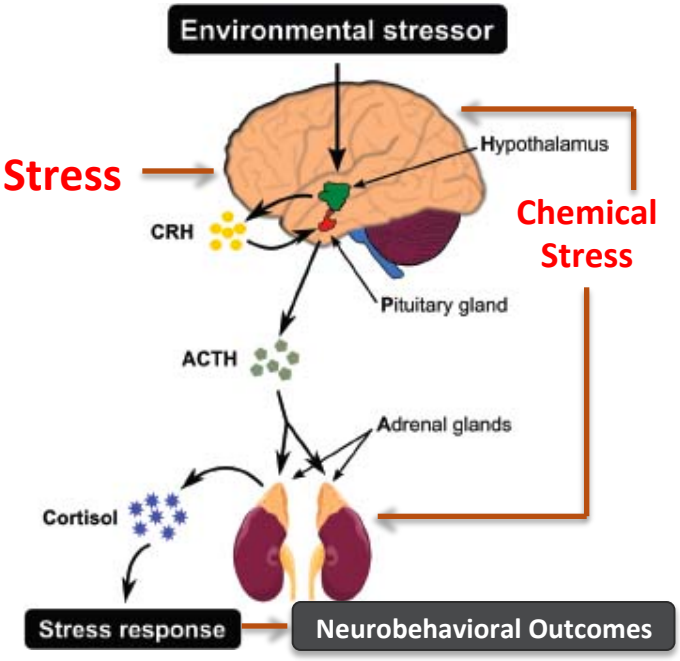


Linking Chemical and Non Chemical Stressors through Mechanisms

Linking Chemical and Non Chemical Stressors through Mechanisms

- Mechanisms describe how stressors cause disease
  - (Mode of action, adverse outcome pathway, etc.)
- Molecules are the transducers of chemical and non-chemical stresses that cause disease
  - Oxidative stress-Infection, Cortisol and stress



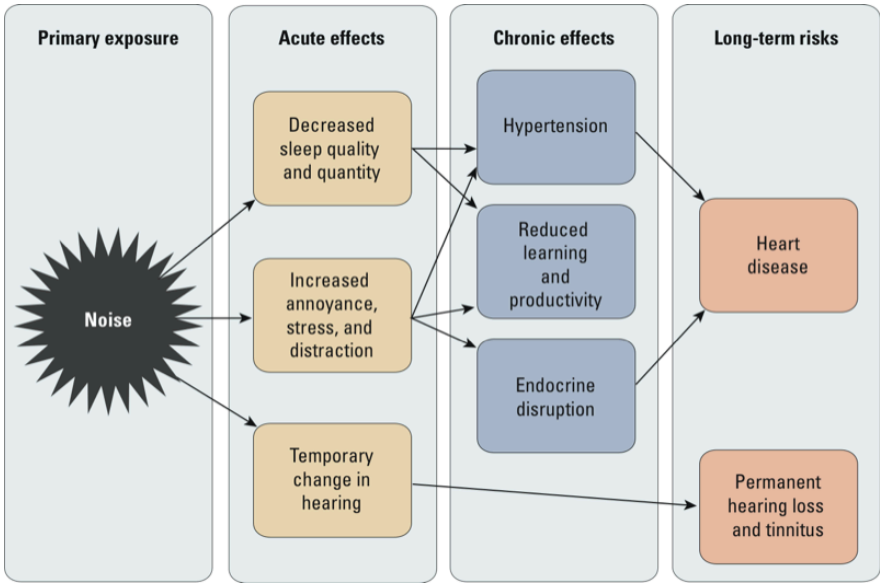


Knudsen, Thomas B., et al. "FutureTox II: in vitro data and in silico models for predictive toxicology." *Toxicological Sciences*143.2 (2015): 256-267.

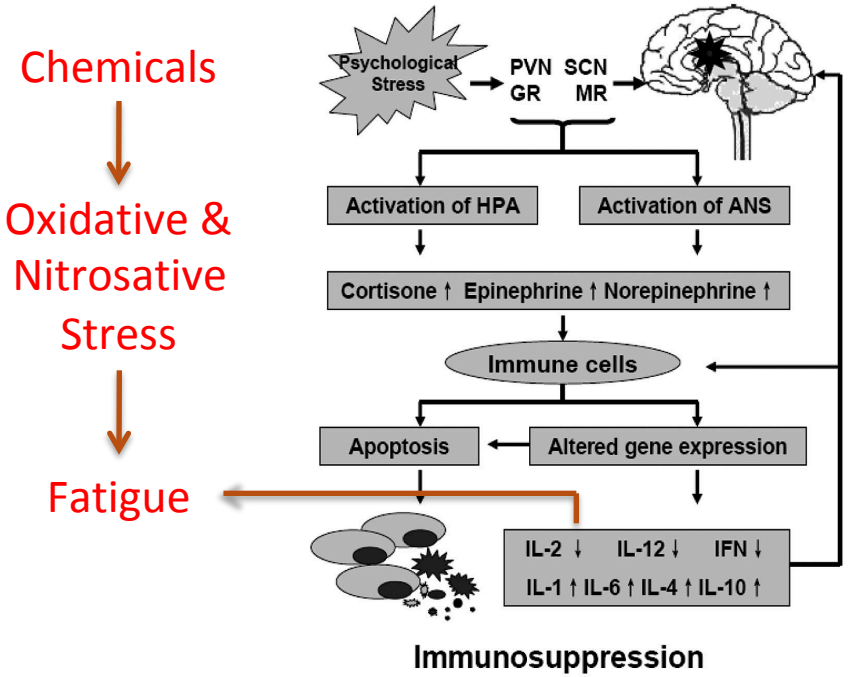
Lanoix, D., and P. Plusquellec. "Adverse effects of pollution on mental health: the stress hypothesis." *OA Evidence-Based Medicine* 1.1 (2013): 1-9.

Linking Chemical and Non Chemical Stressors through Mechanisms

- Chemical and non-chemical stressors have mechanistic and molecular intersections
- Multiple chemical and non-chemical stressors can converge through common mechanisms, key events, and molecular transducers



Hammer, Monica S., Tracy K. Swinburn, and Richard L. Neitzel. "E*nvironmental health perspectives* 122.2 (2014): 115.



Yuan, Aihua, et al. *Experimental and therapeutic medicine* 1.1 (2010): 13-18.

Linking Exposure to Disease through Mechanisms

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- Exposure (stressor, magnitude, period/duration, location) influences
  - Endpoint/Disease
  - Mechanism
  - Severity and or Probability of adverse effect/disease
  - Timing/Onset

Chemical and Non-Chemical Stressors in Disease: Key Research Hypotheses

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- (**AOP)**There is a mechanistic basis for multiple stressors to contribute to a single disease or outcome
- (**AEP**)The level of non-chemical stress measured humans can induce key events in the common AOP.
- (**AEP**)The level of chemical stress measured humans can induce key events in the common AOP.

The Highest Impact Research would Include Testing of Exposure Hypotheses

Conclusions & AEP-AOP Impact on Biomedical & Environmental Health Research

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- The long preference for funding discovery of faster, richer, deeper, more specific, more sensitive assays for biological response and mechanism should shift towards a greater balance with exposure-related research
- Useful conceptual framework for integrating chemical and non-chemical stressors that helps evolve the field toward:
  - Coordinated, mutually supportive hypotheses regarding exposure, mechanism, biomarkers, susceptibility/resistance
  - Mechanistic studies and hazard studies conducted at human-relevant exposure levels
- Impacts
  - Stimulate new research programs at the intersection of exposure and environmental disease equally grounded in mechanism and exposure
  - More comprehensive understanding the environmental causes of disease
  - Research demonstrably more relevant to human health (higher impact)
  - Interventions more likely to procure health benefits (higher significance)

Acknowledgements

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  - ACC
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  - DOE-LDRD
- U.S. EPA
  - Stephen Edwards
  - Cecilia Tan

Backup Slides

Pregnancy Estrome: An Exposure Biology Framework for Ranking EDCs

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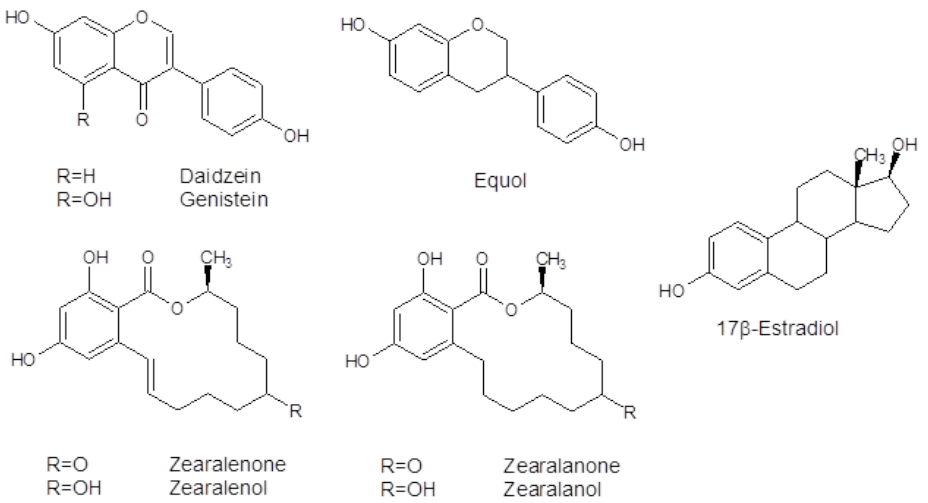

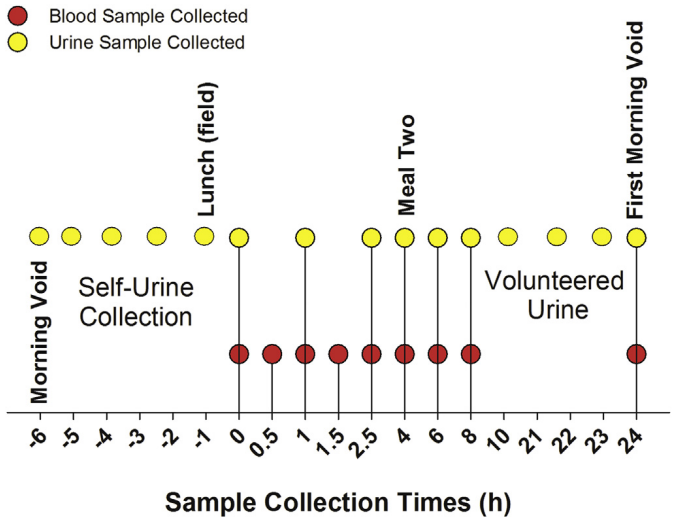

- 30 pregnant women from the SLC area selected for higher BPA exposure (20) and higher isoflavone exposure (10). Included cashiers and individuals handling cash register receipts.
- Field exposure and clinical exposure periods.
- Repeated blood and urine sampling
- Reporting blood BPA, Genistein, Diadzein, Zeralenone, Estradiol, Estriol Estrome, Estetrol (fetal derived estrogen).

Concentrations Endogenous Estrogens are Variable in Individuals

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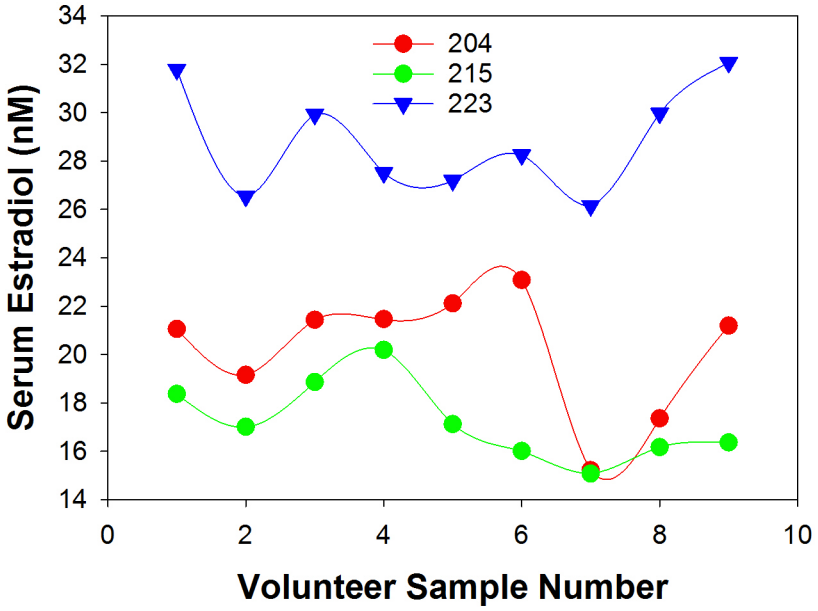

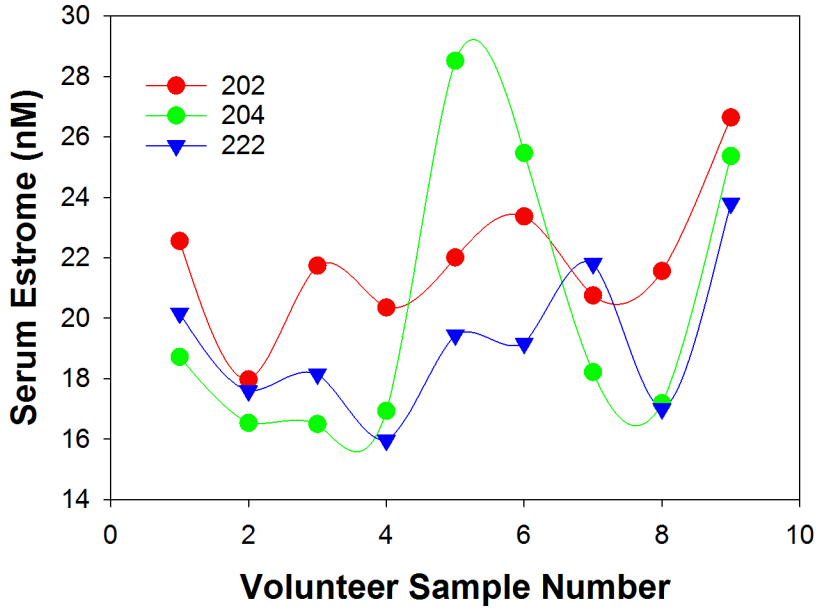

Receptor Occupancy for Ranking EDCs in High Estrogen Physiological Conditions

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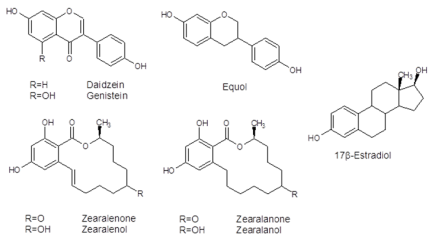
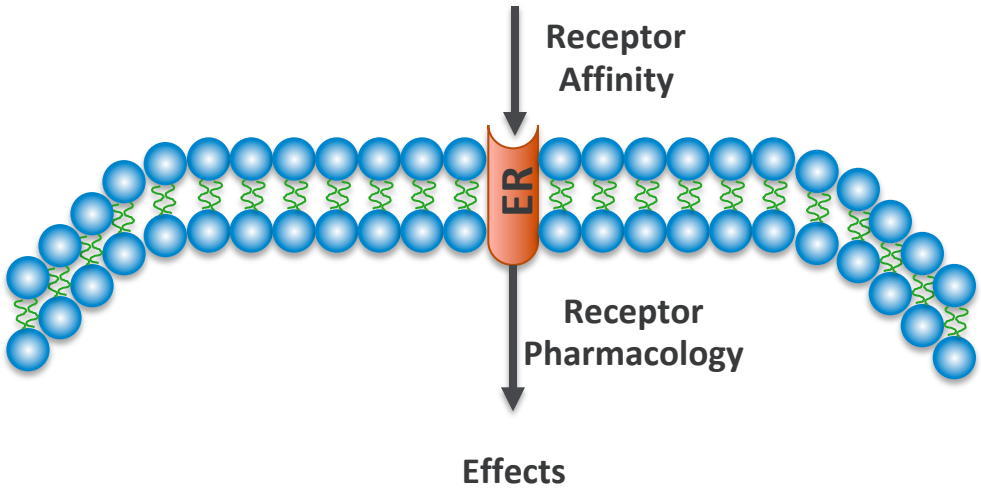


A basic tenet of receptor pharmacology is that a drug's effect is directly proportional to the number of occupied receptors.

E1 E2 E3 E4 GN DZ ZR BPA

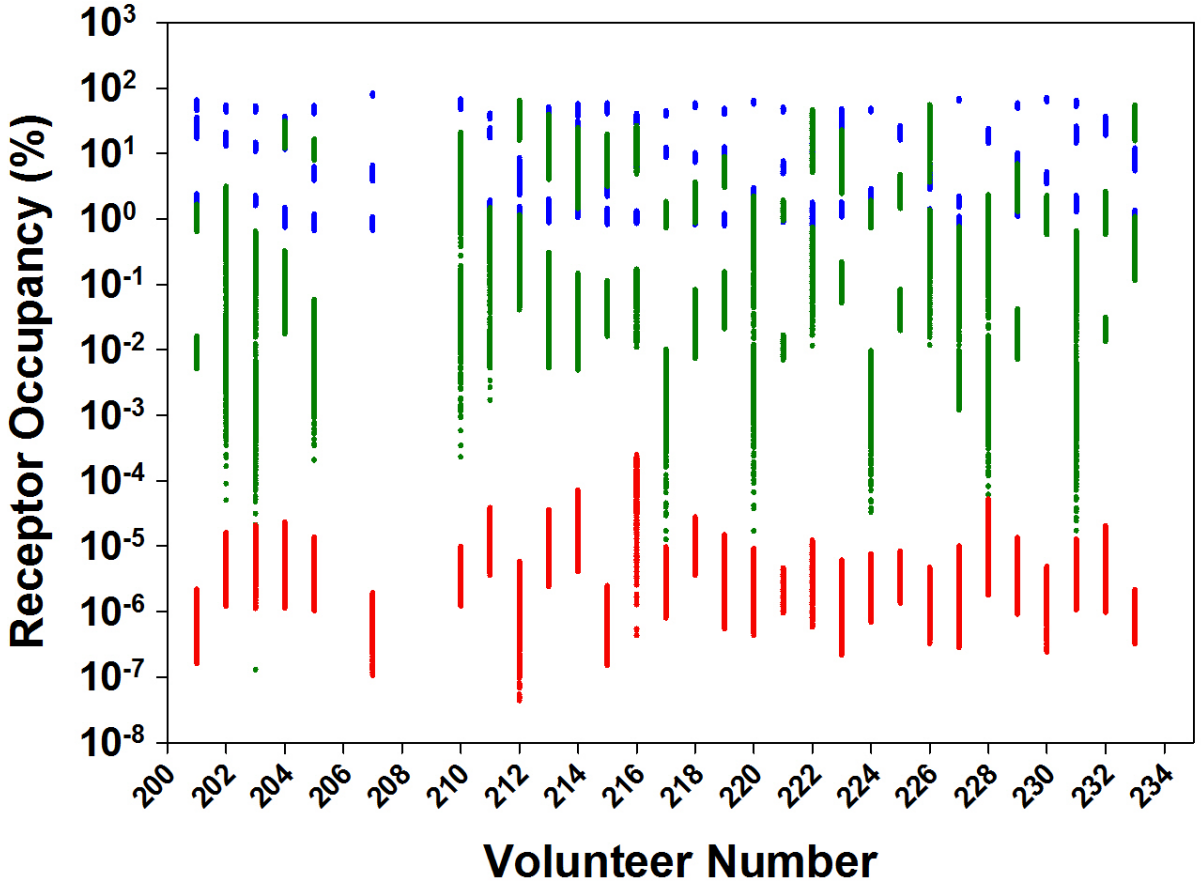


- Occupancy solved using standard competitive equilibrium equations
- Measured or estimated parent compound free concentrations used.
- Measured receptor affinity constants used.
- Variability in receptor signaling potency considered (Monte-Carlo)

$$\text{Response} = \frac{Bound\ Receptors}{Total} \times Relative\ Signaling\ Potency$$

$$\text{Total Response} = \sum_{1}^{9} \frac{Bound\ Receptors}{Total} \times Relative\ Signalling\ Potency$$

Plant Derived Estrogens Contribute More Estrogenicity than the Synthetic Estrogen



Endogenous

Soy Isoflavones

Bisphenol A

Three NAS Reports: Data Acquisition, Integration and Modeling at a Grand Scale

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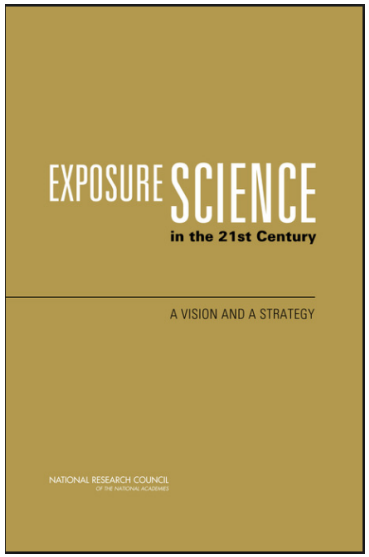
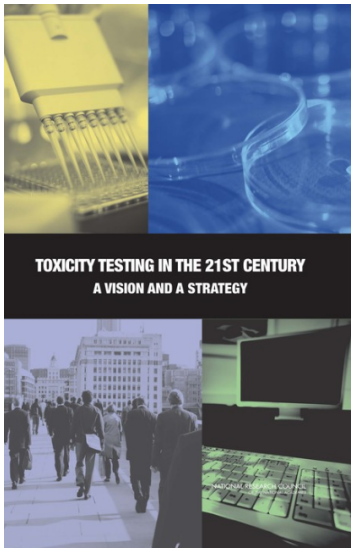
- More comprehensive exposure characterization
- Source to receptor
- **Biokinetic models**
- **Human equivalent exposures**
- **Population exposures**
- **Target site exposures**





- 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

In 10 Years, We cannot Afford to be Where we are Today

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"Dose must thus be viewed as a relatively nebulous parameter when discussing in vitro studies as reported herein."

"It is too hard." "Costs too much." "Too complicated."

Rich, Precise, Accurate

Response

Limited, Imprecise, Inaccurate

The Axis of Ignorance

Exposure

Using 21st Century Science to Improve Risk-Related Evaluations

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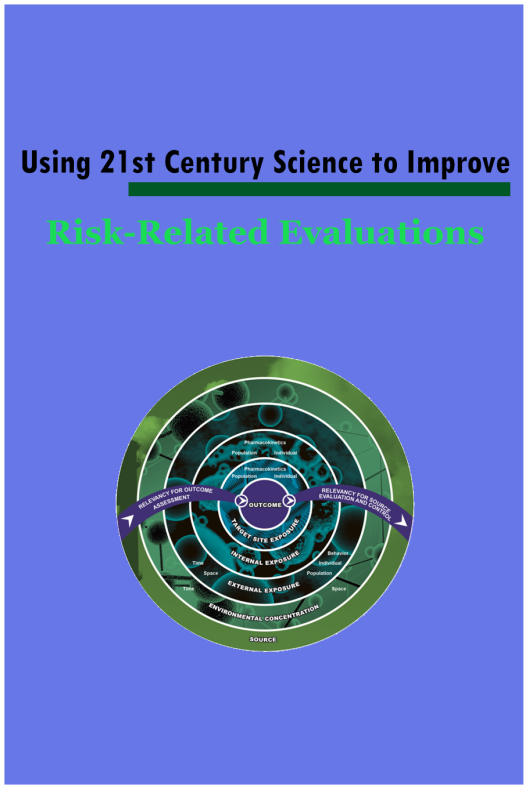

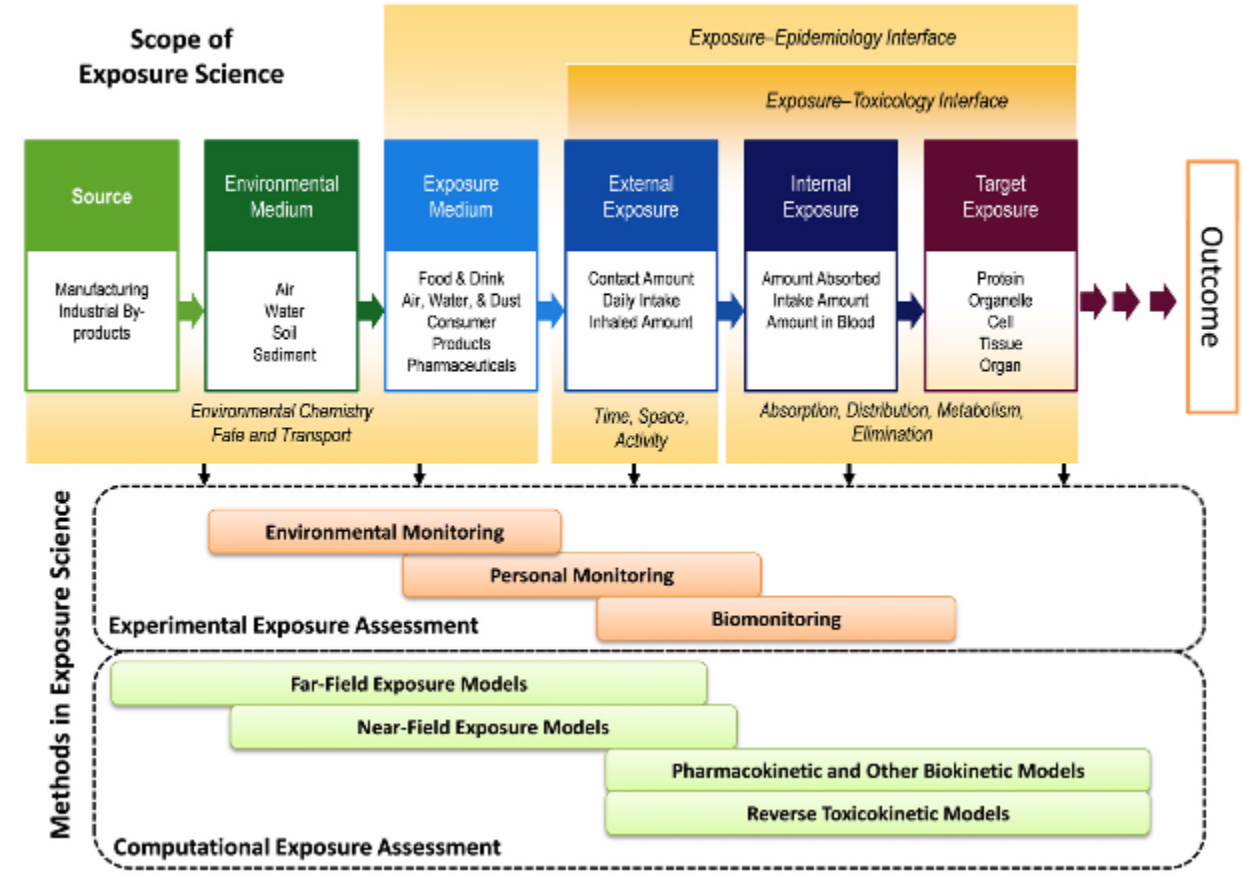

Identify Chemicals or Other Stressors and Quantify Sources and Exposures

- *Challenge:* Humans are exposed to complex uncharacterized mixtures of stressors. Source information is limited. Analytical chemistry is limited to compounds for which standards are available.
- *Recommendation:* Expand current efforts to obtain and organize information on chemical quantities and release rates from products. Expand curated databases of analytical features for identifying compounds. Increase capacity to conduct targeted and nontargeted analyses to identify new and existing chemicals and mixtures.

Align Environmental and Test-System Exposures

- *Challenge:* Aligning exposures and information obtained from experimental systems is required for improving risk based evaluations. Many factors confound alignment across systems.
- *Recommendation:* Quantify test system exposures over time or use reliable estimation methods. Develop models that explicitly translate information between actual exposures and experimental systems.
- *Recommendation:* Chemical concentrations that reflect human exposures as derived from biomonitoring measurements or from predictive models should be considered when designing testing protocols for biological assays. Improving knowledge of process that determine chemical fate in biological and test systems will be necessary to meet this recommendation.

Improve Knowledge of Processes That Determine Chemical Fate in Systems

- *Challenge:* Information on system properties, processes, and transformation pathways that contribute to chemical exposure is nonexistent, incomplete, and inconsistent, and this limits the capacity for more comprehensive, quantitative exposure-based and risk-based evaluations.
- *Recommendation:* Develop databases of chemical properties and information on rates and processes that control chemical fate in vitro and in vivo and in environmental systems. Obtain by experiment or modeling.
- *Recommendation:* Develop and apply methods for measuring and predicting chemical transformation pathways and rates in environmental media, test systems and humans. Use these data to better interpret test system data in the context of human exposures.

Integrate Exposure Information

- *Challenge:* Integration and appropriate application of exposure data from environmental media, biomonitoring samples, conventional samples (blood and urine) and emerging matrices (hair, nails, teeth and meconium) is a scientific, engineering and big-date challenge. Integration of measured and modeled data is a key step is developing exposure narratives and evaluating concordance to increase confidence.
- *Recommendation:* New interdisciplinary projects should be initiated to integrate exposure data and gain experience that can be used to guide data collection and integration of conventional and emerging data streams. High priority should be placed on existing guidance on quality of individual exposure data to include evaluating the quality of integrated data streams.

Expand and Coordinate Exposure Science Infrastructure to Support Decision Making

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- *Challenge:* Most exposure information is fragmented, incompletely organized and not readily available or accessible. The full potential of this information cannot be realized.
- *Recommendation:* Develope the infrastructure and organize data using conceptual and systems based frameworks that are commonly used in exposure assessment that facilitate generation, acquisition, organization, access, evaluation, integration, and transparent application and communication.

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)?