

The Exposome: a Tool for Transforming Exposure Science

David M. Balshaw, PhD

Chief, Exposure, Response, and Technology Branch
Division of Extramural Research and Training
National Institute of Environmental Health Sciences

- **Mission:** to discover how the environment affects people in order to promote healthier lives

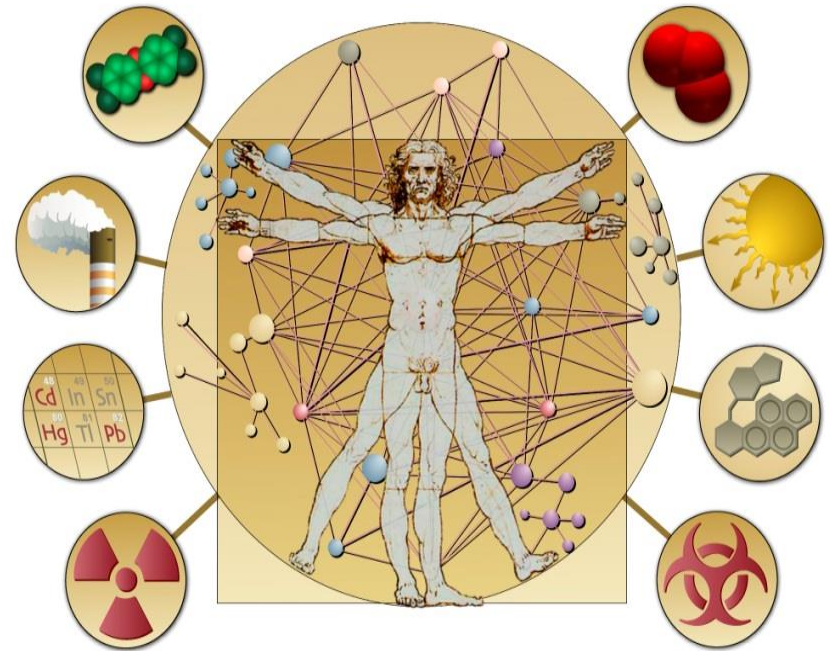
- **Vision:** to provide global leadership for innovative research that improves public health by preventing disease and disability



What is NIEHS doing?

Strategic Goal 3: Transforming exposure science

- Advance characterization of environmental exposures through **improved exposure assessment** at both the individual and population levels
- Define and disseminate the **concept of the exposome**
- Create **tools and technologies**, and the research **capacity**, needed to **characterize the exposome**



NRC Report —Exposure Science in the 21st Century

Commissioned by EPA and NIEHS in 2010

Goals

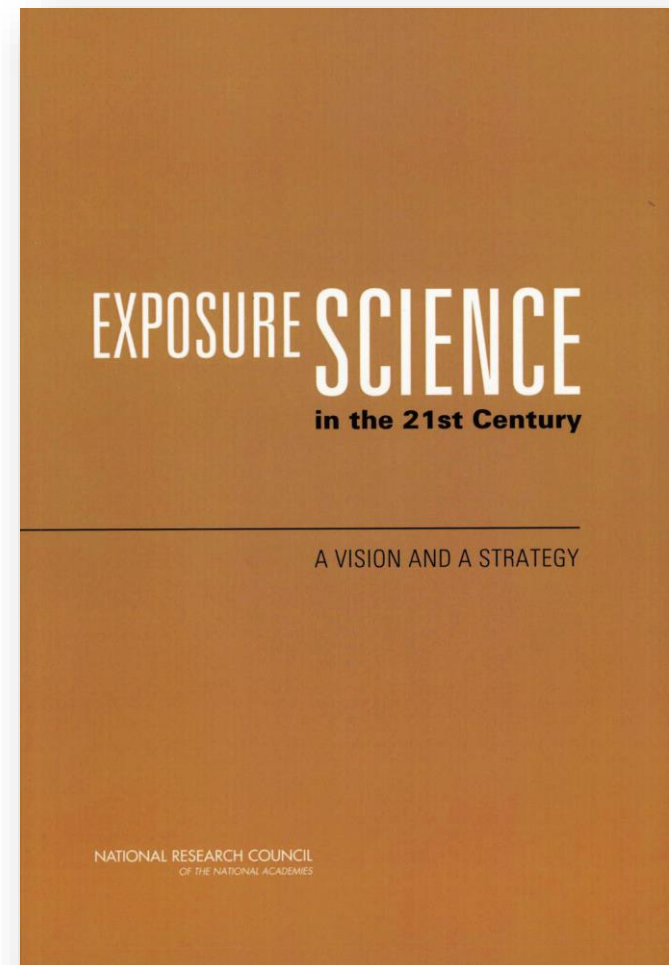
- Provide a transformation for exposure science
- Provide a catalyst to the science

Charge to the Committee

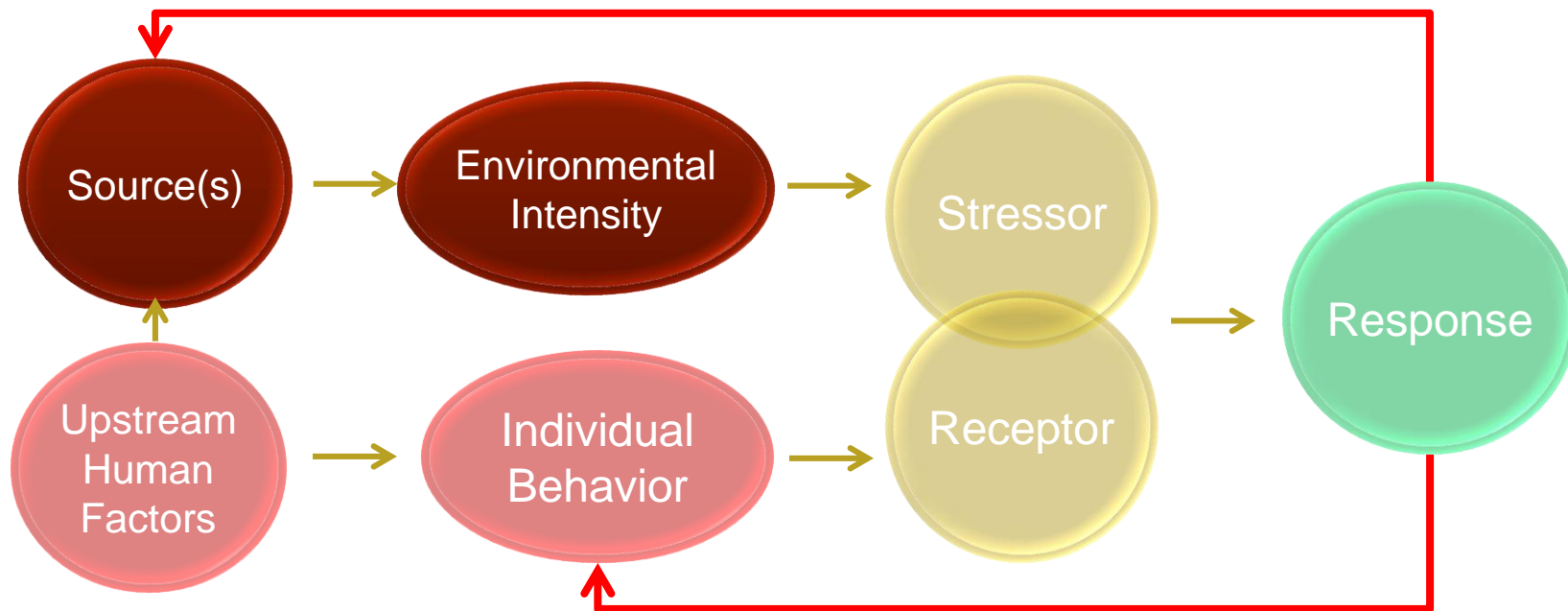
- Develop unifying conceptual framework for advancement of human and ecological exposure science
- Develop a long-range vision for exposure science and strategy for implementing the vision over the next 20 years

Companion to NRC reports *Toxicity Testing in the 21st Century, and Science and Decisions: Advancing Risk Assessment.*

Report released September 7, 2012



What is Exposure?



The Complex Realities of Exposure

Stressor:

Physical, Chemical, Biological, Psycho-social

Source:

Air, Water, Soil, Food, Consumer Products, Drugs

Place:

Home, School, Work, Neighborhood,
Community, City, State, Region

Time:

Fetal, Child, Adolescent, Young Adult,
Adult, Older-adults, Elderly

Route of Contact:

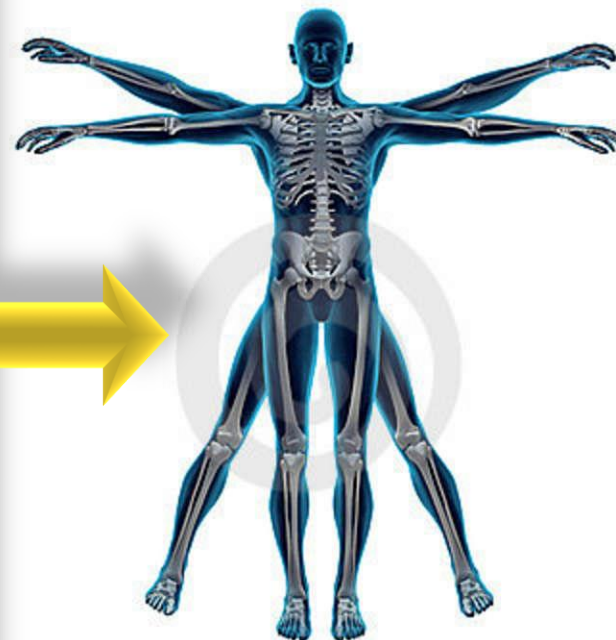
Skin, Lungs, Diet

Distribution:

Lungs, Neuro, Skin, GI, other organs

Targets:

Biological pathways



The Exposome (Wild): The totality of exposure an individual is subjected to from conception to death...the 'environmental' correlate to the genome.



There are multiple conceptualizations of the EXPOSOME...

Wild

- **All life-course environmental exposures** from prenatal period onwards; includes internal body processes, external exposures, and lifestyle factors.

Rappaport and Smith

- Total exposures throughout life, where the “environment” is the body’s internal chemical environment and “exposures” are all the **biologically active chemicals in this internal environment**.

Buck Louis

- **Mixture of environmental exposures**, including man-made and naturally occurring chemicals, physical agents (e.g., noise, vibration, temperature), **macro level factors** (e.g., population density, sanitation), and **lifestyle factors**.

Miller

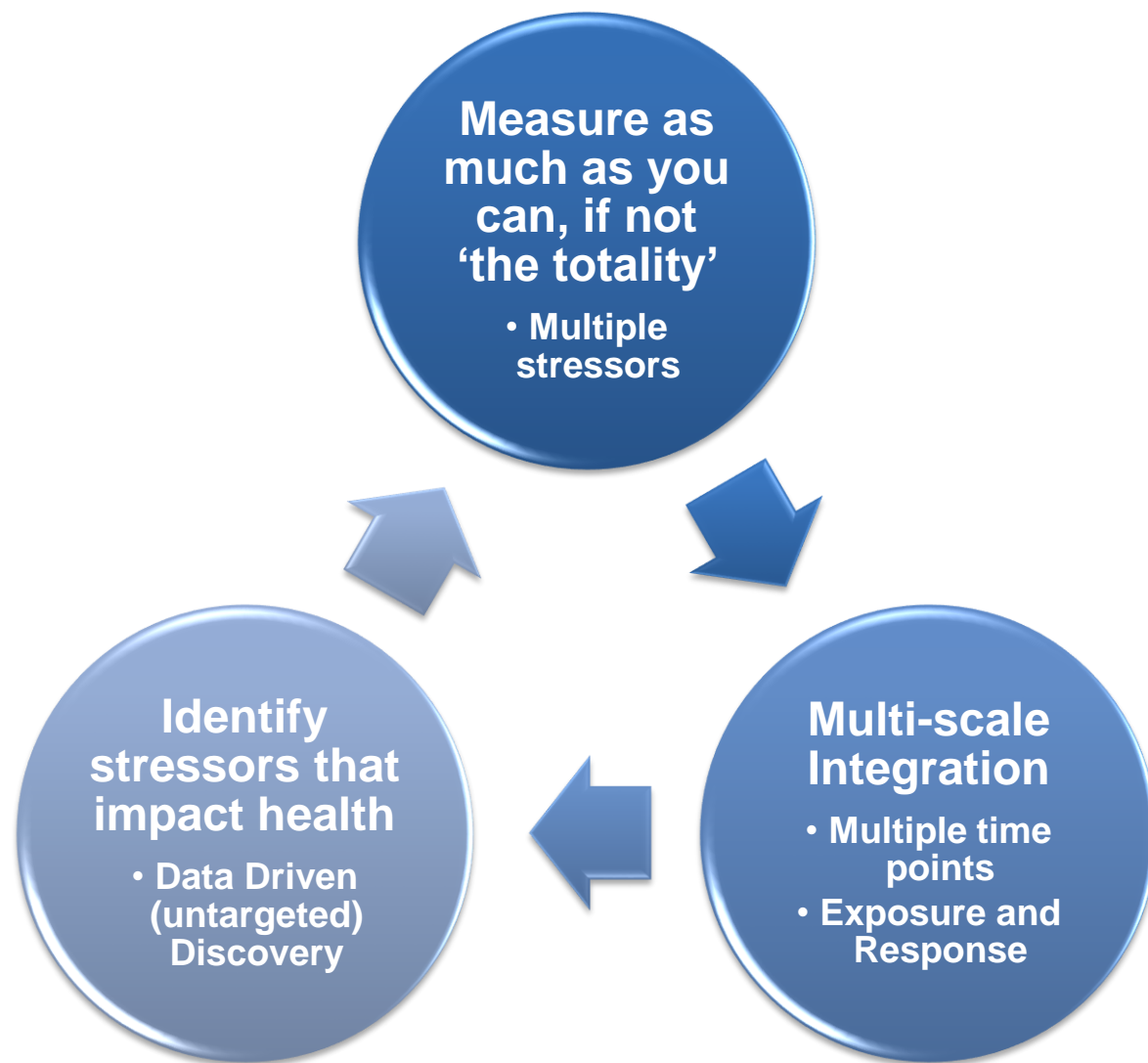
- The **cumulative measure** of environmental influences and **associated biological responses** throughout the lifespan including exposures from the **environment, diet, behavior, and endogenous processes**.

NRC Report

- “**Eco-exposome**” extends concept from point of contact between stressor and receptor, **inward into organism and outward to general environment**.

... and a need to develop a unifying conceptual framework.

Common Elements of The Exposome Concept



Challenges

Sociological

- Advancing and defining the exposome concept
- Integration of different stakeholder perspectives
- Willingness to do untargeted discovery

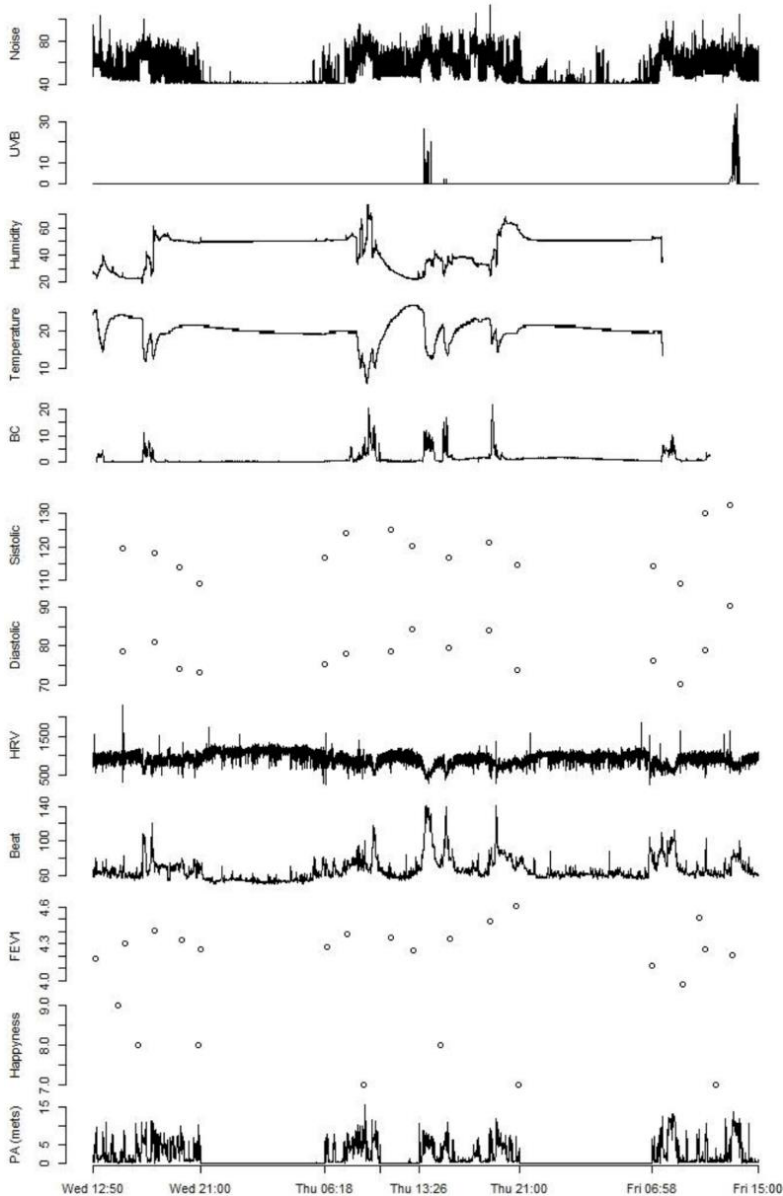
Technological

- Integration external exposure and internal response
- Technologies for multi-analyte exposure assessment
- Conceptual frameworks for data-driven and untargeted analysis
- Advances in statistical methods to handle the complex, interrelatedness, and dynamic nature of exposure data

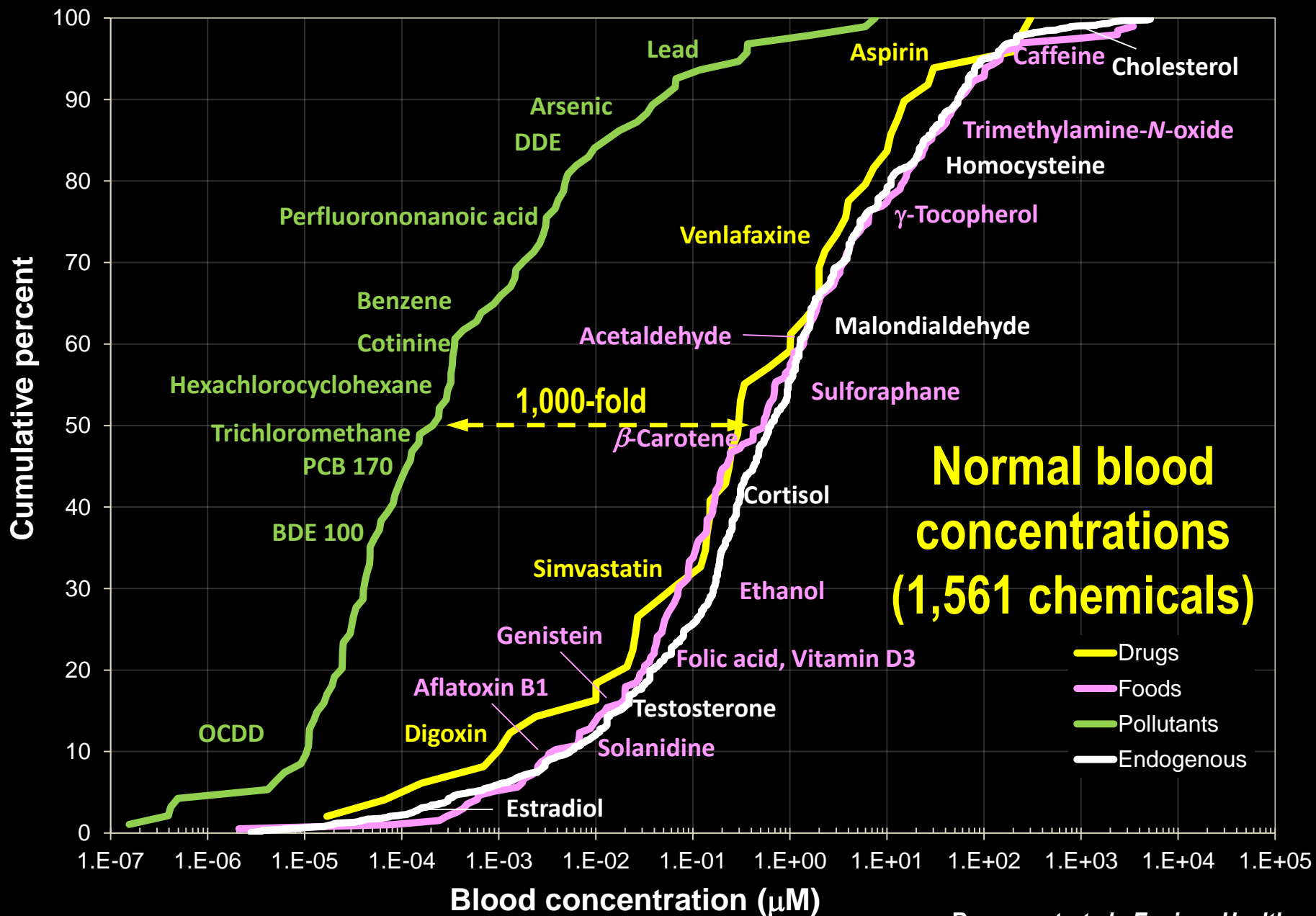
Logistical

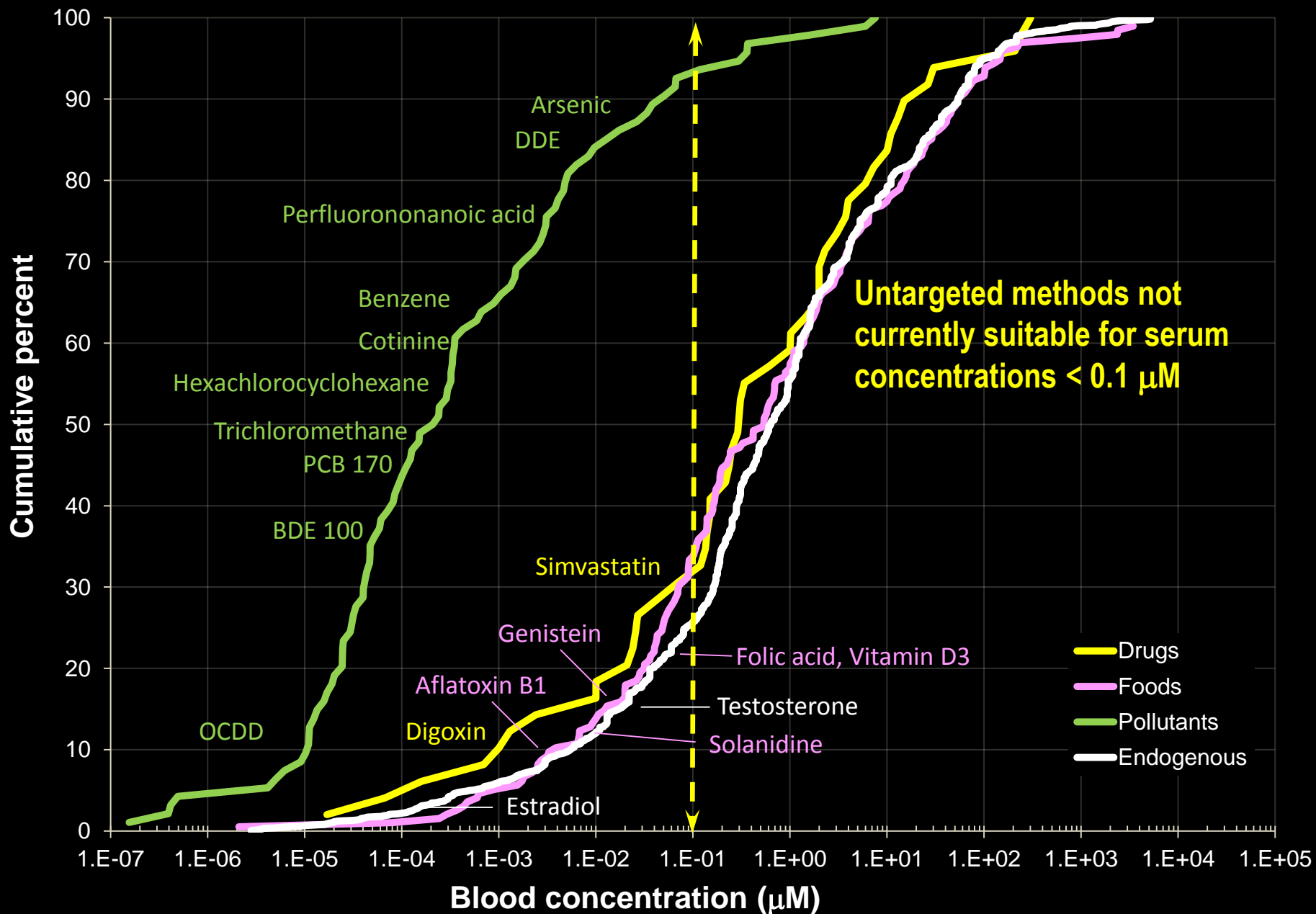
- Time scale: Lifetime; Windows of Susceptibility; Prospective vs. Retrospective
- Sample collection, size, power and analysis
- Collaboration and Data sharing

The Challenge of External Exposure Assessment in the context of the Exposome

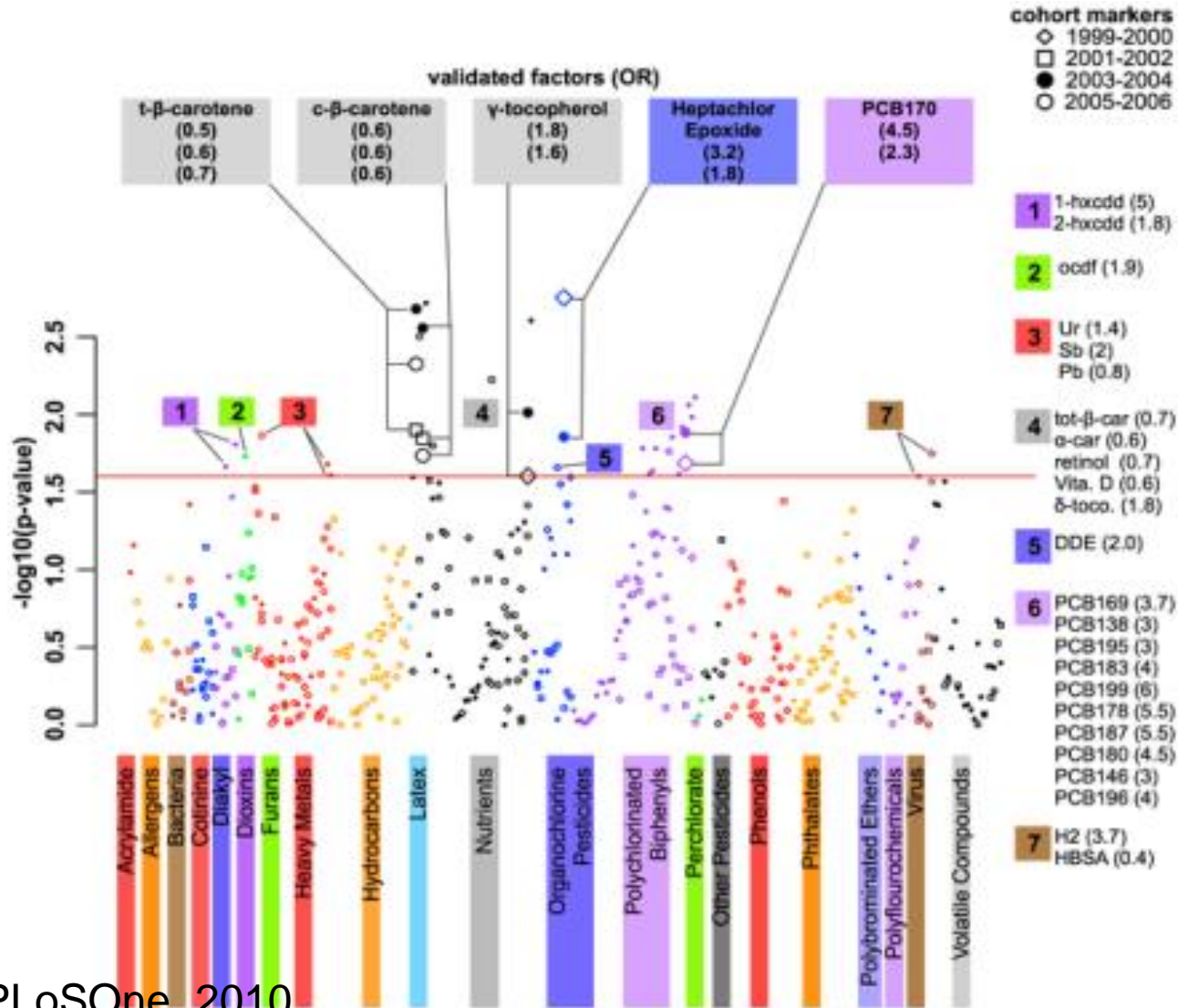


The Challenge of Internal Exposure Assessment in the context of the Exposome





Environment Wide Association Studies – targeted analysis of NHANES



The Challenge of Response Assessment in the context of the Exposome

Biological consequences of exposures

- There are specific molecular, cellular, and physiological effects AND responses
- Consequences include effects, responses, impact, etc.
- Ultimately, these alterations in biology impact human health and are the cause of disease
- Exposures have an impact on our bodies

Does the exposome represent a biological index of nurture?

‘Nurture’ refers to all the environmental variables that impact who we are.

Invoking the concept of nurture with the exposome may appear to add an undesirable layer of complexity; however, it expands the exposome from a quirky concept of exposure assessment to a fundamental need in science.



Allostasis (Sterling, Eyer, McEwan)

- Allostasis: maintaining stability through change.
- Allostasis emphasizes that the internal milieu varies to meet perceived and anticipated demand
- Developed in the context of stress research with a strong emphasis on neuroendocrine systems

Resilience

- Resilience: the ability to avoid deleterious behavioral changes in response to chronic stress
- Resilience is essentially describing the ability to avoid allostatic load and maintain allostasis/homeostasis
- Opposite of susceptibility/vulnerability?

NIEHS Exposome Workshop

Jan 14-15, 2015



Integrated and prioritized recommendations

- overarching themes

1. Establish an exposome clearinghouse as a resource to facilitate exposome research and broad data sharing
2. Improve and expand exposome technologies and methods linking environmental exposure, body burden and biologic effects
3. Practical considerations and exposome promotion strategies

1) Exposome clearinghouse – A resource center to facilitate exposome research

- Accessible and open source
 - existing tools and methods for exposure assessment
 - big data analytics and generic validated computational tools
 - identify a “base dataset” for exposome-related data mining
- Exposure data infrastructure
 - repository, databases, data libraries
 - reporting standards, standardized protocols, language standards, and data harmonization
 - data sharing policies, protocols and tools for use
 - ethical and use guidelines (protection of privacy)
 - NIH-wide mandate for exposome data sharing
 - curated database of environmental exposure and behavior assessment questionnaires

1) Exposome clearinghouse – Continued

- Searchable system for available samples and cohorts
 - freezer Match system
 - use of samples from targeted analyses for untargeted analyses
 - cohorts where exposome data could be added
 - exposome reference materials to cross-reference and standardize facilities in untargeted exposome analysis
- Exposure census
 - Geographic Census of Exposures
 - Population Census of Exposures
- Create global exposome Initiative; coordinate efforts internationally

2) Improve methods and technologies

- External exposure
 - technologies for measurement of multiple priority stressors
 - applicability in large populations
 - Improve exposure models
- Biomonitoring
 - increase coverage and lower analytical costs for low abundant chemicals
 - alternative technologies to mass spectrometry to broaden exposure monitoring
- Biological response
 - approaches to quantify/define allostatic load
 - integration of complex exposure and response data with biological pathways
- Epidemiology
 - Methods for inference and causality with the exposome
- Data and bioinformatics
 - big data mining methods (analytical and visualization)
 - encourage a shift in focus from 'one exposure-one phenotype' to building networks of exposures, genes, and phenotypes

3) Practical considerations and exposome promotion strategies

- Incentivize global parties (research and private sector) to integrate the exposome in their programs
- Provide educational and outreach opportunities (training)
- Use/leverage existing resources and encourage secondary analyses of samples
- Prioritization strategy and criteria for measurements (internal, external, phenotypes)
- Need for larger exposome research grants and transdisciplinary centers (NCI TREK)
- To start, develop use cases

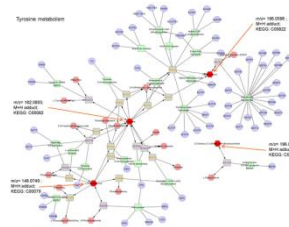
Use cases discussions and recommendations

- Group 1 focuses on how to implement the exposome as a tool to understand the nature of exposure, identify associations between exposure and human health and investigate the mechanisms underlying those associations
 - Developed a series of study ideas that would advance development of methods to measure both external and internal exposome
 - Use fit-for purpose approach to select a suit of exposure assessment tools based on the characteristics and the size of the study population
- Group 2 emphasizes the multistage process nature of exposome research
 - First stage is association discovery and hypothesis generation
 - Need to be followed by validation (hypothesis driven) and prevention

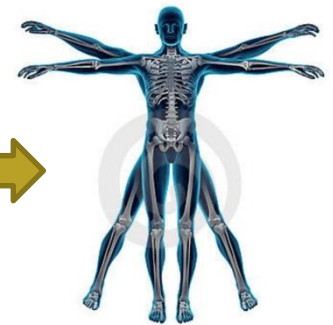
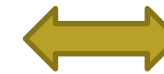
Children's Health Exposure Analysis Resource (CHEAR)

- Dec 12, 2014 NIH ended the National Children's Study
- Jan 30, 2015 Concept for redirection of NCS funds to meet original goals of understanding impact of the environment on children's health approved by NIH Council of Councils
- NIEHS is developing CHEAR infrastructure
 - Access to comprehensive targeted and untargeted analytical capacity (i.e. the exposome)
 - Assess biological response
 - Statistical/interpretive support
 - Data Repository/data/metadata standards
 - Community resources

The Exposome



Inflammation
 Oxidative Stress
 Endocrine Signaling
 DNA repair
 Cell Cycle control
 Energetics



Exposomics

To learn more: NIEHS Exposome Webinar Series

- Regular discussions on the exposome
 - Gary Miller, Emory/HERLCULES
 - Stephen Rappaport, UC Berkeley
 - Denis Sarigiannis, AUTH/HEALS Consortium
 - Martine Vrijheide, CREAL/HELIX Consortium
 - Paolo Vineis, Imperial/EXPOsOMICS
 - Shoji Nakayama, NIES/JECS, October 23, 2014
 - Chirag Patel, Harvard Med School, Dec 2, 2014
- Registration
 - http://tools.niehs.nih.gov/conference/exposome_webinar_2014/
 - Email: exposome@niehs.nih.gov

Thank You!
Questions?