United States Environmental Protection Agency

Risk-Based Decision Making in Public and Population Health

Exposure Assessment and Future Directions in Exposure Science

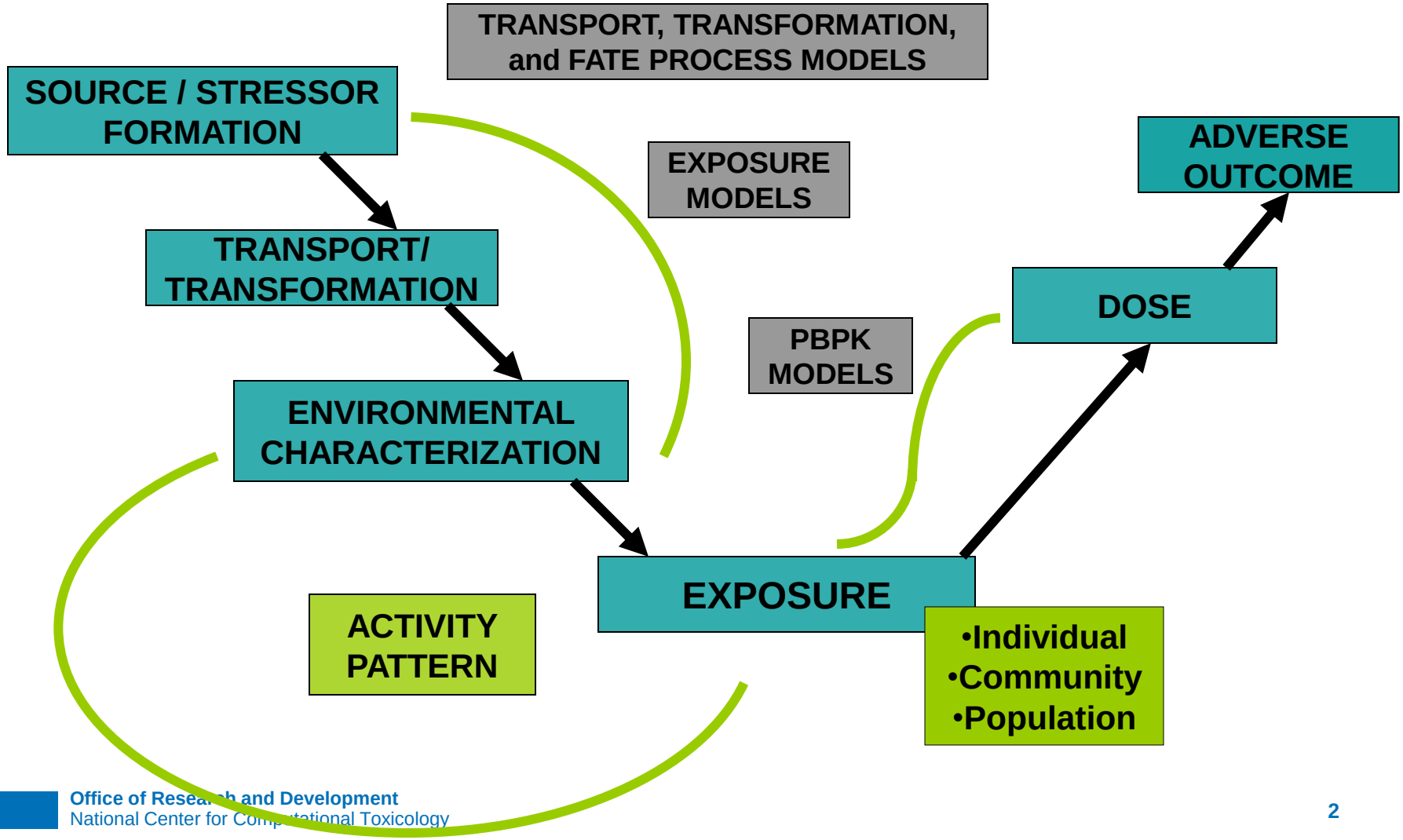
ELAINE COHEN HUBAL
US EPA, NATIONAL CENTER FOR COMPUTATIONAL TOXICOLOGY

Disclaimer. Although this work was reviewed by EPA and approved for presentation, it may not necessarily reflect official Agency policy.

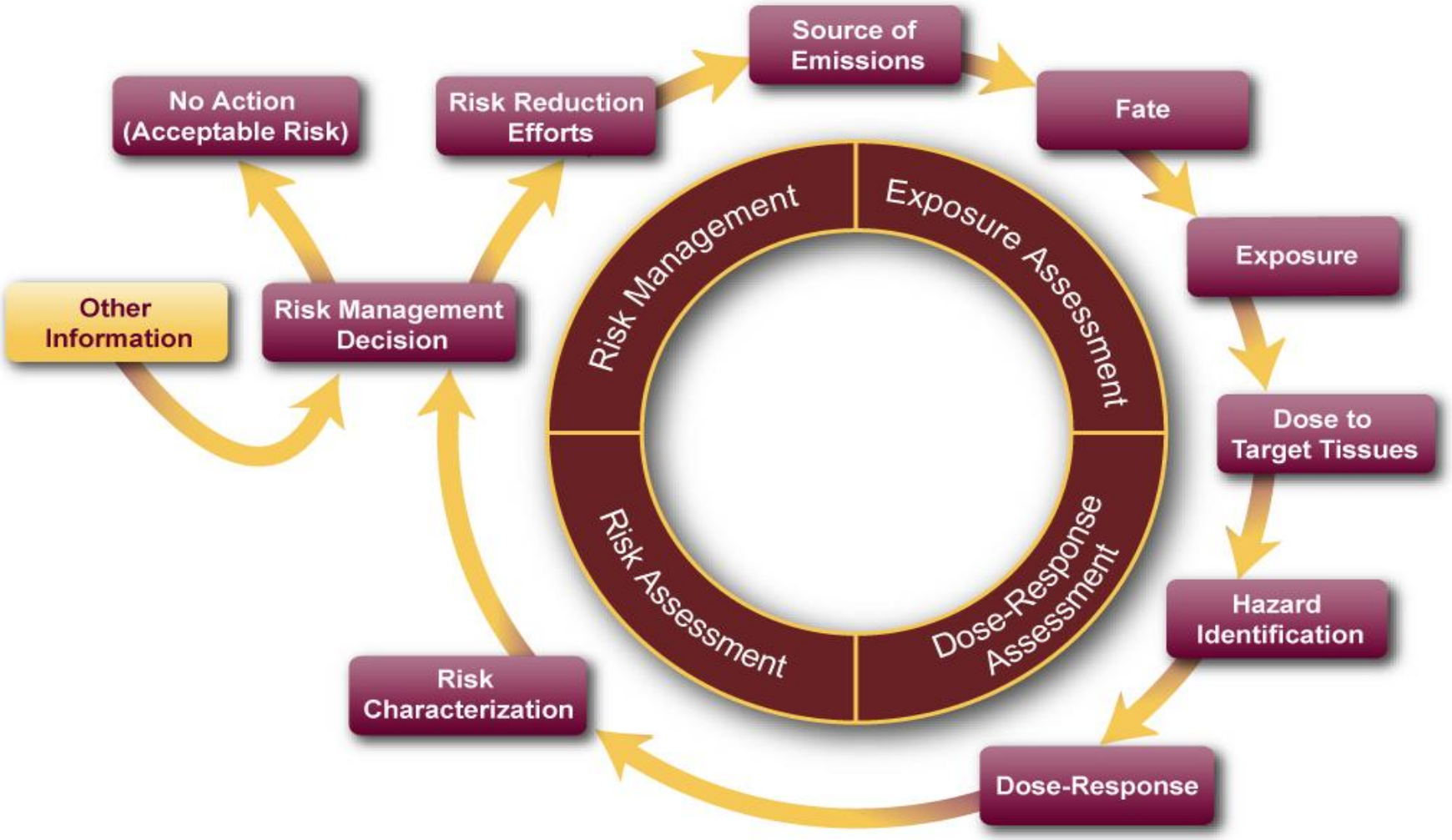
United States
Environmental Protection
Agency

Exposure Assessment

Purpose of Exposure Assessment



Exposure in Risk Assessment and Management



United States Environmental Protection Agency

Exposure Assessment

- Exposure is the contact between a stressor and a human or ecological receptor.
- Risk analysis step in which receptor interaction with the exposure stressor of concern is evaluated.
- To assess exposure to a particular stressor we need to know
  - Properties of the stressor
  - Sources, pathways, routes
  - Pattern of exposure (magnitude, frequency, duration, location)
  - Characteristics of receptor
- Sometimes we can measure exposure directly
- Often we need to estimate exposure

United States Environmental Protection Agency

Problem Formulation

- Scope of assessment
  - Scale (national, site specific, far-field, near-field)
  - Receptor (vulnerable life stages and groups)

- Conceptual model
  - Guide for collection of exposure data and other required information
  - Traditionally, follow source-to-effects paradigm
  - Shift to target-oriented view

United States Environmental Protection Agency

Exposure Assessment Approaches

- Questionnaire based metrics (epidemiology)
- Surrogate exposure metrics (ambient measures)
- Exposure measurement (direct or point-of-contact)
- Biomonitoring (dose reconstruction)
- Modeled estimates (indirect or scenario evaluation)
  - Often used to conduct risk assessments required to make regulatory decisions.

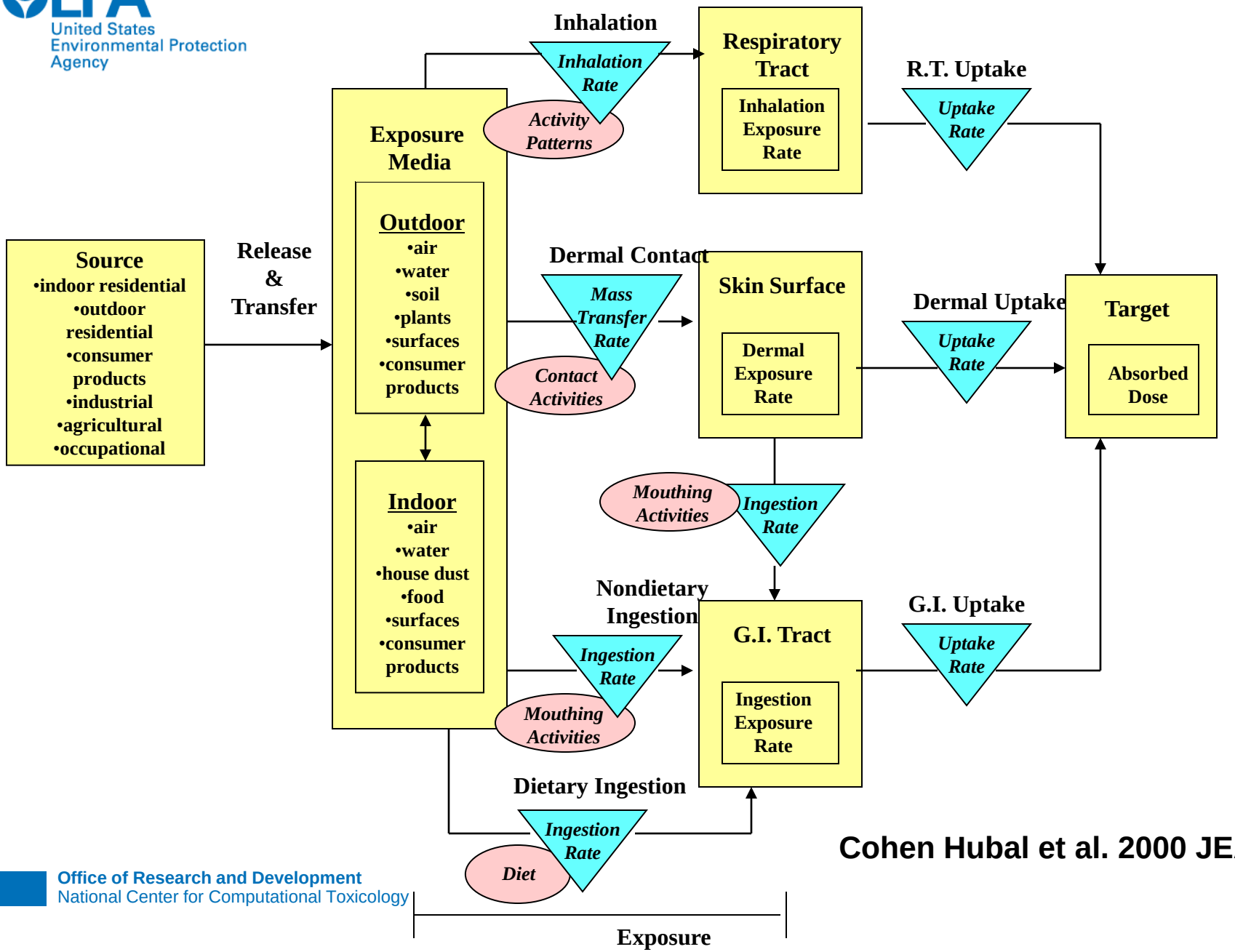
United States Environmental Protection Agency

Exposure Data and Models

- Exposure measurement data
- Exposure media concentrations
- Exposure factor data
  - Contact rates of target with exposure media
  - Contaminant transfer efficiency
  - Contaminant uptake rates through portal of entry
  - Human activities

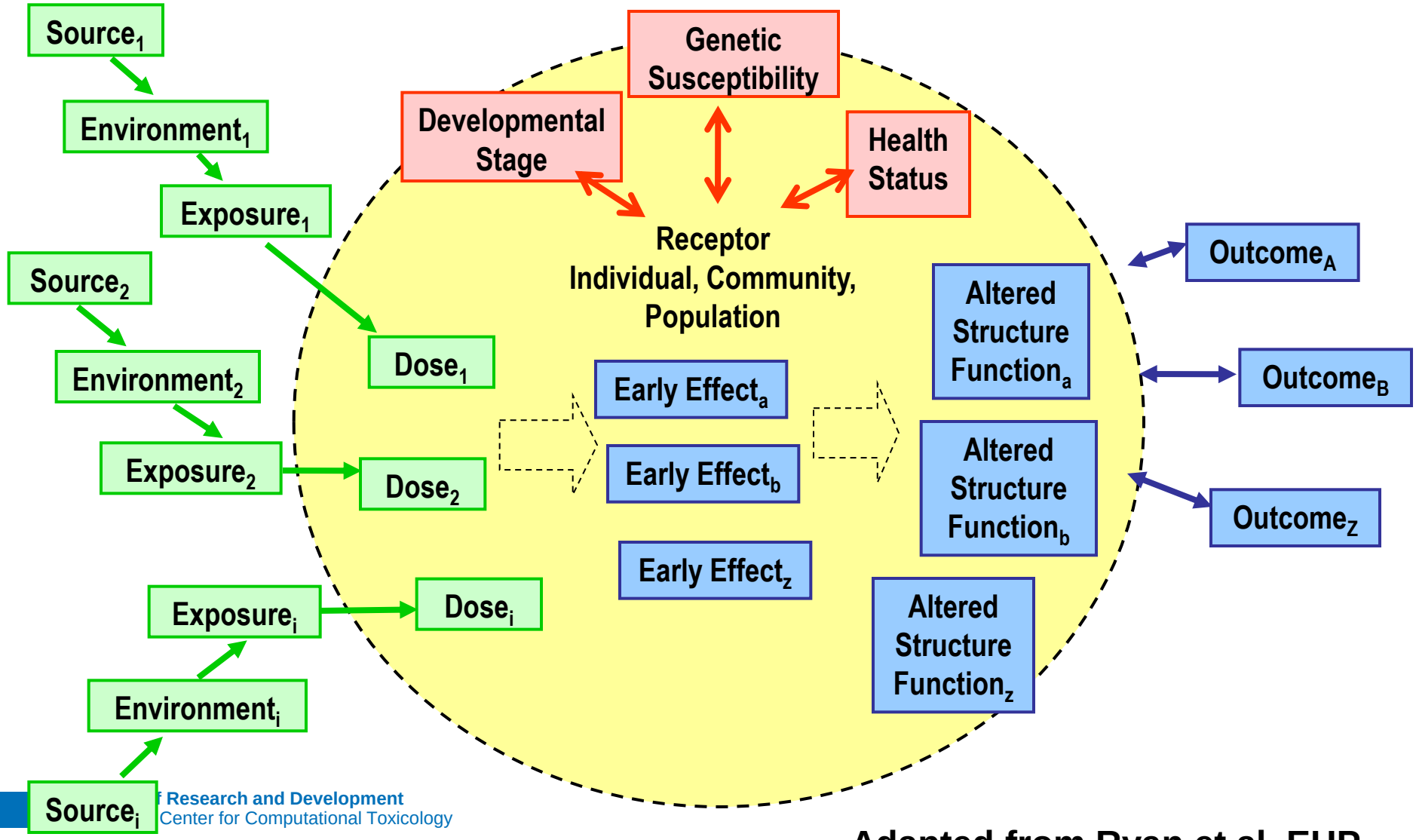
- Aggregate models
- Dietary models
- Waste Site models
- Consumer product models
- Air models
- Occupational models

Children's Residential Exposure to Pesticides



Cohen Hubal et al. 2000 JEAEE

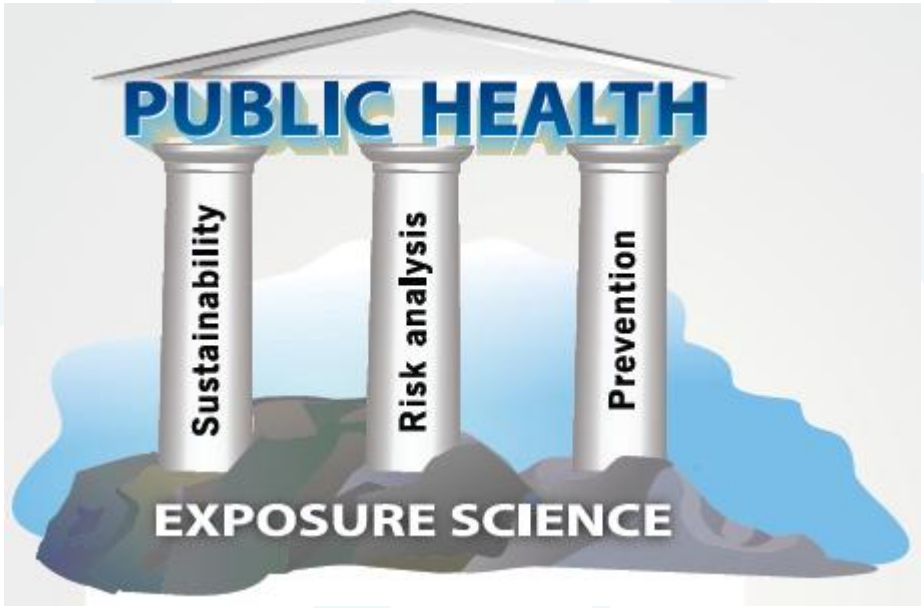
Receptor Oriented Model



Adapted from Ryan et al. EHP

EPA
United States
Environmental Protection
Agency

Future Directions in Exposure Science



United States Environmental Protection Agency

Future Challenges for Exposure Science

- Sustainability: Improve the health of individuals and communities today without compromising the health and welfare of future generations
- Risk analysis: Incorporate exposure science more effectively and efficiently into decisions
- Prevention: Shift from treatment to prevention of diseases through improved understanding of the role of environmental factors in etiology of disease

Hubal et al., JESEE 21:119, 2011

High-Throughput Screening Assays

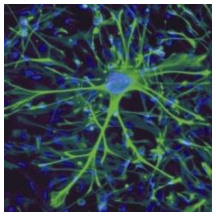
batch testing of chemicals for pharmacological/toxicological endpoints using automated liquid handling, detectors, and data acquisition

LTS **MTS** **HTS** **uHTS**

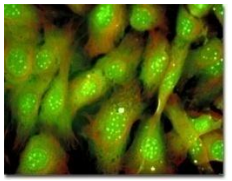
10s-100s/yr

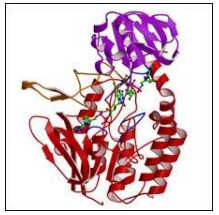
Gene-expression

10s-100s/day



1000s/day





10,000s-100,000s/day

Human Relevance/ Cost/Complexity

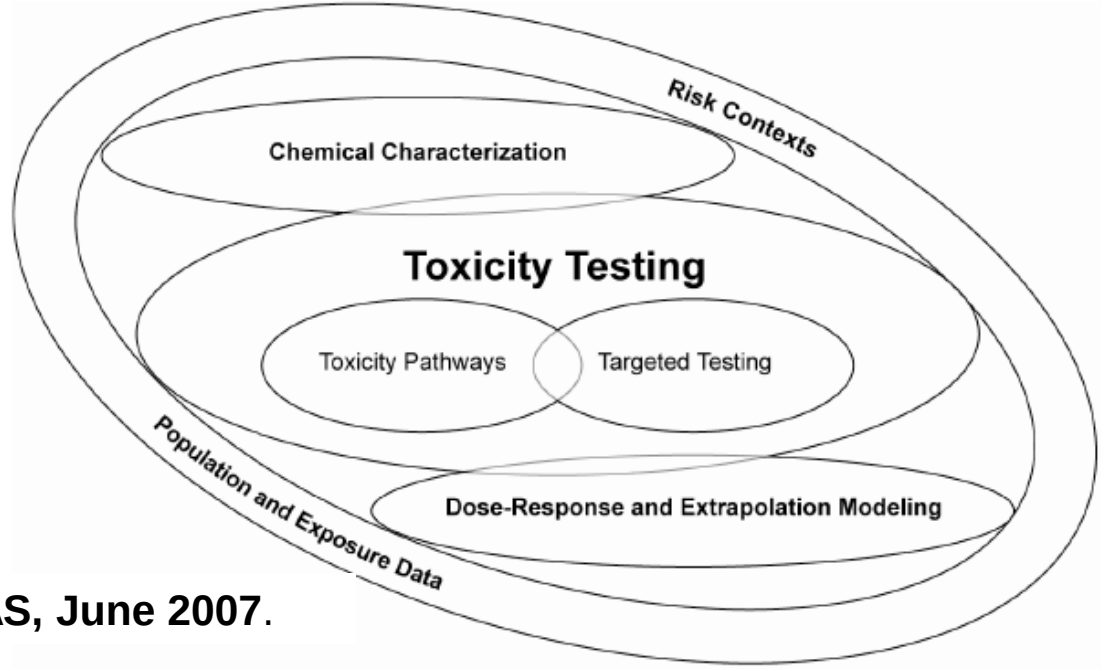
Throughput/ Simplicity

Toxicity Testing in the Twenty-first Century: A Vision and a Strategy

- Key aspect of the NRC vision is that new tools are available to examine toxicity pathways in a depth and breadth that has not been possible

- An explosion of high-throughput-screening (HTS) data for *in vitro* toxicity assays will become available over the next few years ---- **Data are available now!**

How will this new toxicity information be *integrated with exposure information* to assess potential for real-world human health risk?

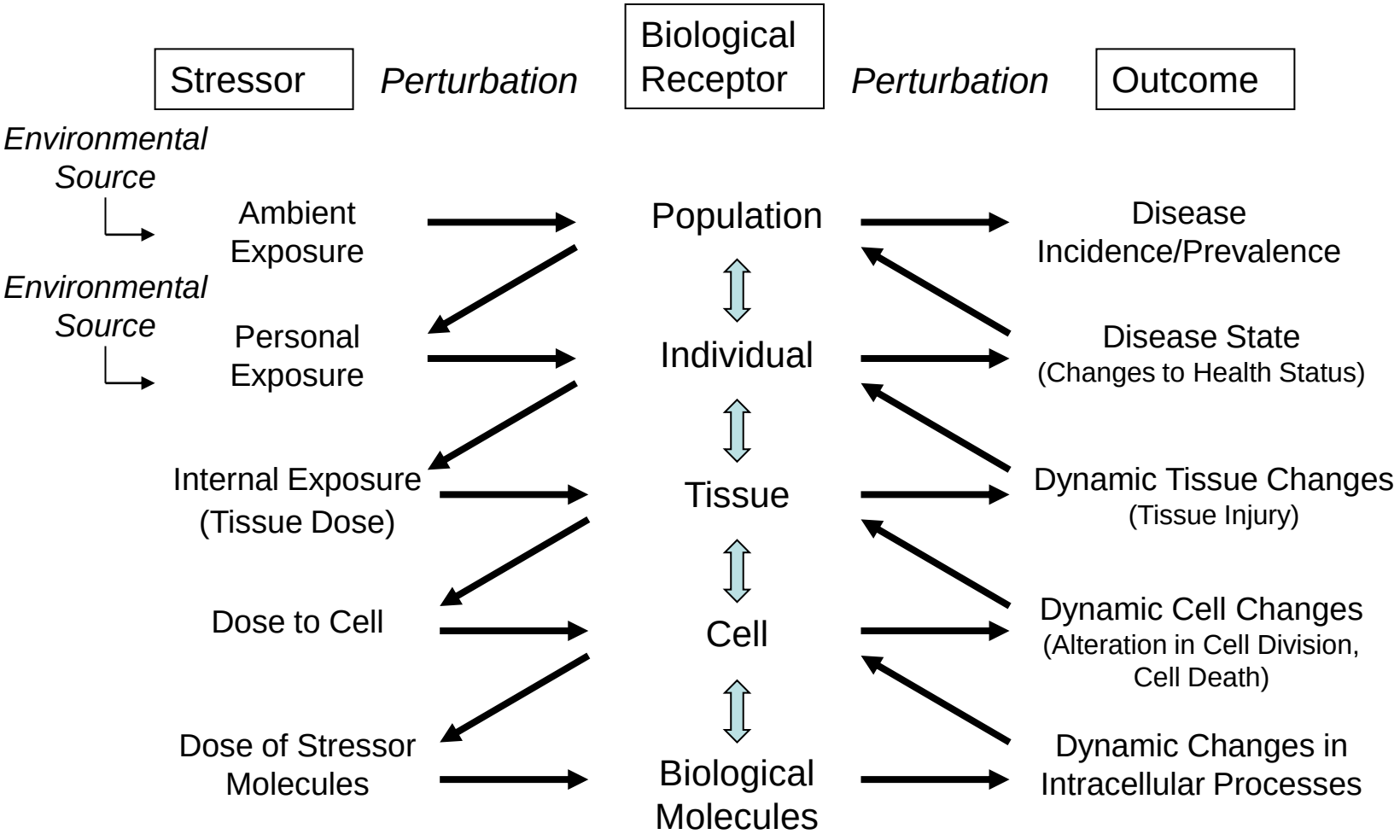


NAS, June 2007.

FIGURE 2-3 The committee's vision is a process that includes chemical characterization, toxicity testing, and dose-response and extrapolation modeling. At each step, population-based data and human exposure information are considered, as is the question of what data are needed for decision-making.

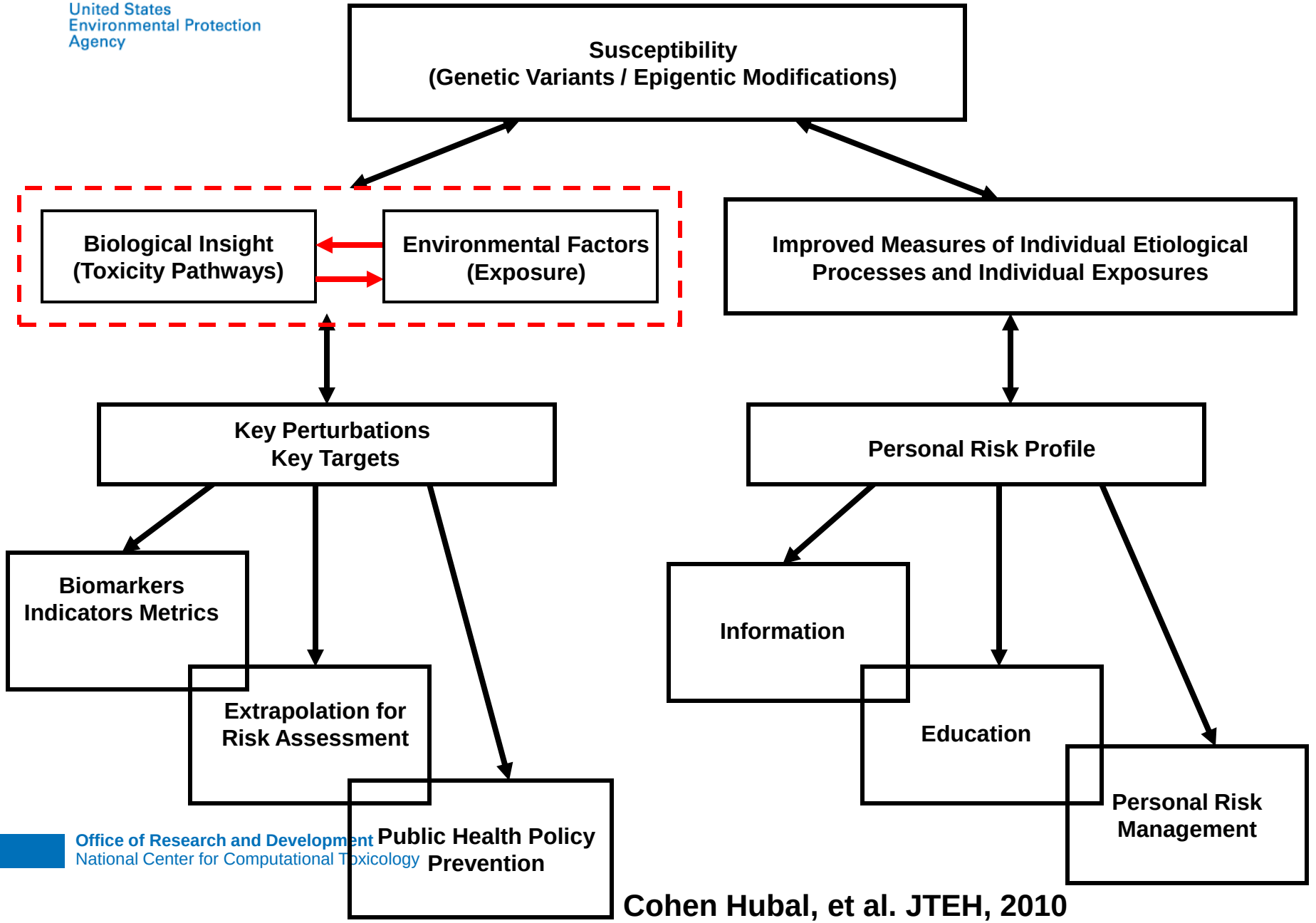
United States Environmental Protection Agency

Comp Tox: Exposure at All Levels of Biological Organization



Cohen Hubal, JESEE, 2008

Exposure for Decision Making



Cohen Hubal, et al. JTEH, 2010

United States Environmental Protection Agency

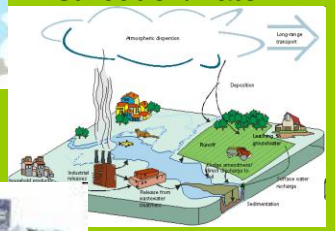
ExpoCast™: Exposure Science for Prioritization and Toxicity Testing

- Recognizes critical need for exposure information to inform
  - Chemical design and evaluation
  - Health risk management
- Goal
  - Advance characterization of exposure required to ***translate*** findings in computational toxicology to support exposure and risk assessment
  - **Together with ToxCast™ help EPA determine priority chemicals**
- Approach
  - **Mine and apply scientific advances and tools in a broad range of fields**
  - Develop novel approaches for evaluating chemicals based on potential for *biologically-relevant* human exposure

Environment

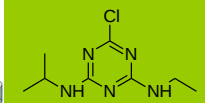
Sources

Distribution/Fate



Products

Contact



Chemicals

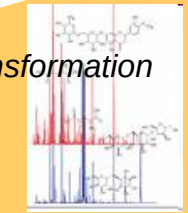
Exposure Media

Exposure

Uptake

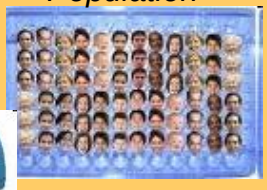
Background Exposure

Biotransformation



Biomonitoring

Population



Host Susceptibility

Human

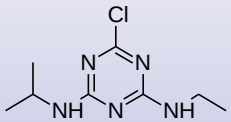
Rapid Prioritization

Relate real-world exposures with toxicity pathway perturbations

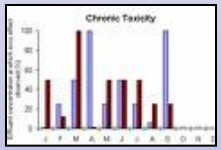
Select doses for toxicity testing

Translate in vitro results for risk assessment

HTS assays



Toxicity endpoints



In vivo bioassays

Data Repositories

Mechanistic Models

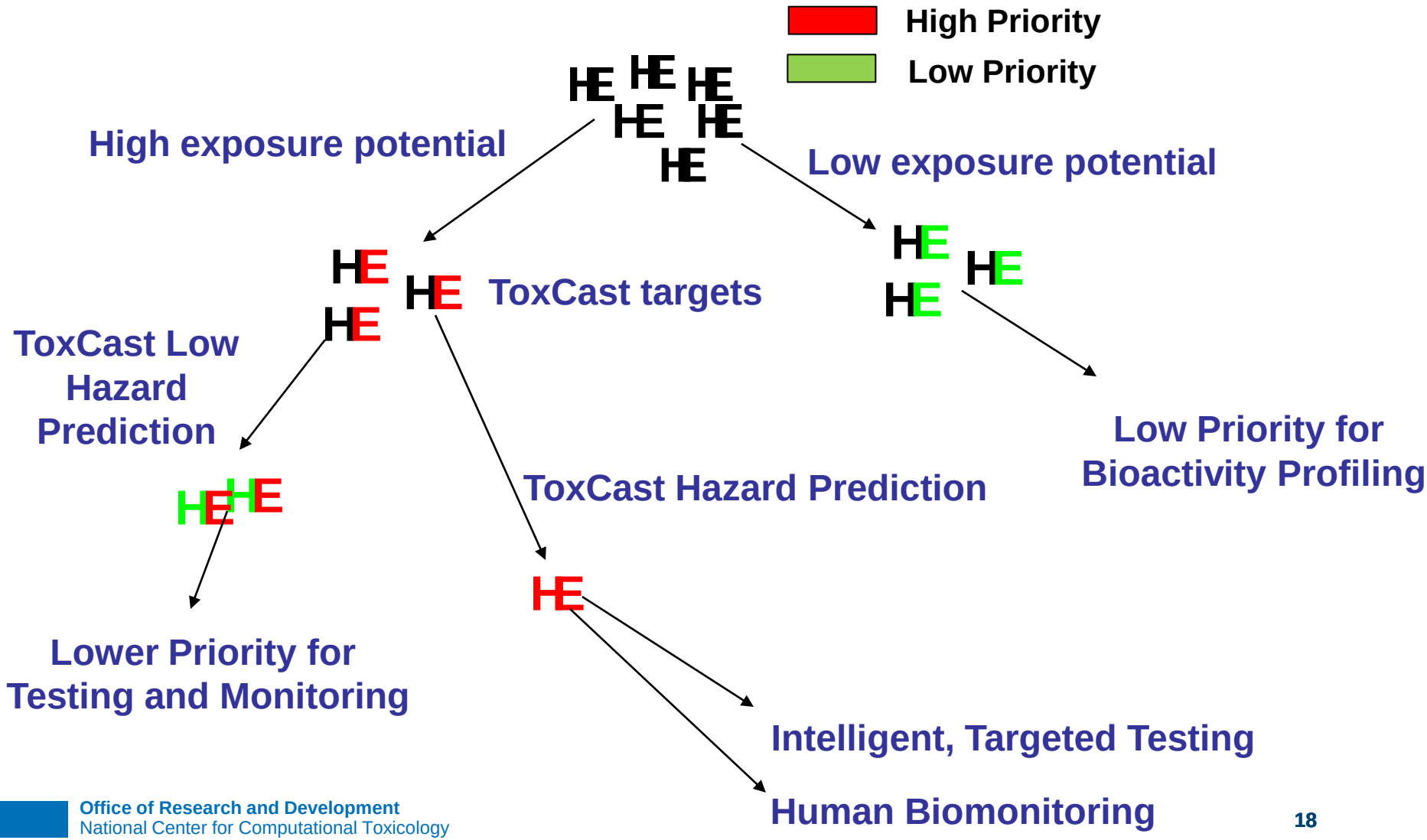
Informatics Approaches

Knowledge Systems

Network Models

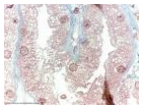
Exposome

Prioritization:
Using Hazard and Exposure Information



High-Throughput Risk Assessment

Pharmacodynamics

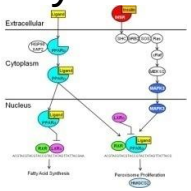


Adverse Effect

MOA

Key Events

Toxicity Pathway



HTS Assays

Biological Pathway Activating Concentration (BPAC) Probability Distribution

BPADL

Probability Distribution for Dose that Activates Biological Pathway

Pharmacokinetics

Dose-to-Concentration Scaling Function (C_{ss}/DR) Probability Distribution

PK Model

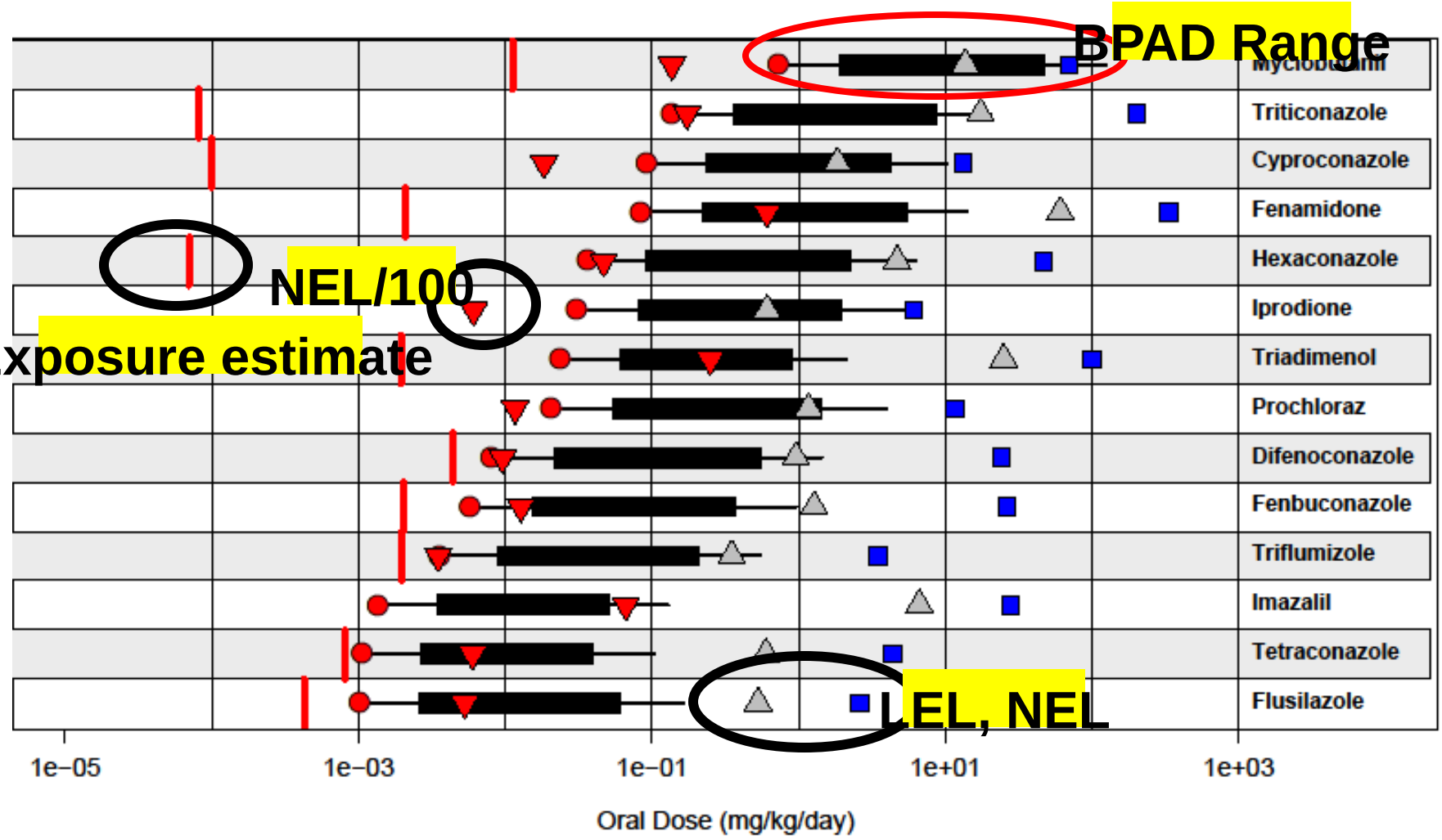
Populations

Plasma Protein Binding

Intrinsic Clearance

Judson et al, *CRT* (2011)

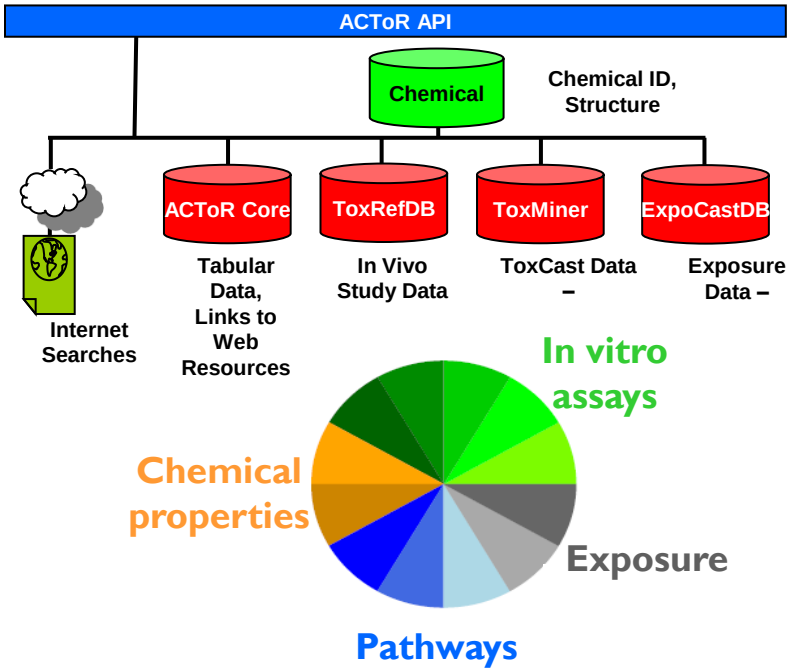
Biological Pathway Altering Dose (BPAD)
Conazole / CAR/PXR results



Judson et al, *CRT* (2011)

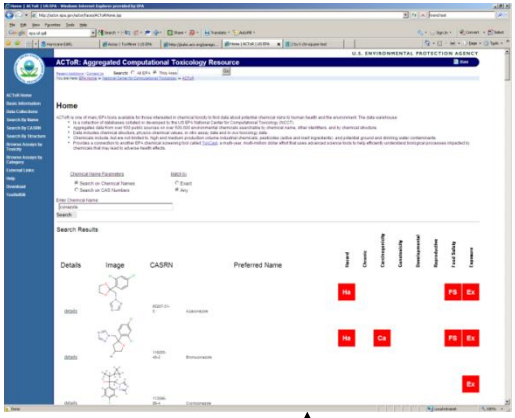
Prioritization: Recent ExpoCast Activities

- **Data Access**
  - Incorporating and Linking Exposure Information into ACToR
  - ExpoCastDB
- **Mining**
  - Integrated Chemical Prioritization Scheme
  - *Partnering to Develop Exposure Indices for Rapid Prioritization of Chemicals in Consumer Products*
  - *Intake Production Ratio*
- **Modeling**
  - Prioritization Model Challenge
  - High Throughput Exposure Estimates
  - *Rapid modeling of SVOC exposure in indoor environment*



ACToR: Aggregated Computational Toxicology Resource

http://actor.epa.gov/



ACToR API

Chemical

Chemical ID, Structure

Internet Searches

ACToR Core

Tabular Data, Links to Web Resources

ToxRefDB

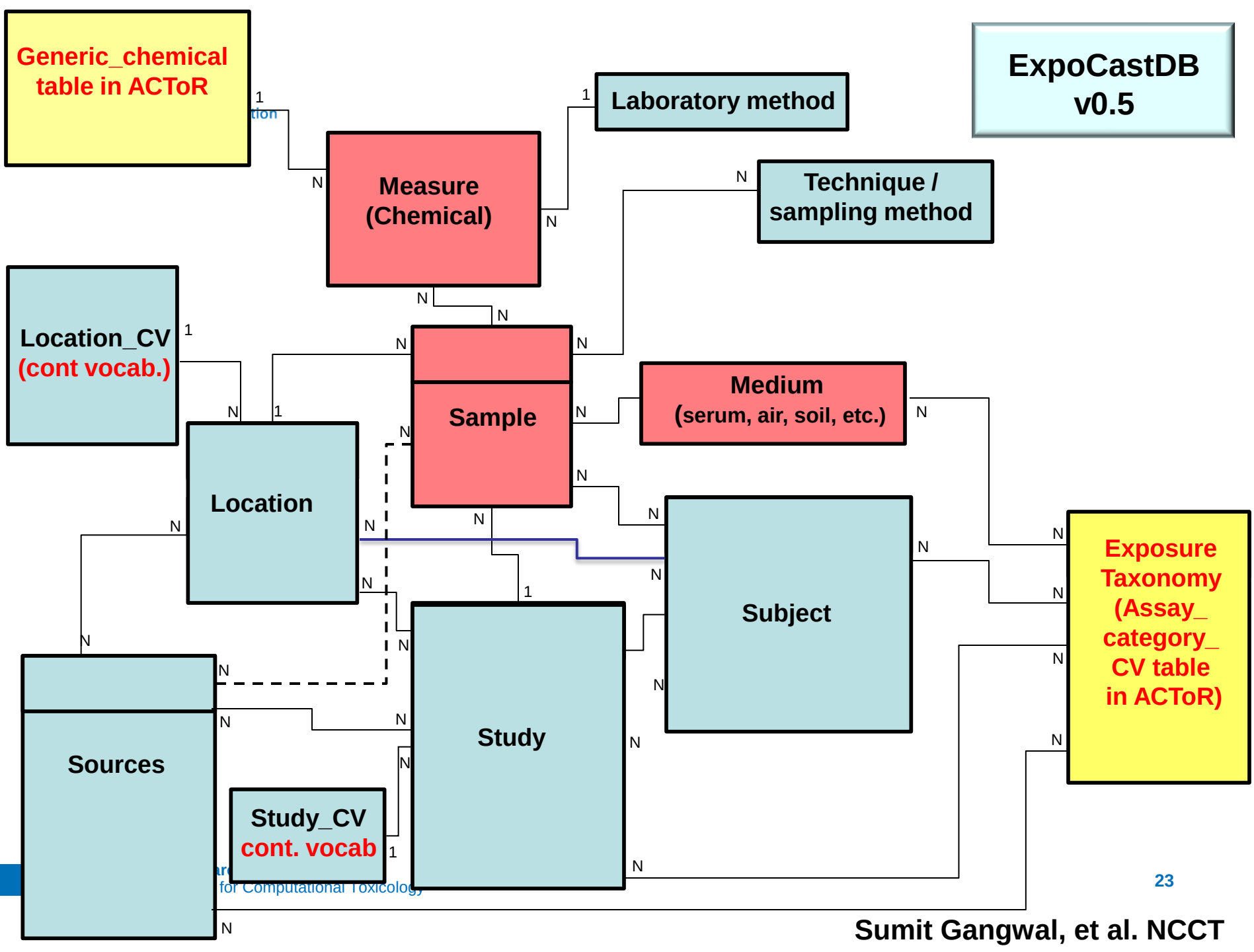
In Vivo Study Data - OPP

ToxMiner

ToxCast Data – NCCT, ORD, Collaborators (Currently Internal)

ExpoCastDB

Exposure Data – NERL, NCCT (Just Released)



Sumit Gangwal, et al. NCCT

Rationale for an integrated chemical prioritization scheme

- Integration over multiple domains of information
- Extensibility to incorporate additional types of data
- Transparency in score derivation and visualization
- Flexibility to customize components for diverse prioritization tasks

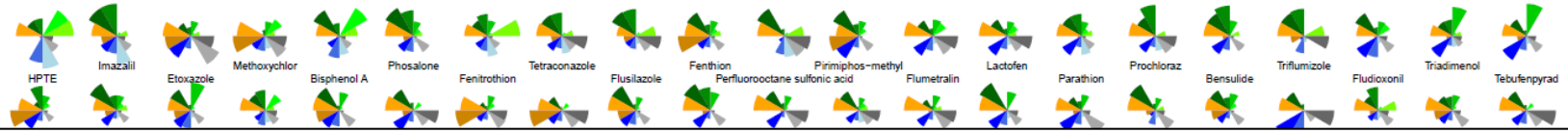
ToxPi (Toxicological Priority Index)

Putative endocrine profiles

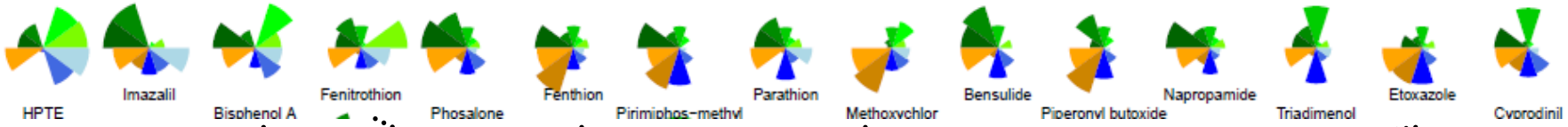
A numerical index that can be used for ranking (instead of absolute thresholds) is more flexible for different prioritization tasks.
Can better accommodate new data, new chemicals, data adjustments, etc.

Reif et al., 2010, *Environ. Health Perspect.*

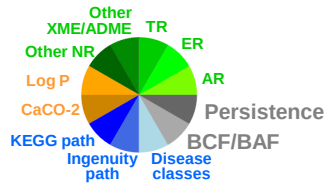
Incorporating Exposure Information: ToxPi Endocrine Scores

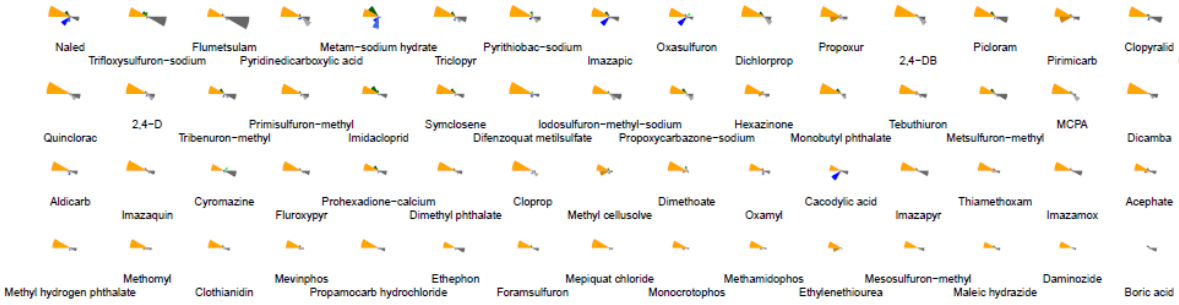


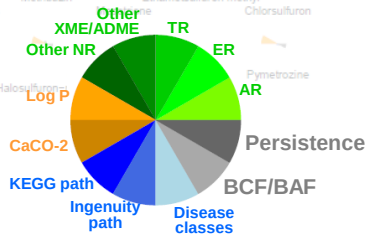
Previous top 15 prioritized chemicals by



New top 15 prioritized chemicals with





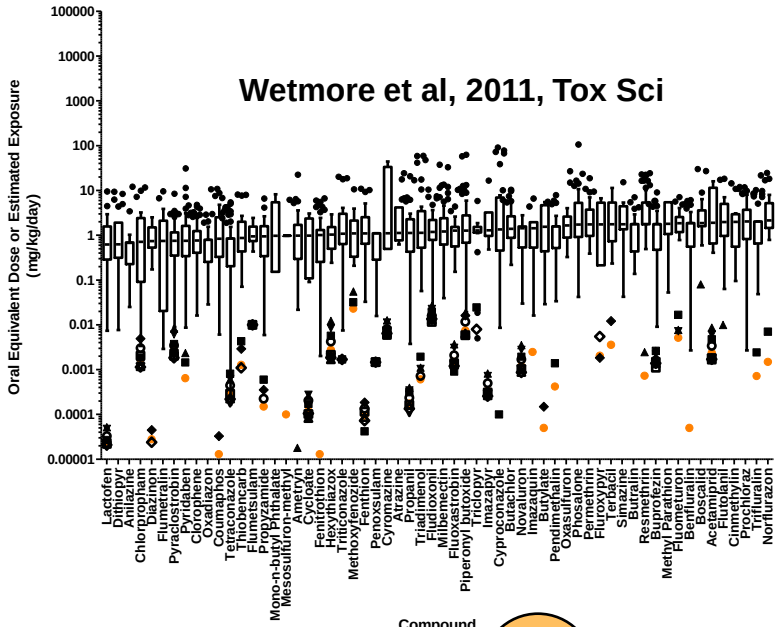


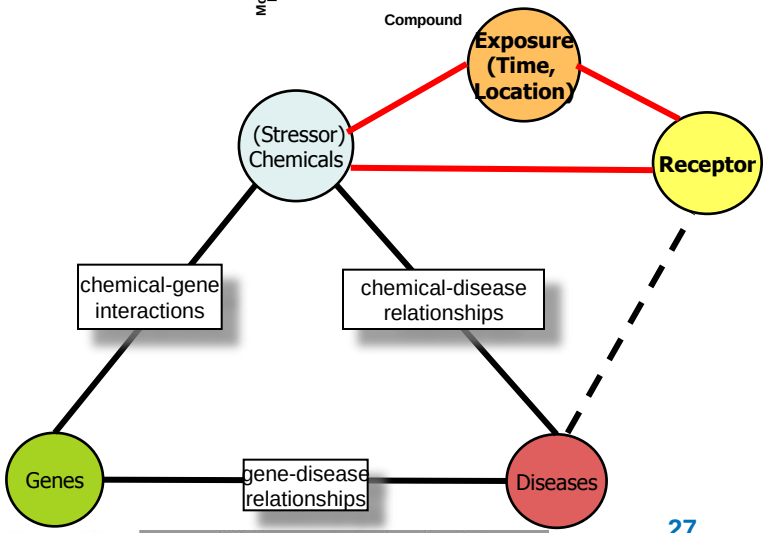
Comp Tox: Recent ExpoCast Activities

- **Inform Design of Toxicity Testing**
  - Selecting Doses for ToxCast *In Vitro* Testing – Nanomaterials
  - Application of Biogeographical Methods to Chemical Co-Occurrence Data to Identify Priorities for Mixture Research

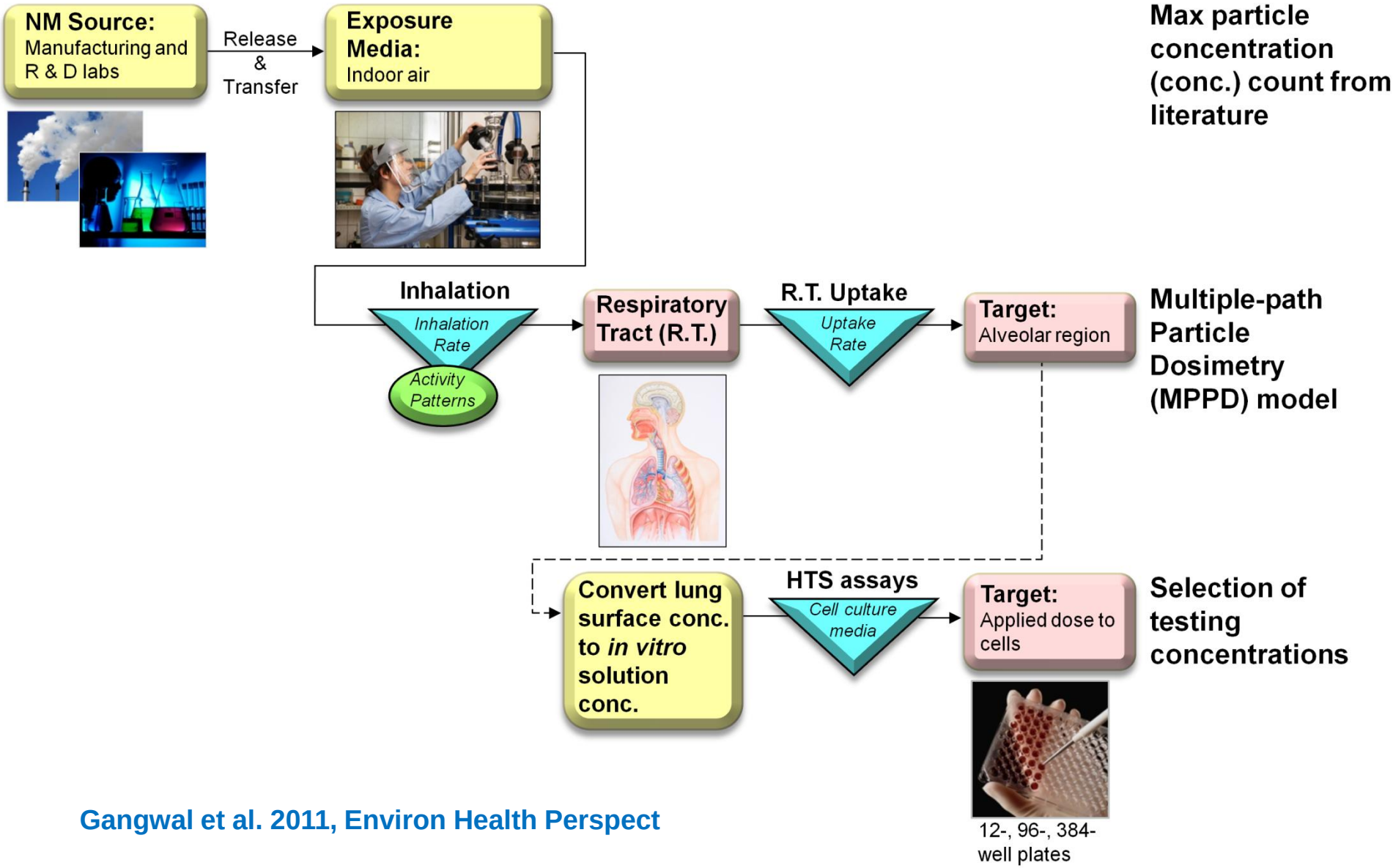
- **Translate in vitro Results for Risk Assessment**
  - *Combining ToxCast, Dosimetry and Exposure*
  - *ExpoDat2012: Exposure determinants for high throughput risk assessment (HTRA)*

- **Relate Real-World Exposures with Tox Pathway Perturbations**
  - *ExO: An Exposure Ontology*





Comp Tox: Selecting Doses for ToxCast Nano Pilot



Gangwal et al. 2011, Environ Health Perspect

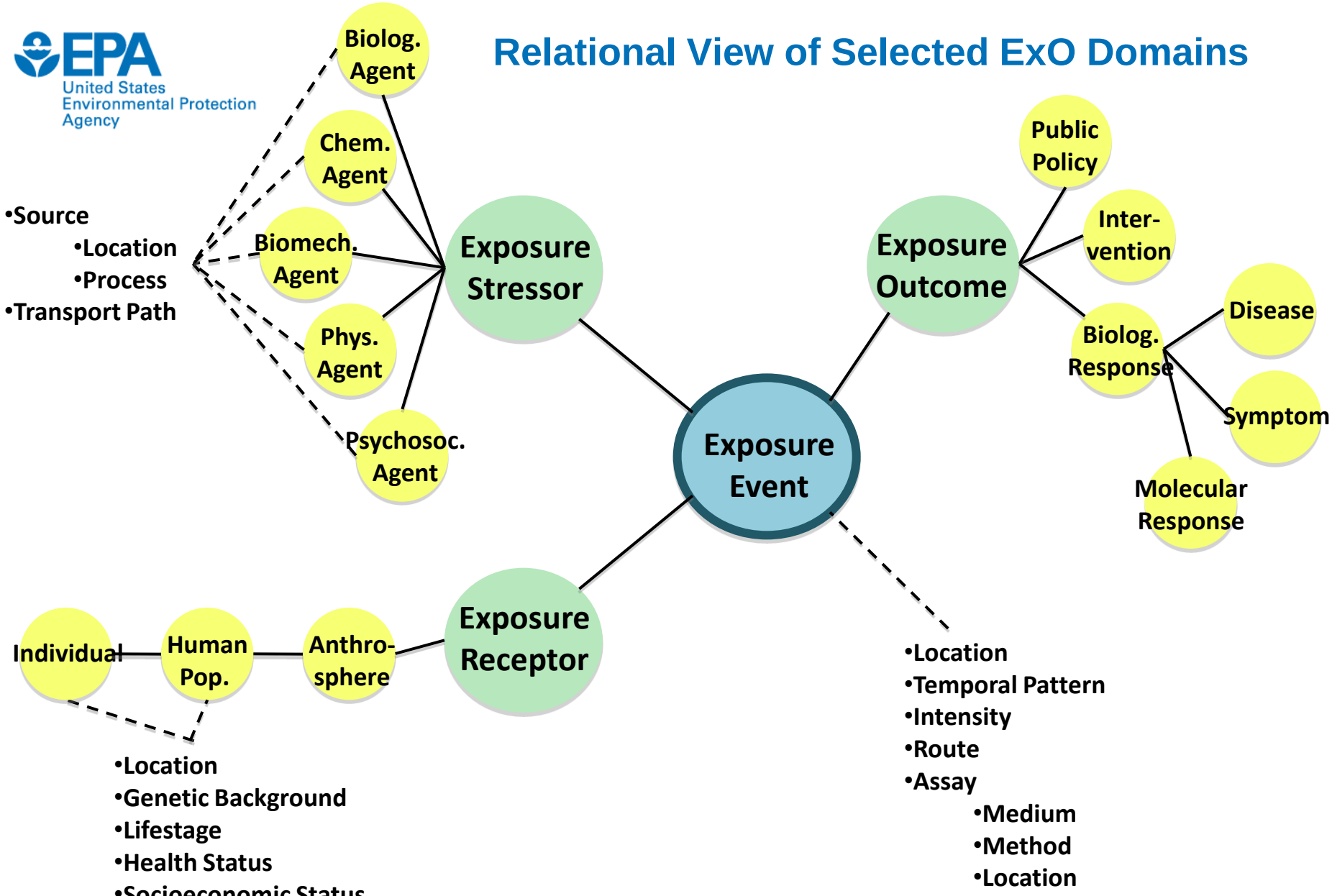
United States Environmental Protection Agency

Exposure Ontology, ExO: Definitions of Central Concepts

- **Exposure Stressor** - An agent, stimulus, activity, or event that causes stress or tension on an organism and interacts with an exposure receptor during an exposure event.
- **Exposure Receptor** - An entity (e.g., a human, human population, or a human organ) that interacts with an exposure stressor during an exposure event.
- **Exposure Event** - An interaction between an exposure stressor and an exposure receptor.
- **Exposure Outcome** - Entity that results from the interaction between an exposure receptor and an exposure stressor during an exposure event.

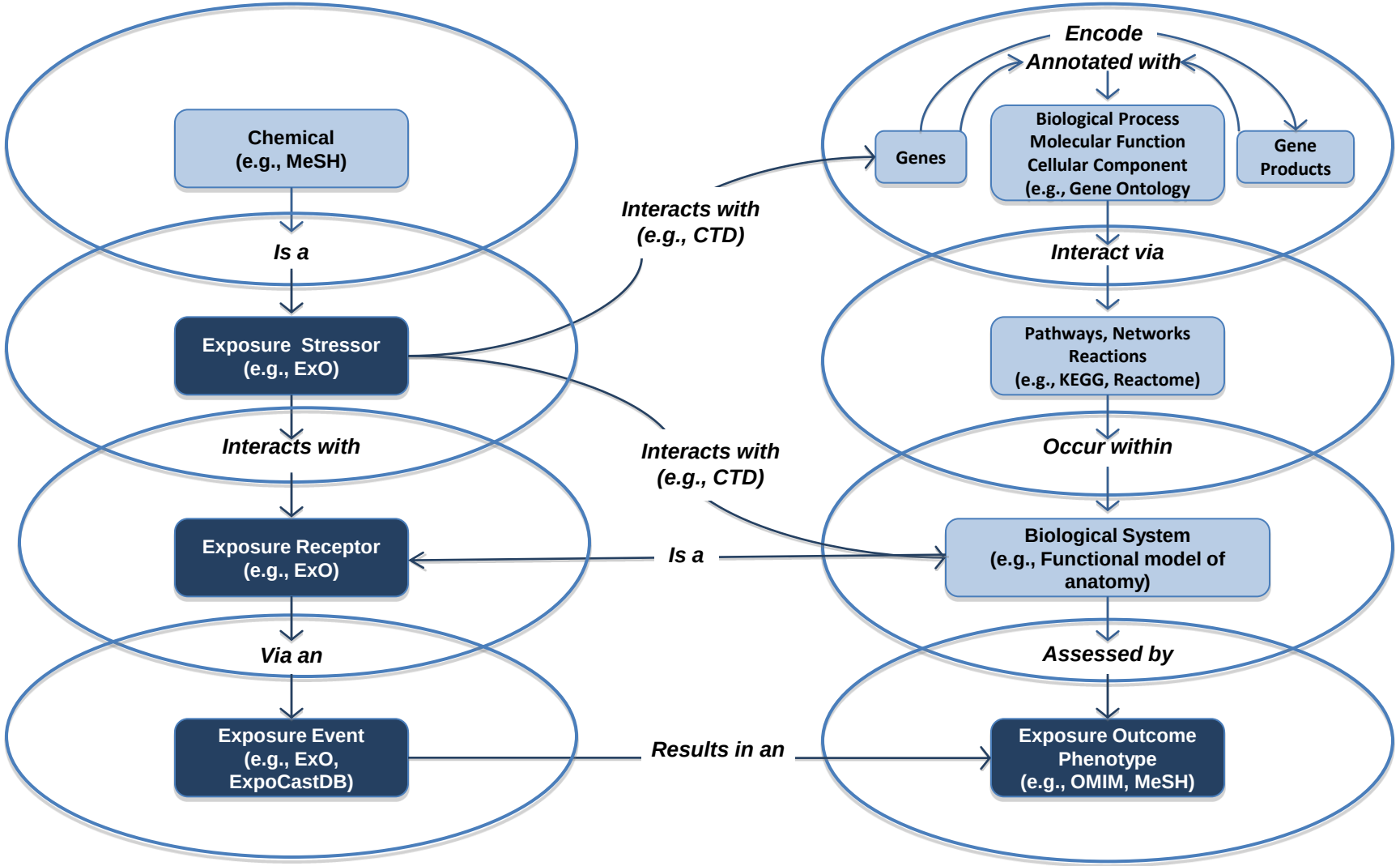
Mattingly et al, EST, 2012

Relational View of Selected ExO Domains



Mattingly et al, 2012, EST

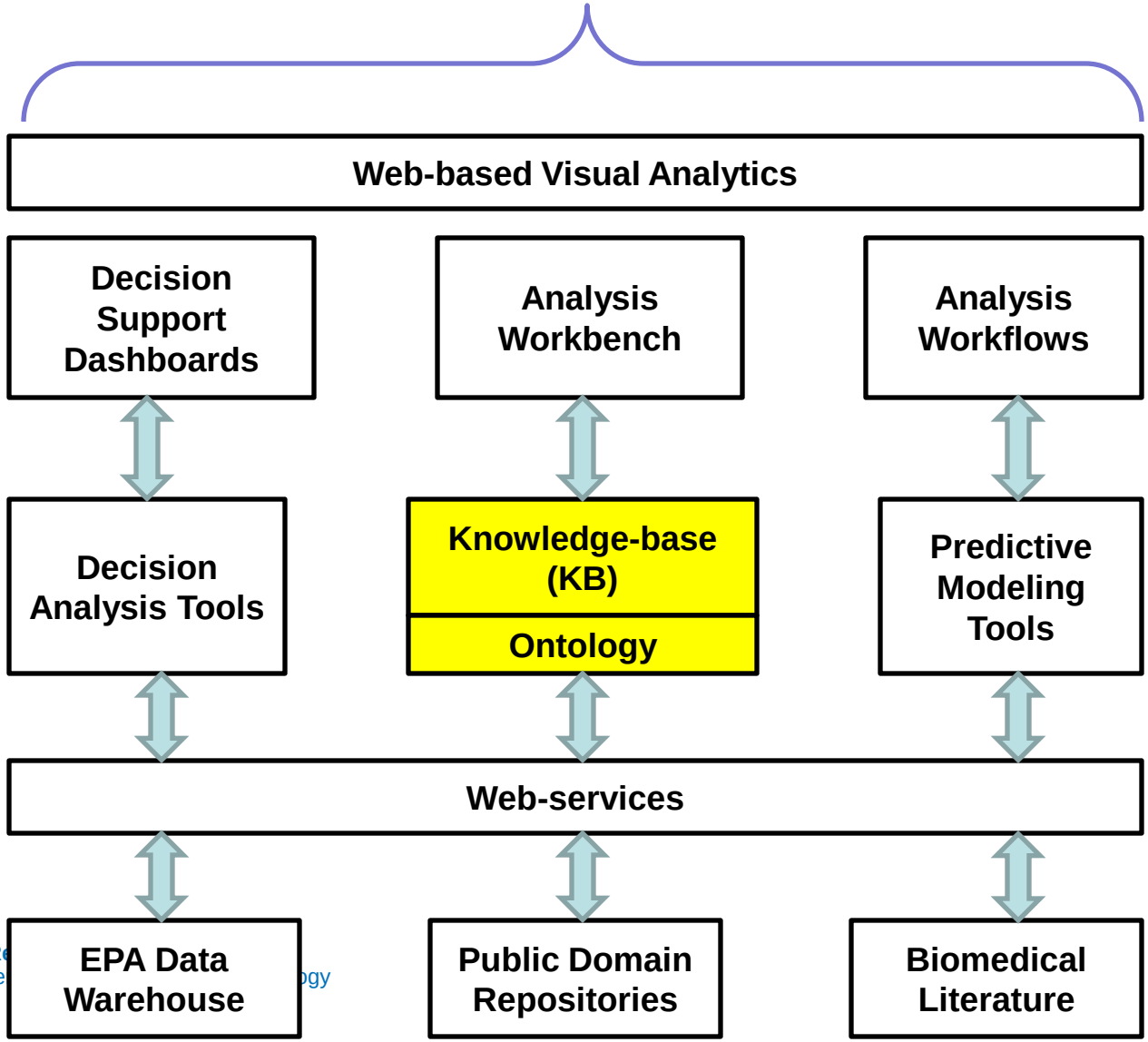
High-level schematic of Exposure Ontology (ExO) integration within a broader biological context.



Mattingly et al, EST, 2012

Knowledge Management and Decision Support Tools For EPA Chemical Safety for Sustainability Research

Customized Dashboards for Programs



United States Environmental Protection Agency

Knowledge Management and Decision Support Tools for CSS

- Data Management Warehouse (e.g., ACToR)
  - federate raw data generated by CSS/EPA and available in the public domain on: chemical structure, production, environmental fate, human use, ecological and health effects, **exposure,** etc.
- Ontologies for Interoperability
  - publicly available ontologies will be used to specify the semantics to integrate experimental data from multiple sources, as well as the inputs and outputs of diverse predictive tools (e.g. empirical models, pathway analysis, systemsmodels, etc.).
- Knowledge-based management system (KB):
  - Develop KB systems that use the above ontologies to acquire, organize, store and share the complex information flows across diverse CSS activities on chemical inherency, production, **exposure,** hazard, pathways and sustainability metrics.

Exposure Assessment: *Key Messages*

- Exposure is the contact between a stressor and a human or ecological receptor.
- Exposure Science is the bridge between the sources of chemical, physical and biological agents and human health
- Exposure Science provides crucial information to estimate real-life risks to health and to identify the most effective ways to prevent and reduce these risks.

Future Directions in Exposure Science: *Key Messages*

- Sustainability: Improve the health of individuals and communities today without compromising the health and welfare of future generations
- Risk analysis: Incorporate exposure science more effectively and efficiently into decisions
- Prevention: Shift from treatment to prevention of diseases through improved understanding of the role of environmental factors in etiology of disease

Hubal et al., JESEE 21:119, 2011