United States Environmental Protection Agency

ExpoCast™: Exposure Science for Prioritization and Toxicity Testing

EPA Chemical Prioritization Community of Practice
June 24, 2010

Elaine Cohen Hubal
National Center for Computational Toxicology

United States
Environmental Protection
Agency

"...to integrate modern computing and information technology with molecular biology to improve Agency prioritization of data requirements and risk assessment of chemicals"

Providing Decision Support Tools for High-Throughput Screening, Risk Assessment and Risk Management

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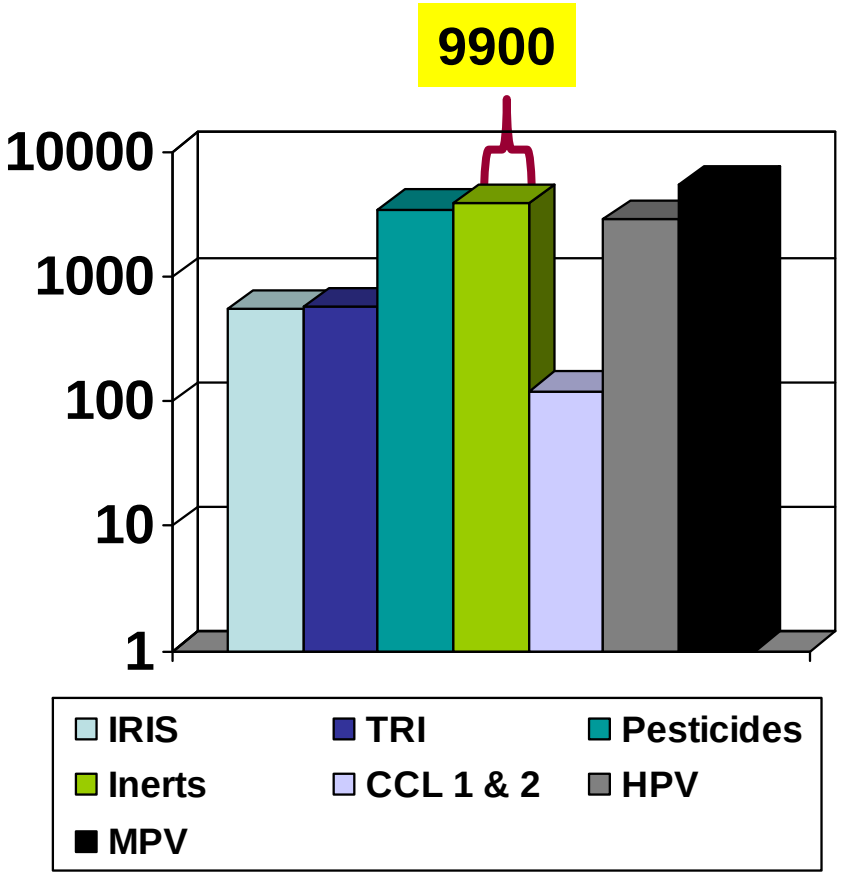
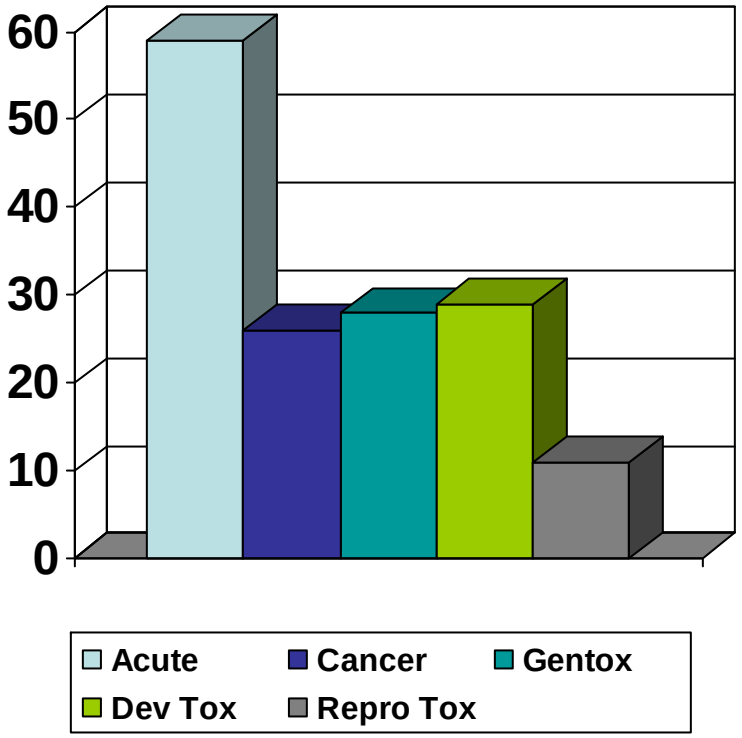
Managing Chemical Risks: Faster Science for Better Decisions

Too Many Chemicals



Too Little Data (%)



High-Throughput Screening Assays

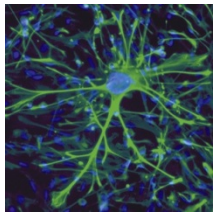
batch testing of chemicals for pharmacological/toxicological endpoints using automated liquid handling, detectors, and data acquisition

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

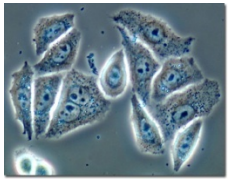
10s-100s/yr

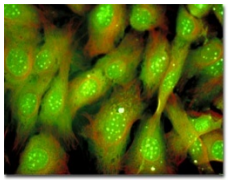
Gene-expression

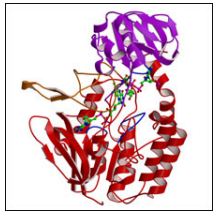
10s-100s/day



1000s/day







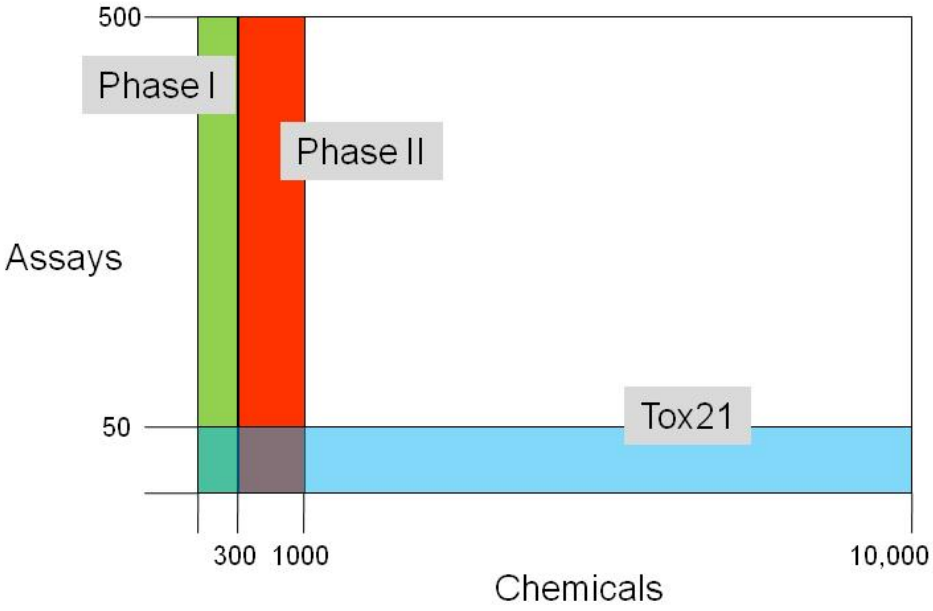
10,000s-100,000s/day

Human Relevance/ Cost/Complexity

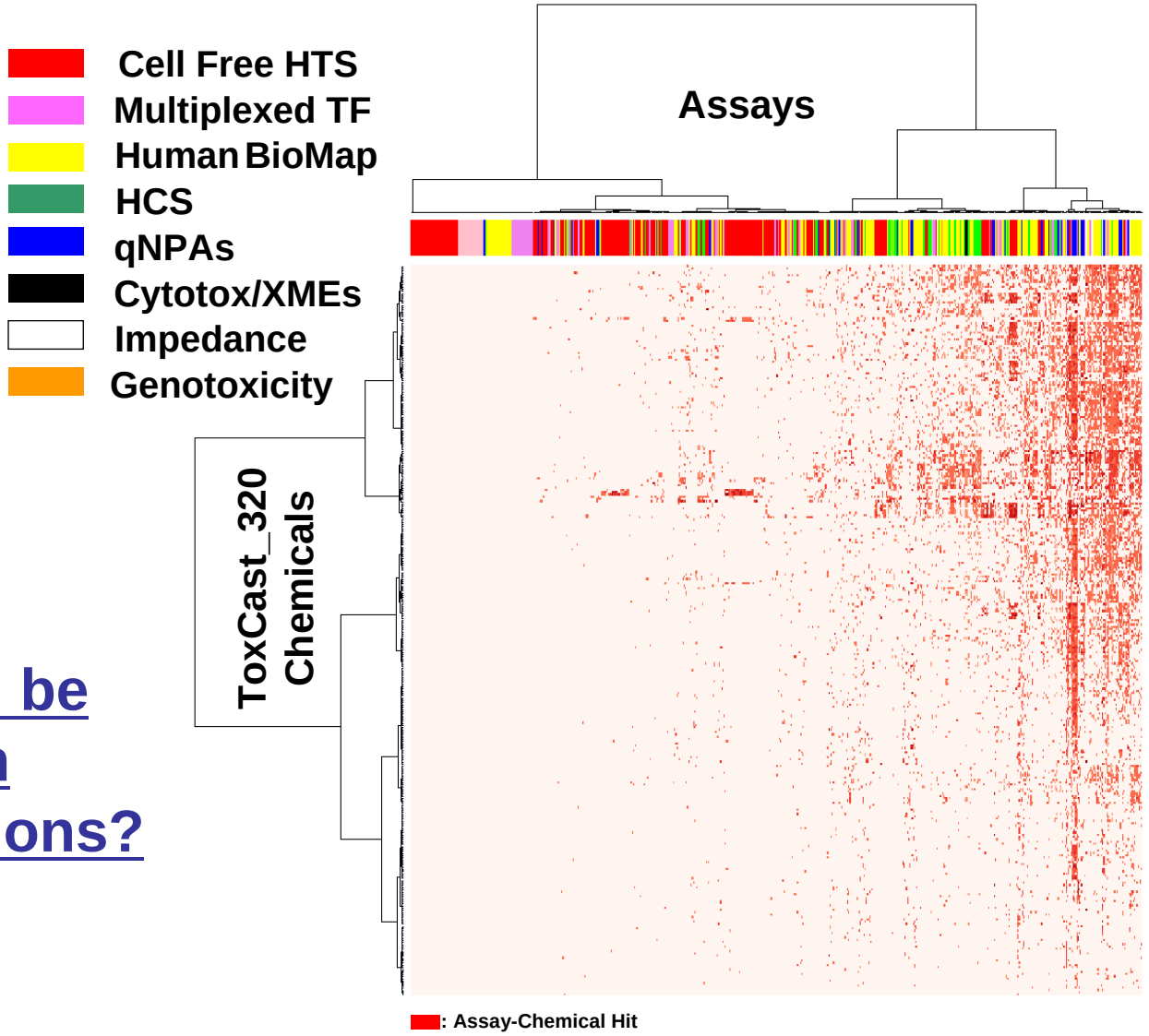
Throughput/ Simplicity

ToxCast™ Phase I to Phase II and Tox21

	Phase I	Phase II	Tox21
Actives	272	120	700
Inerts	24	100	1000
Antimicrobials	33	100	500
HPV	35	170	1300
MPV	7	60	1500
Green	4	60	500
PCCL	73	150	500
Nano	0	40	0
Pharma	0	150	2500
Consumer/Food additives	0	0	1500
Total	**309**	**700**	**10000**



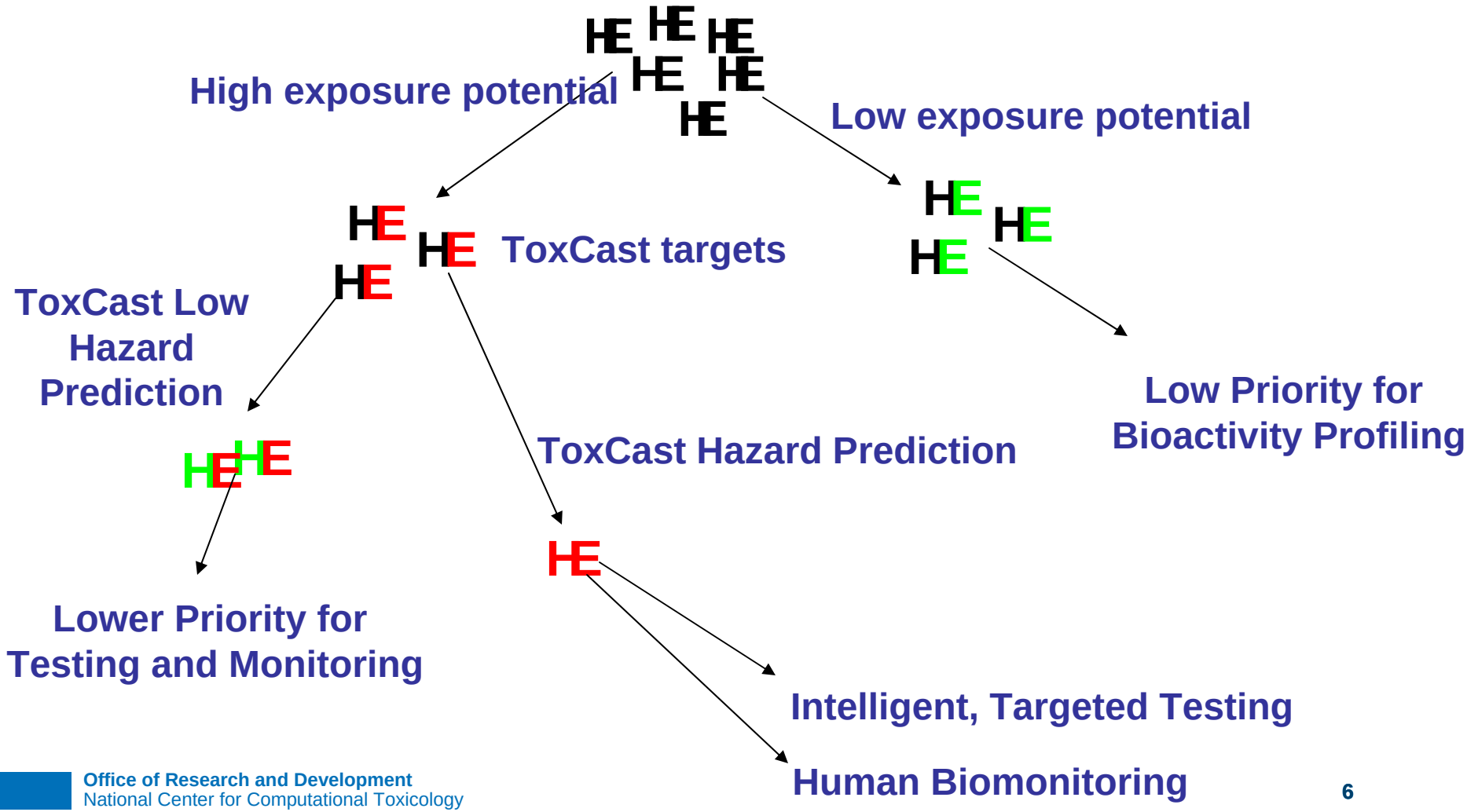
Phase I ToxCast In Vitro Bioactivity



How will this new toxicity information be *translated* to inform public health decisions?

Judson et al, *EHP* (2010)

The Future State: Using Hazard and Exposure Information for Prioritizing Testing and Monitoring



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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

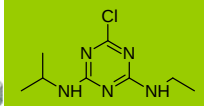
Environment

Sources

Distribution/Fate

Products

Contact



Chemicals

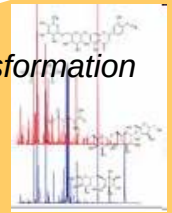
Exposure Media

Exposure

Uptake

Background Exposure

Biotransformation



Biomonitoring

Population

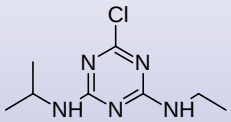
Host Susceptibility

Rapid Prioritization

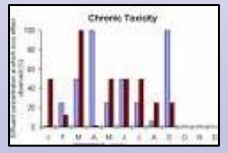
Relate real-world exposures with toxicity pathway perturbations

Select doses for toxicity testing

HTS assays



Toxicity endpoints



In vivo bioassays

Translate in vitro results for risk assessment

Data Repositories	Mechanistic Models	Informatics Approaches	Knowledge Systems	Network Models	Exposome

TOOLS

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Priority Exposure Research for Computational Toxicology

- Accessible and linkable exposure databases
- Exposure-based screening tools for accelerated chemical prioritization

Advanced exposure science required to address ultimate goals of evaluating chemical safety and understand etiology of complex disease

- Systems exposure science
- Biologically-relevant exposure metrics
- Environmental informatics and advanced computational models

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Prioritization

- Workshop
- Exposure data access activities
- Considering exposure information for prioritization

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Exposure-Based Chemical Prioritization Workshop: Exploring Opportunities for Collaboration

RTP, NC, April 6-7, 2010

http://epa.gov/ncct/expocast/workshop.html

Participants Included:

U Ottawa
U Michigan
U Toronto
EOHSI/UMDNJ
LBNL
Exxon Mobile

Health Canada
RIVM
EU JRC
US FDA
US CPSC
US EPA (OPPTS, ORD, GLNPO)
Washington State

Workshop Highlights – Mandates for Prioritization

Health Canada (Christine Norman)

- Completing assessments for 500 high priorities
- Focus on **3000 medium priority**, complete by 2020
  - 36% organic, 11% inorganic, 14% polymers, 27% UVCB
  - 58% zero data, another 23% data poor

US CPSC (Treye Thomas)

- **Thousands of products** in and around the home
- Challenges in exposure
  - Product Ingredients, Consumer Use Information
  - Method Validation, Probabilistic Methods
  - International Cooperation
  - Nanotechnology

US EPA GLNPO (Ted Smith)

- **P&B screening not appropriate** for important groups of chemicals in commerce (e.g., ionic)
- Surveillance strategy based on Adverse Outcome Pathway framework

Workshop Highlights – Tools and Approaches

Benchmarking prioritization models (Olivier Jolliet)

- Start with parsimonious model, develop and evaluate a suite of consistent tools to assess same metrics, but at different levels and detail
- Evaluate the relative importance of parameters and intermediary steps in the screening results
- USEtox development process (Model evaluation; Publication and expert review; Approval by International Life Cycle Panel)
- Intake Fraction (fraction emission taken in by population)

Ground truthing prioritization schemes (Bette Meek)

- Broadly draw on existing experience on limited # chemicals to inform efficient evaluation of the rest (e.g., **use more important than volume**)
- Identify chemicals for quantitative anchoring of “surrogates”
- Select simplest most discriminating determinants
- “Design” to limit exposure

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Workshop Highlights – Tools and Approaches

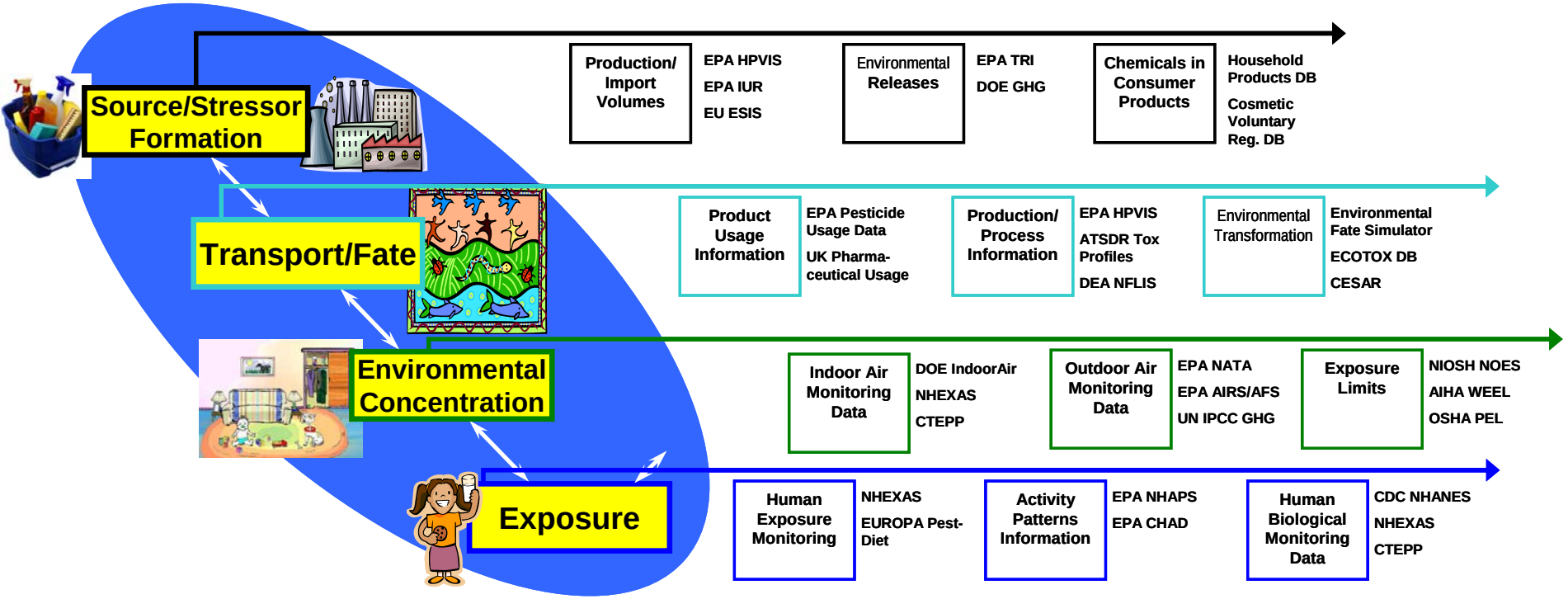
Value of information (Michael Sohn)

- Approach for comparing decisions/consequences where uncertainty is important
- Can be used to combine different types of limited data (e.g., biomarker, monitoring, modeling)
- Grade relative rankings
- Extrapolate from known chemicals to unknown

Limits of persistance and bioaccumulation (Jon Arnot)

- **P & B categorization data should not be used** for exposure-based priority setting for humans and ecological receptors
- Mass balance multimedia exposure models can provide alternative "holistic" hypotheses linking emissions to exposures (e.g., RAIDAR)
- Integrated testing strategies required for property data and QSAR development to expand "domains" of knowledge and predictability

Incorporating Exposure Data Sources into ACToR



Peter Egeghy, NERL

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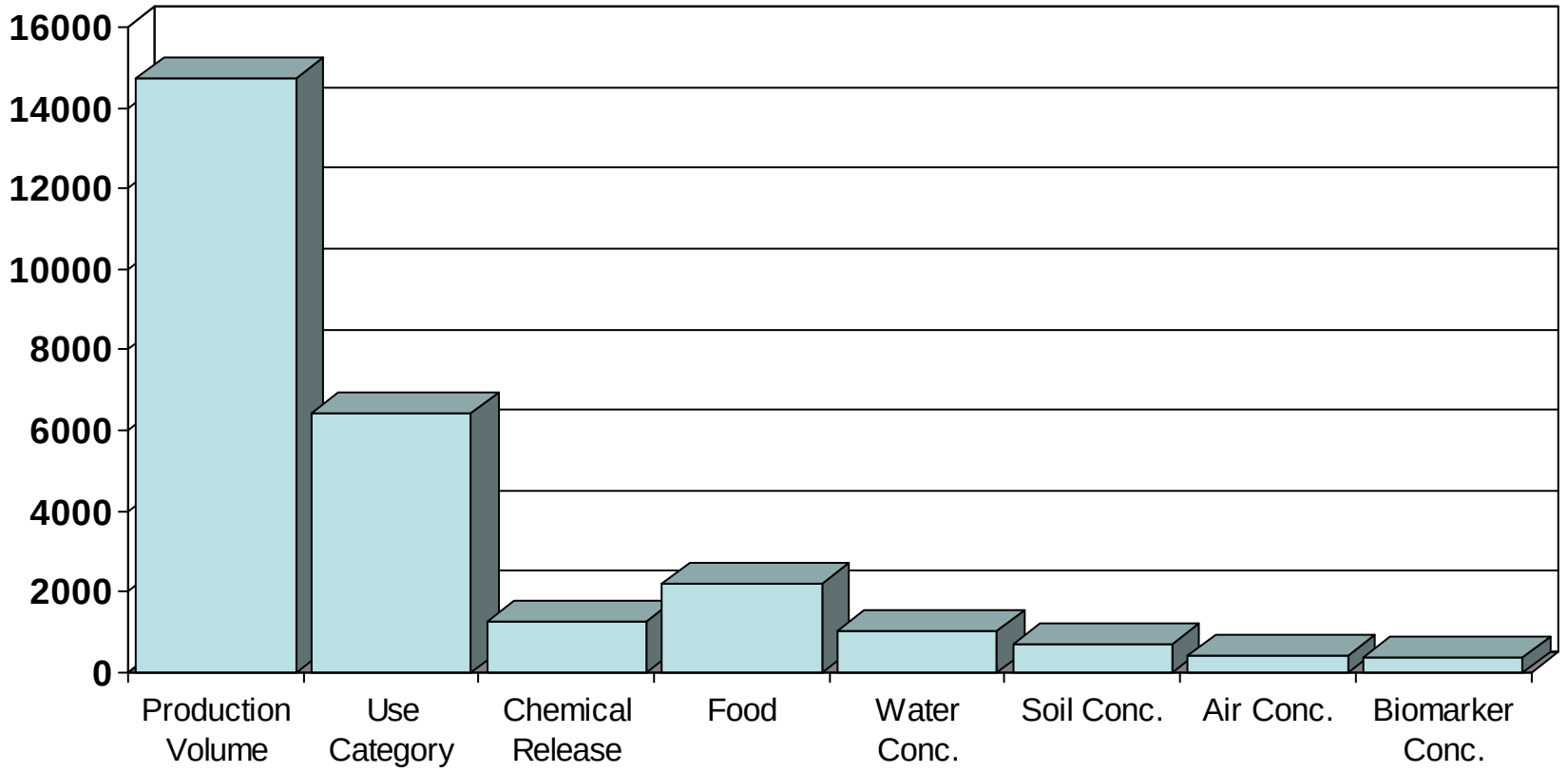
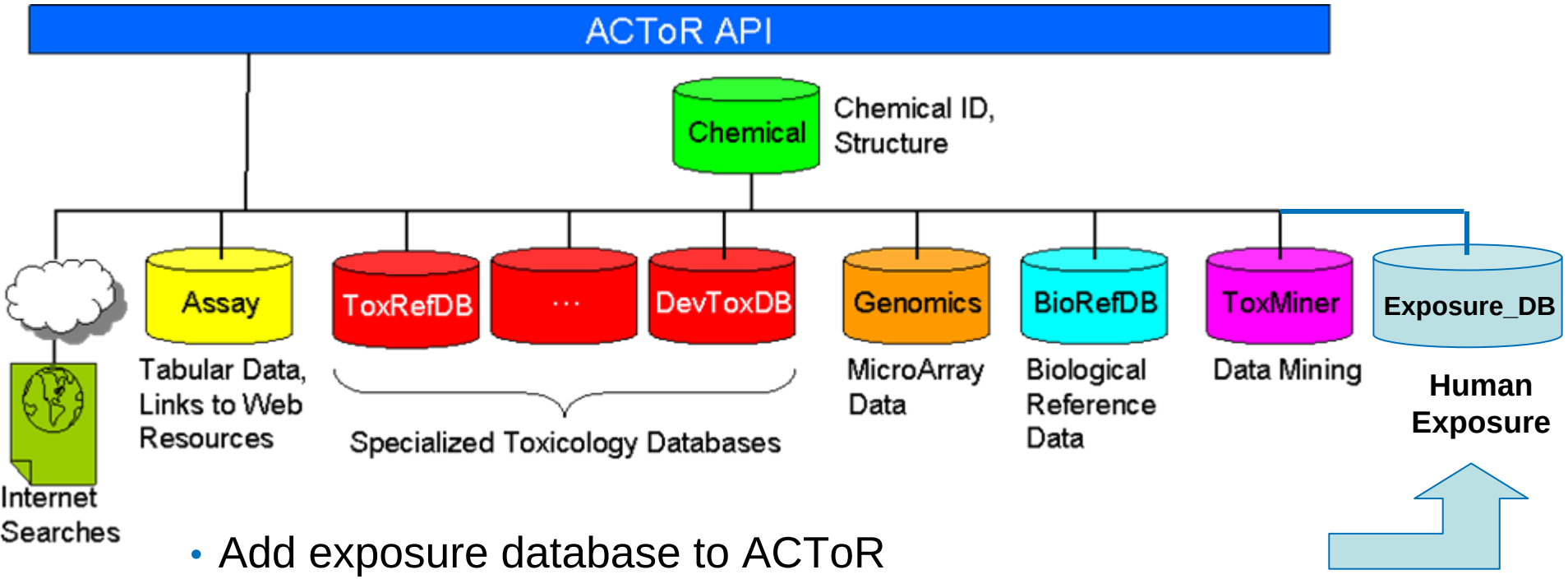
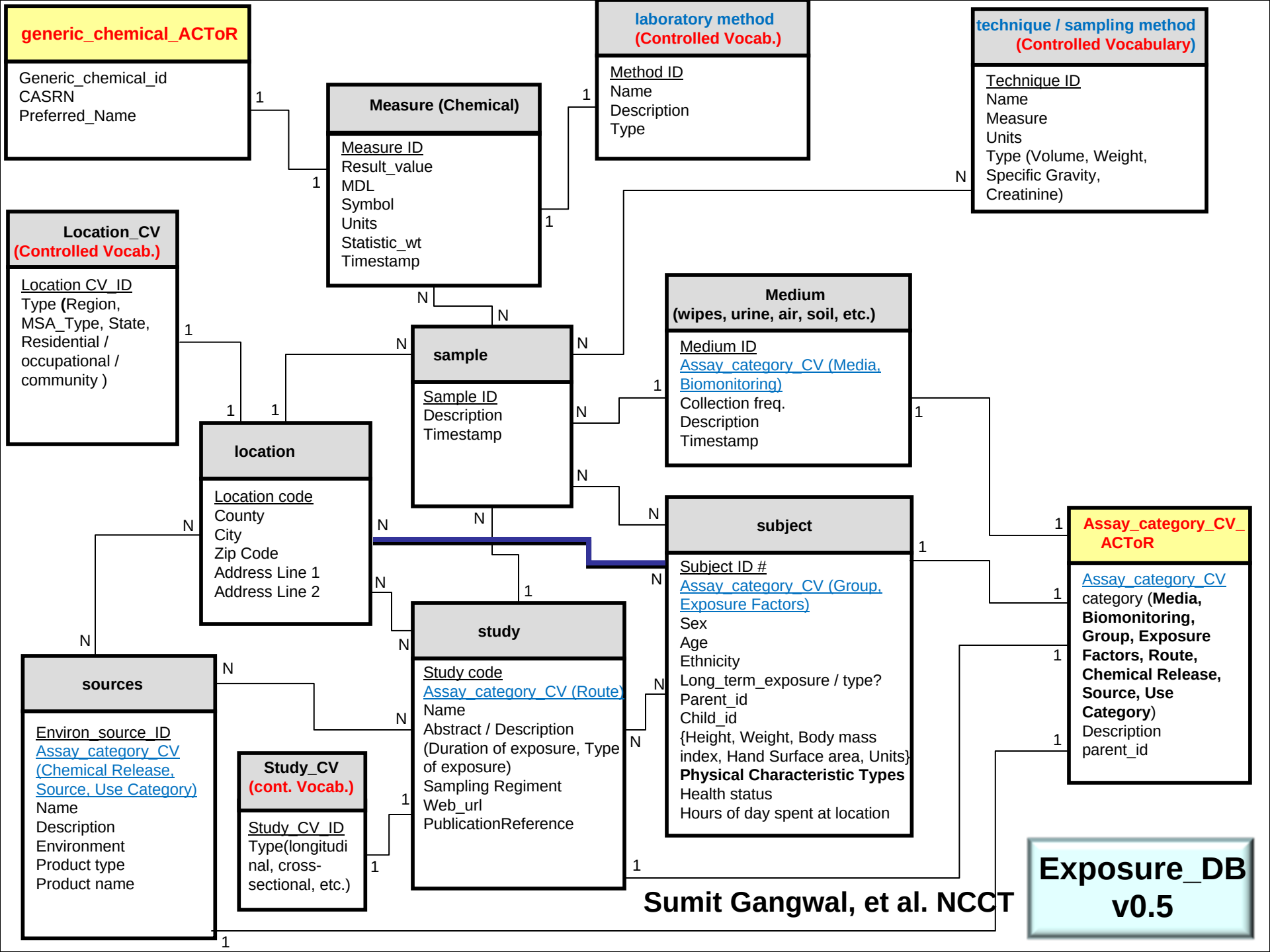
Number of Unique Chemicals in ACToR by Data Type



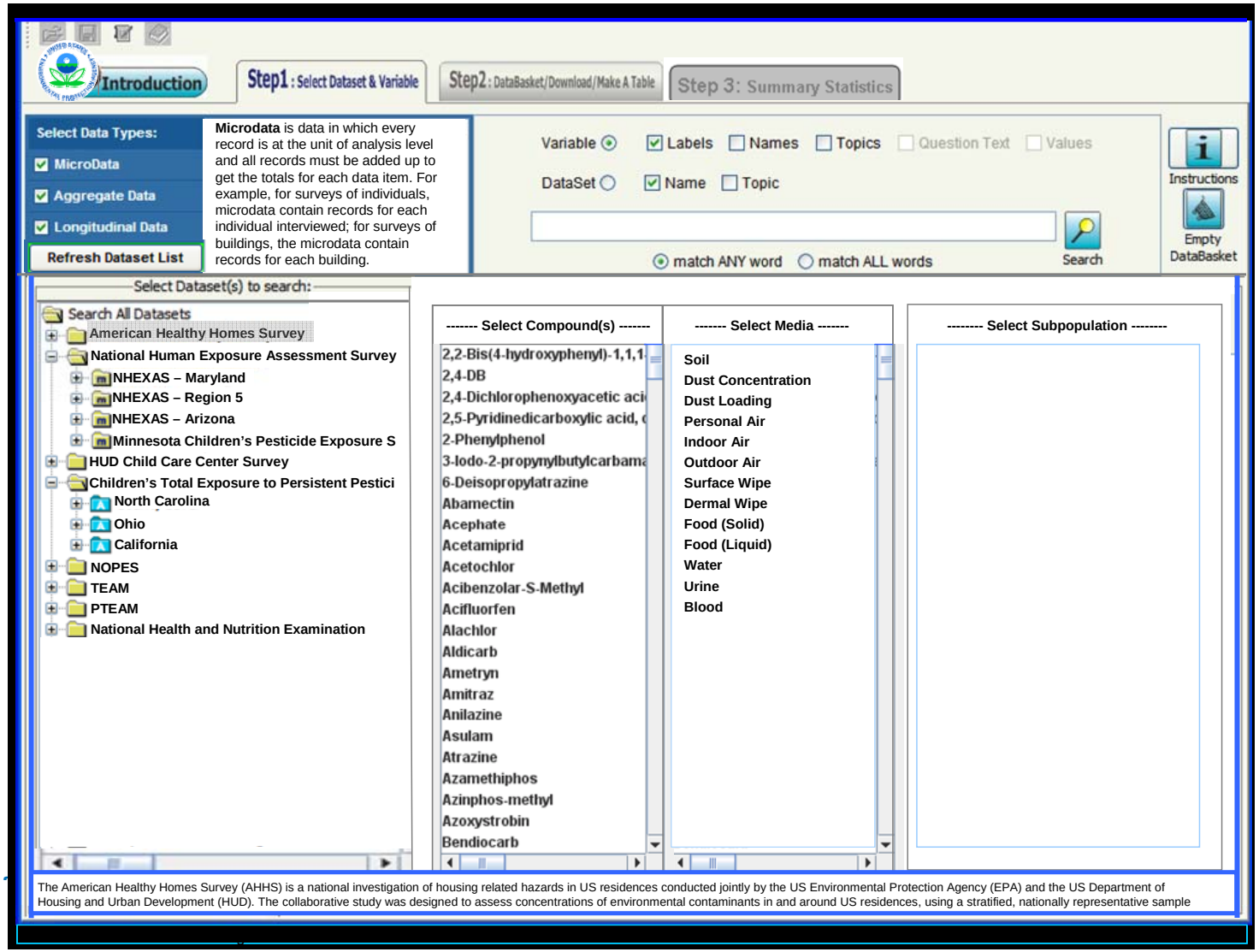
In Development: ExpoCast DataBase (Exposue_DB)



- Add exposure database to ACToR
- Separate interface with inner workings of ACToR to take advantage of linkages to toxicity information
- Provide capability to download customized datasets, obtain summary statistics and distributional parameters


generic_chemical_ACToR
Generic_chemical_id
CASRN
Preferred_Name
laboratory method (Controlled Vocab.)
Method ID
Name
Description
Type
technique / sampling method (Controlled Vocabulary)
Technique ID
Name
Measure
Units
Type (Volume, Weight, Specific Gravity, Creatinine)
Measure (Chemical)
Measure ID
Result_value
MDL
Symbol
Units
Statistic_wt
Timestamp
Location_CV (Controlled Vocab.)
Location CV_ID
Type (Region, MSA_Type, State, Residential / occupational / community)
sample
Sample ID
Description
Timestamp
Medium (wipes, urine, air, soil, etc.)
Medium ID
Assay_category_CV (Media, Biomonitoring)
Collection freq.
Description
Timestamp
location
Location code
County
City
Zip Code
Address Line 1
Address Line 2
subject
Subject ID #
Assay_category_CV (Group, Exposure Factors)
Sex
Age
Ethnicity
Long_term_exposure / type?
Parent_id
Child_id
{Height, Weight, Body mass index, Hand Surface area, Units}
Physical Characteristic Types
Health status
Hours of day spent at location
Assay_category_CV_ ACToR
Assay_category_CV
category (Media, Biomonitoring, Group, Exposure Factors, Route, Chemical Release, Source, Use Category)
Description
parent_id
study
Study code
Assay_category_CV (Route)
Name
Abstract / Description
(Duration of exposure, Type of exposure)
Sampling Regiment
Web_url
PublicationReference
sources
Environ_source_ID
Assay_category_CV (Chemical Release, Source, Use Category)
Name
Description
Environment
Product type
Product name
Study_CV (cont. Vocab.)
Study_CV_ID
Type(longitudinal, cross-sectional, etc.)
Sumit Gangwal, et al. NCCT
Exposure_DB v0.5

In Development: ExpoCast DataBase (ExpoDB)



Integrated Chemical Prioritization Scheme

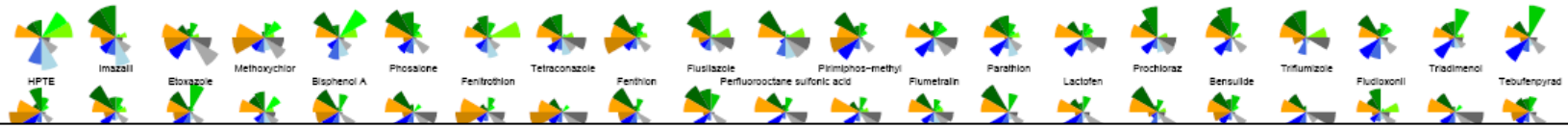
- Integrate over multiple domains of information
- Extend to incorporate additional types of data
- Transparently derive and visualize
- Customize components for diverse prioritization tasks

ToxPi (Toxicological Priority Index)

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.

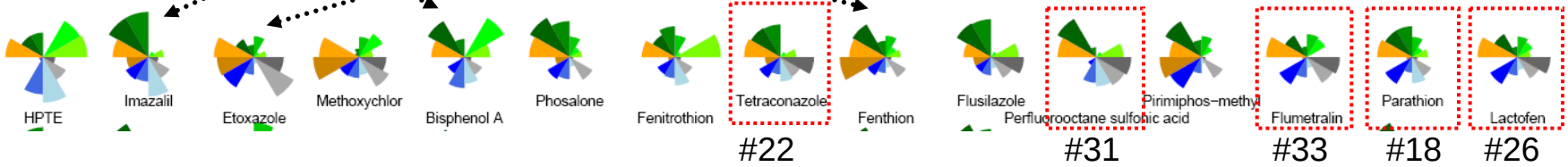
Incorporating exposure information (P&B): Preliminary ToxPi endocrine scores

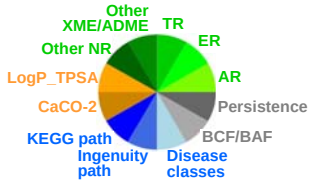
(sorted by overall ToxPi score)

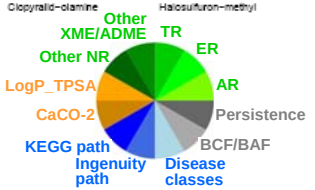


Previous top 15 prioritized chemicals by overall ToxPi score

New top 15 prioritized chemicals with exposure domain







Sumit Gangwal, et al. NCCT

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LRI RfP: *Developing Exposure Indices for Rapid Prioritization of Chemicals in Consumer Products*

- Leverage the best existing exposure models and ToxPi platform
- Derive exposure classification indices (i.e., components-slices) that could be used to incorporate exposure information into ToxPI.
- Consider multiple metrics to cover important aspects of exposure space and product lifecycle:
  - Physical -Chemical properties
  - Product characteristics (manufacture, formulation, use, lifecycle)
  - Emission characteristics (indoor/outdoor, media of release, amount available for release/contact)
  - Pathways (media, routes)
  - Scale (far-field, near-field)
  - Target characteristics (individual, population, lifestage, lifestyle, susceptibility)
  - Dosimetry (ADME)
- Demonstrate application of an index on a range of compounds and on a large number of compounds (on the order of 100-1000).

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Translation

New technologies must be applied to *BOTH* toxicology and exposure science if the ultimate goal of evaluating chemical safety is to be achieved.

- Systems framework
- Biologically-relevant exposure metrics
- Knowledge-base infrastructure

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Will fundamental knowledge of toxicity pathways improve understanding of real-world human-health risk?

- Assessing complex human-health risks requires that **hazard**, **susceptibility**, and **exposure** are all reliably characterized.
- Currently, balance of efforts to improve measuring hazard and exposure less than ideal.
- Accurate assessment of many environmental exposures remains an outstanding and largely unmet challenge in toxicology and risk assessment.
- **To realize the NRC vision, we face a critical need for advanced exposure science.**

Adapted from Wild, 2005

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Some Exposure Questions

- **What are the effects of low dose exposures**
  - What are biologically-relevant exposures?
  - What are the effects resulting from real-world exposure (i.e., what are environmentally-relevant hazards)?

- **How do windows of susceptibility impact long-term health**
  - What is the potential for exposure during critical windows of susceptibility?
  - How can the most important exposures be measured and characterized?

- **How can mixtures of chemicals and multiple stressors alter susceptibility and response**
  - Over the developmental time course, what is the potential for exposure to mixtures of chemicals and multiple stressors?
  - What are the key metrics required to characterize critical aspects of mixtures (i.e., combinations of stressors over time that are likely to interact and impact susceptibility and response)?

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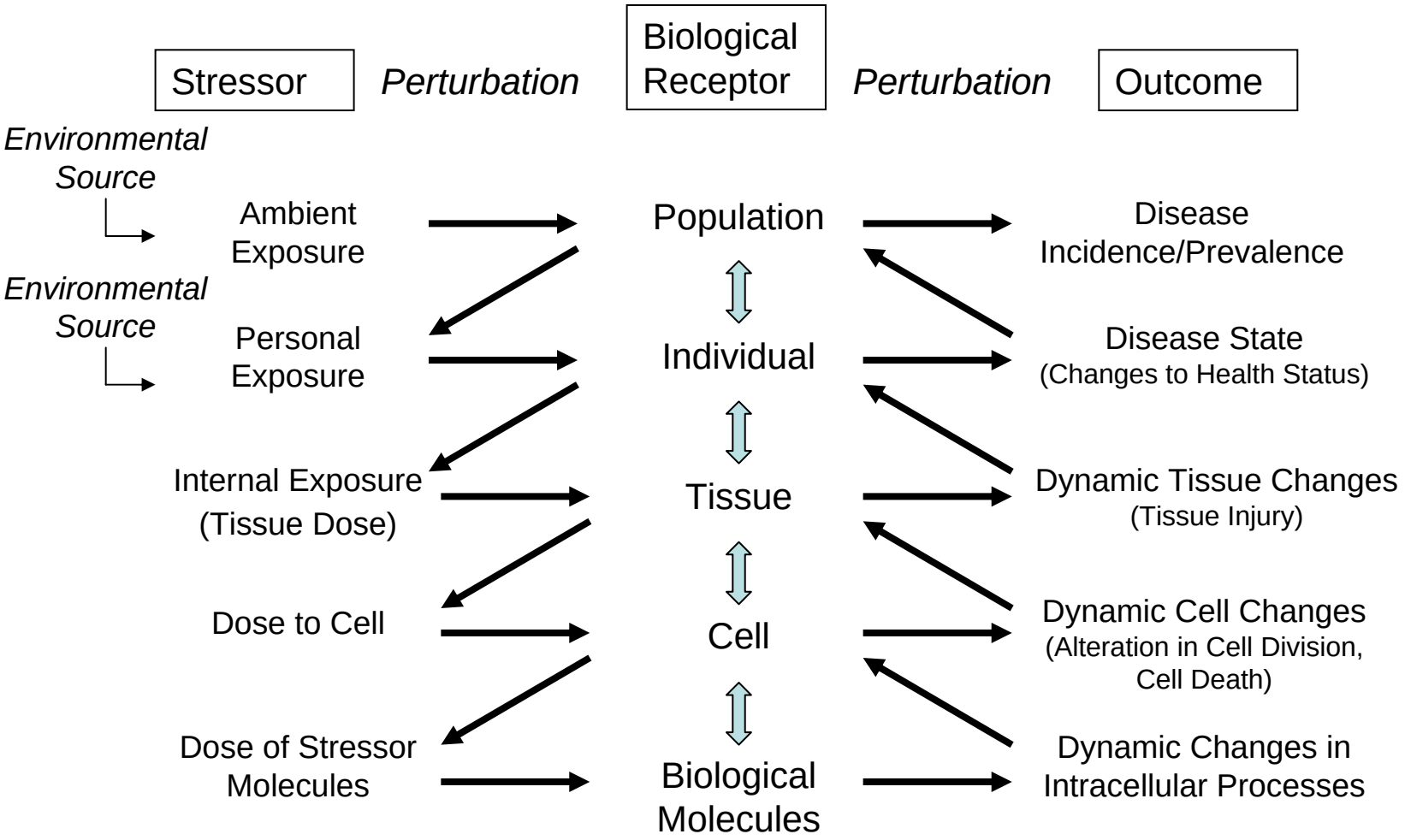
Systems Biology: Exposure at All Levels of Biological Organization



Cohen Hubal, JESEE, 2008

Figure 1

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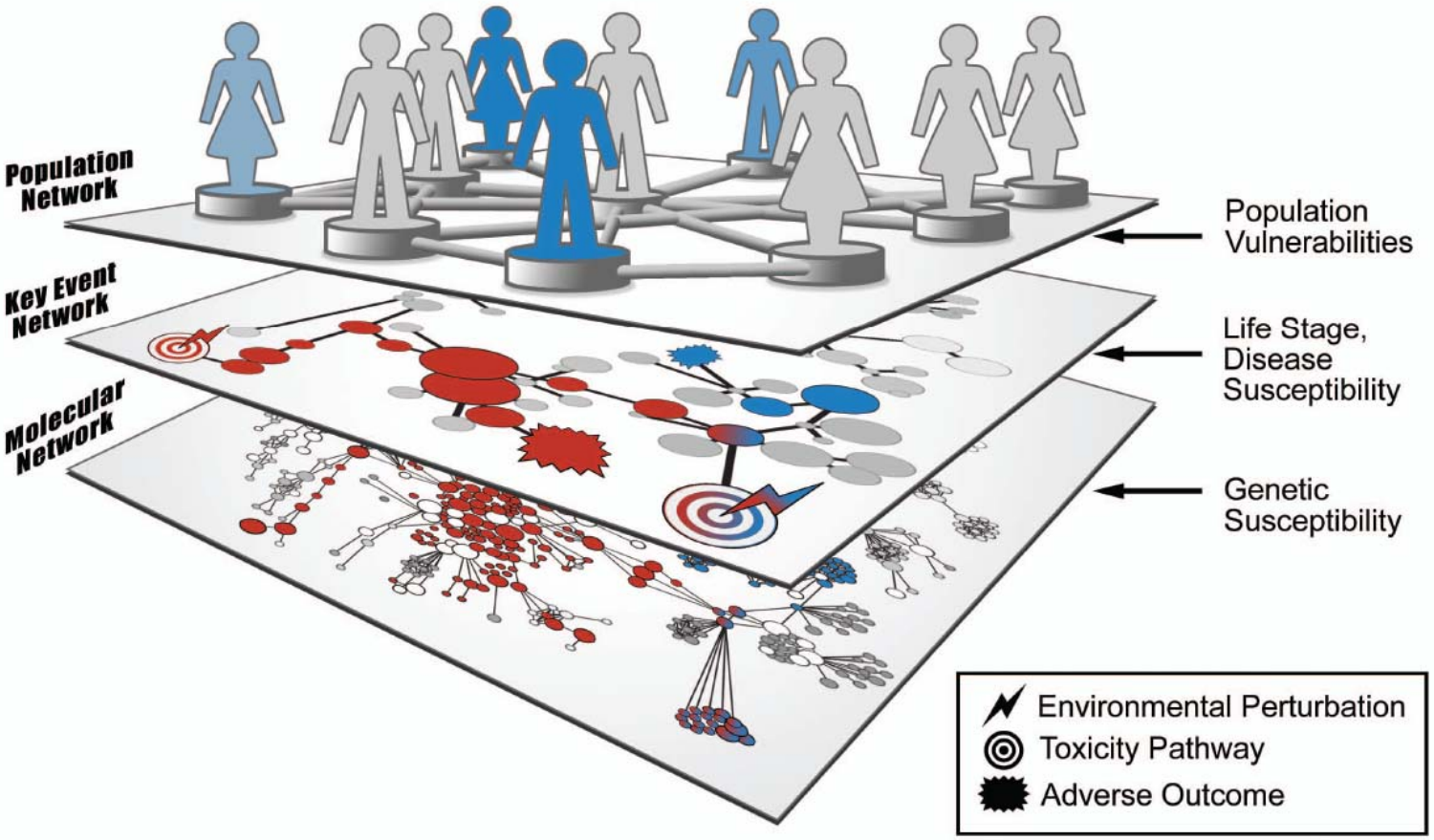
Systems Exposure Science : Extending Network Analysis

Consider coupled networks spanning multiple levels of biological organization



Adapted from Edwards & Preston (2008), Tox Sci, 106(2):312-318

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Biologically-Relevant Exposure Metrics

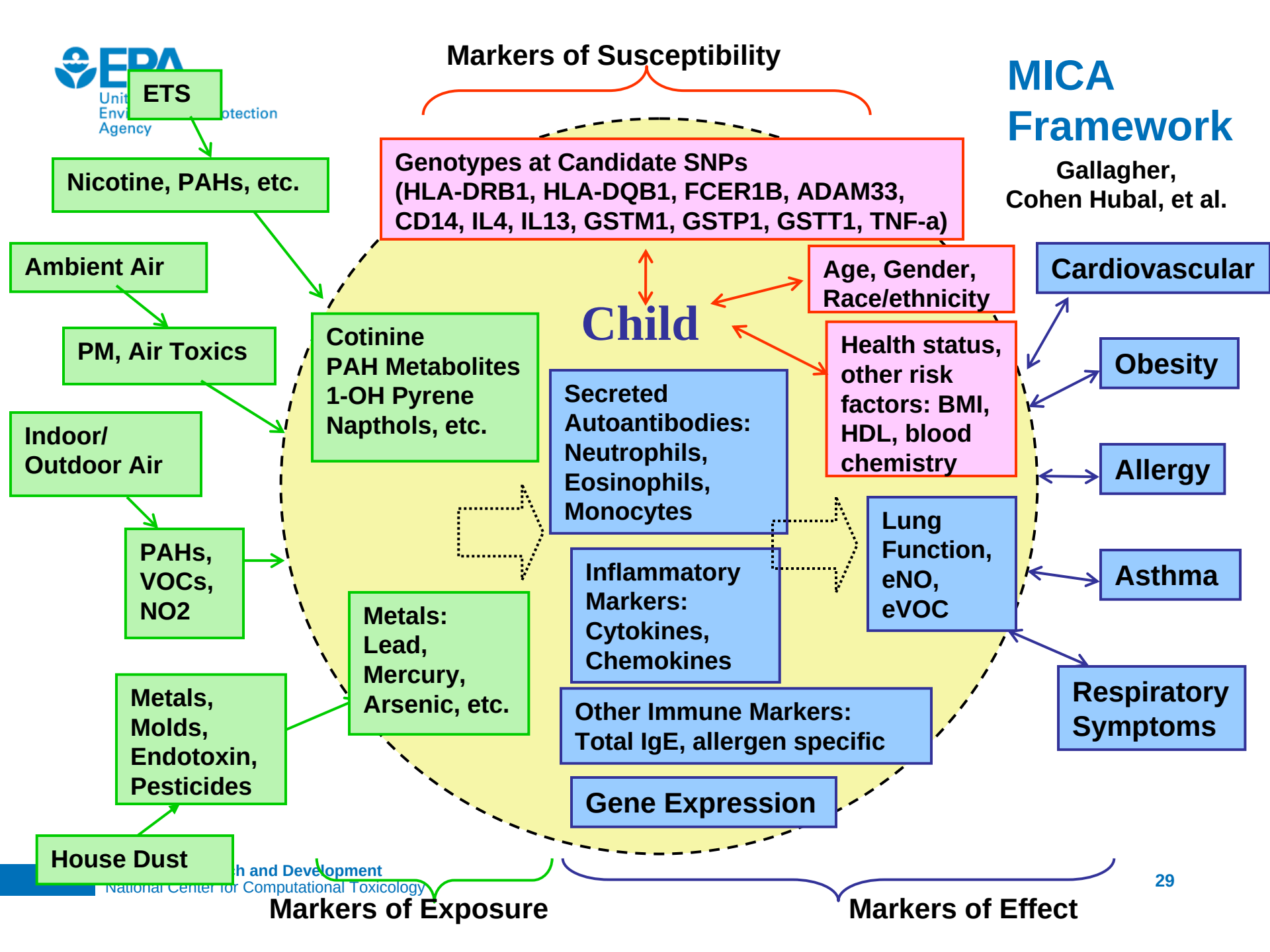
Markers required that can be directly associated with key events in disease processes and with individual exposure profiles

- 'Omic technologies showing potential to yield a new generation of exposure metrics (Wild, 2009)

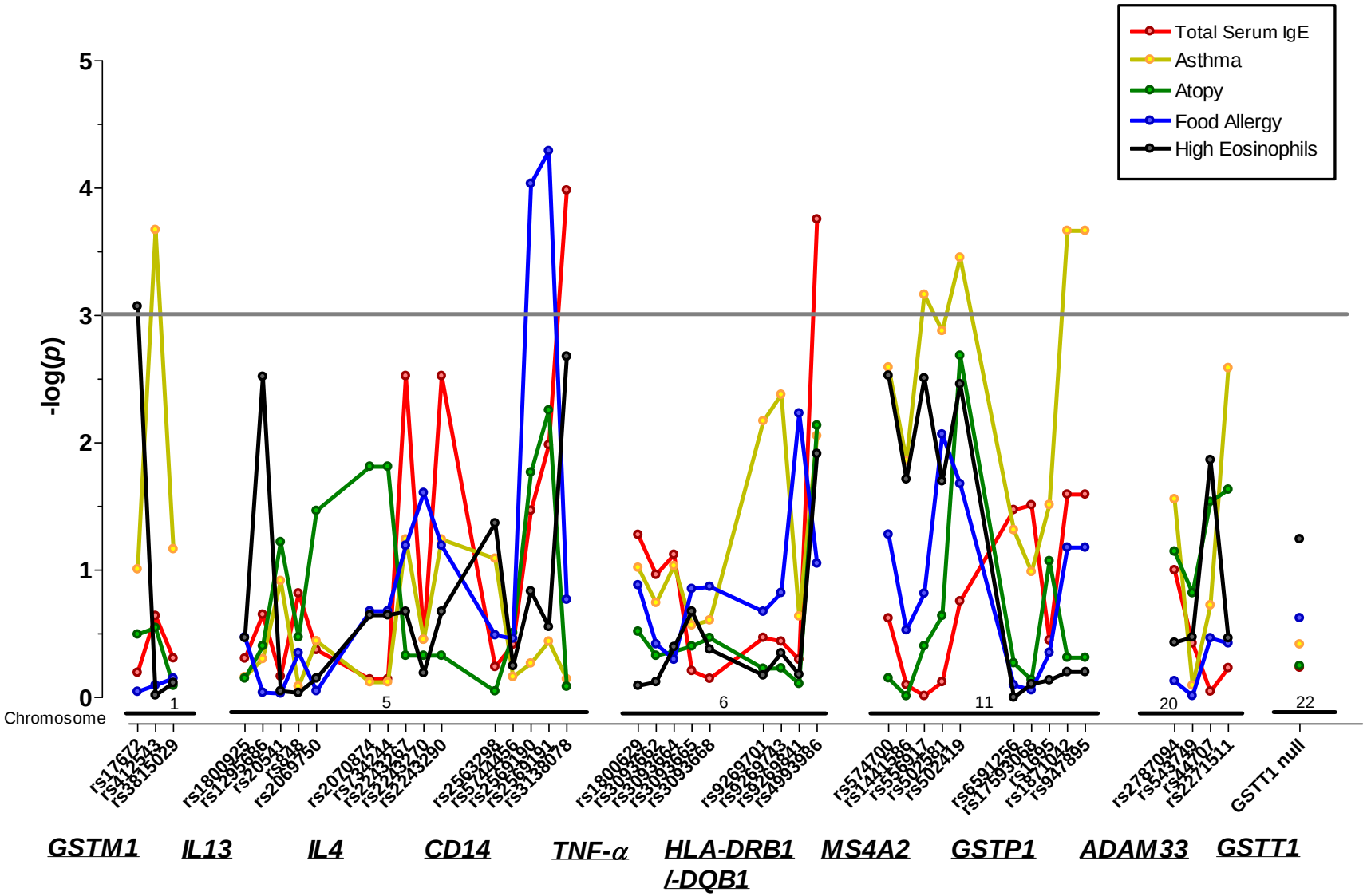
  (Altered global gene expression associated with exposures to arsenic, cigarette smoke, benzene, metal fumes and air pollution)

- Better environmental biosensors required to study gene-environment interactions associated with complex disease (Collins 2007)

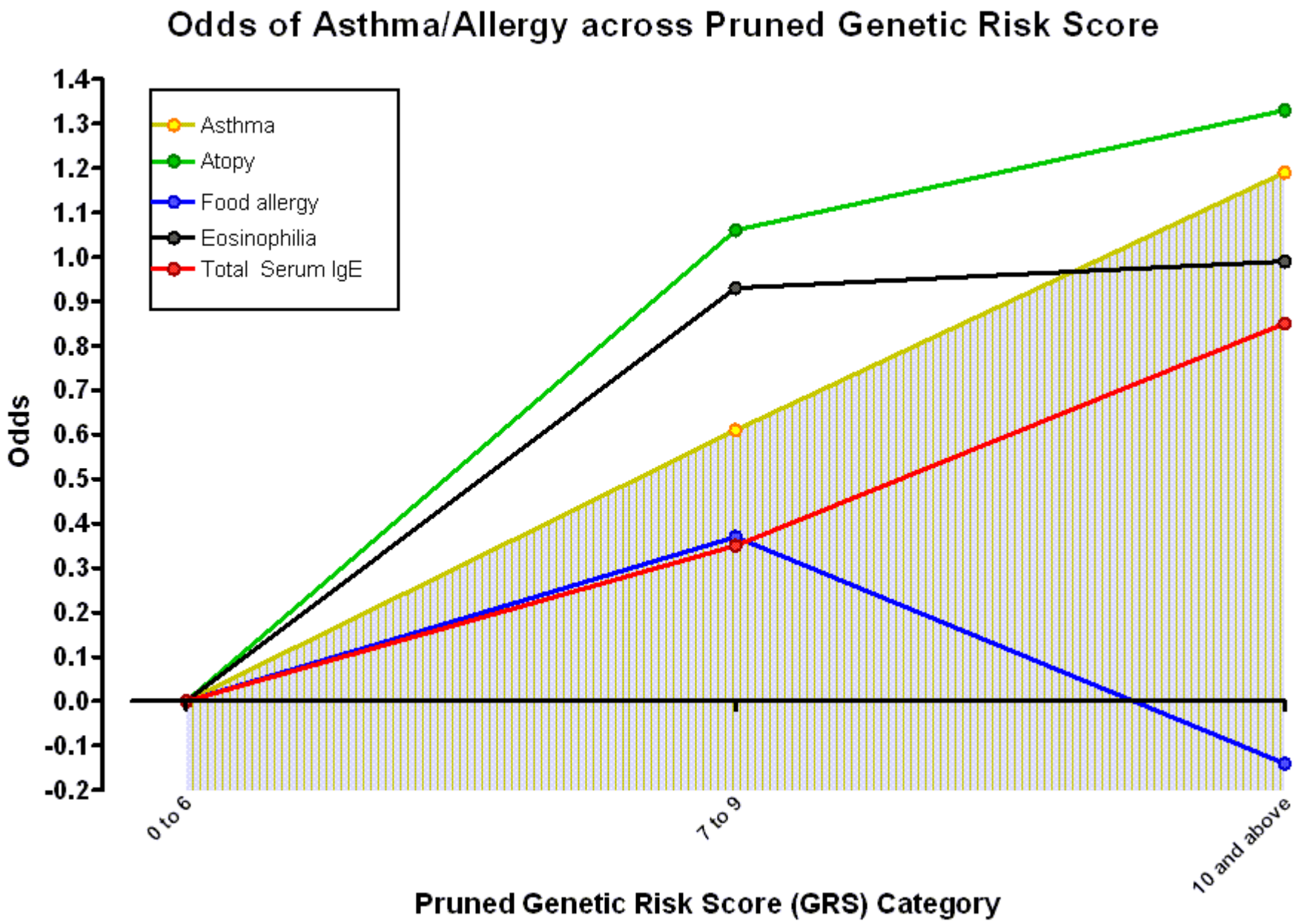
  (Nano-scale sensor arrays can be developed to detect specific sets of environmental agents (Andreescu et al, 2009))


Markers of Susceptibility
MICA Framework
Gallagher, Cohen Hubal, et al.
ETS
Nicotine, PAHs, etc.
Ambient Air
PM, Air Toxics
Indoor/ Outdoor Air
PAHs, VOCs, NO2
Metals, Molds, Endotoxin, Pesticides
House Dust
Genotypes at Candidate SNPs (HLA-DRB1, HLA-DQB1, FCER1B, ADAM33, CD14, IL4, IL13, GSTM1, GSTP1, GSTT1, TNF-a)
Child
Age, Gender, Race/ethnicity
Health status, other risk factors: BMI, HDL, blood chemistry
Cotinine
PAH Metabolites
1-OH Pyrene
Napthols, etc.
Secreted Autoantibodies: Neutrophils, Eosinophils, Monocytes
Metals: Lead, Mercury, Arsenic, etc.
Inflammatory Markers: Cytokines, Chemokines
Other Immune Markers: Total IgE, allergen specific
Gene Expression
Lung Function, eNO, eVOC
Cardiovascular
Obesity
Allergy
Asthma
Respiratory Symptoms
Markers of Exposure
Markers of Effect
h and Development
National Center for Computational Toxicology
29

SNP Associations with Asthma/Allergy: Plot of Statisical Significance



Negative log-transformed *p*-value (-log(*p*)) indicative of statistical significance for the association between each SNP and trait.
Higher -log(*p*) values correspond to higher statistical significance.
SNPs with -log(p)>3.0 were significant after Bonferroni correction for multiple comparisons.


Odds of Asthma/Allergy across Pruned Genetic Risk Score
Asthma
Atopy
Food allergy
Eosinophilia
Total Serum IgE
Odds
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
0 to 6
7 to 9
10 and above
Pruned Genetic Risk Score (GRS) Category

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Albumin Adducts as Measures of Total Human Exposure," Dr. Rappaport, UC Berkeley – LRI funded research

- Human serum albumin (HSA) scavenges toxic electrophiles from the blood to produce constellation of adducts.
- Because HSA adducts reflect the totality of systemic exposures to electrophiles, these can be used to classify systemic exposures from both environmental and lifestyle stressors
- Proof of concept that HSA adducts can be used to quantify exogenous and endogenous exposures of interest
  - Polycyclic aromatic hydrocarbons (PAHs), which produce a host of reactive metabolites
  - Formaldehyde, which has both exogenous and endogenous sources
- Experiments to optimize methods for characterizing HSA adducts, increase throughput, and validate
- Use archived specimens of blood from PAH-exposed workers, formaldehyde-exposed workers, and the general population (including MICA cohort)
- Goal to motivate a new generation of simple, biologically-based methods for assessing human exposures in health studies.
- Given the small amount of HSA required (1 mg or less) methods should be ideal for applications involving precious archived specimens

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Exposure-Hazard Knowledge System

- Computational Techniques – Two Branches

  A combination of discovery and engineering (mechanistic)-based modeling approaches for hypothesis development and testing are required.

- **Knowledge-discovery**
  - **Data-collection, mining, and analysis**
  - **Required to extract information from extant data on critical exposure determinants, link exposure information with toxicity data, and identify limitations and gaps in exposure data.**

- Mechanistic (dynamic) simulation
  - Mathematical modeling at various levels of detail
  - Required to model the human-environment system and to test our understanding of this system.

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Exposure-Hazard Knowledge System

- Translation of HTP hazard information requires holistic risk assessment knowledge system
  - Include ontologies, databases, linkages
  - Facilitate computerized collection, organization, and retrieval of exposure, hazard, and susceptibility information

- Standardized exposure ontologies required to
  - Define relationships, allow automated reasoning, facilitate meta analyses
  - Develop biologically-relevant exposure metrics
  - Design *in vitro* toxicity tests to measure environmentally-relevant hazard
  - Incorporate information on susceptibility and background exposures to individual and population-level risks

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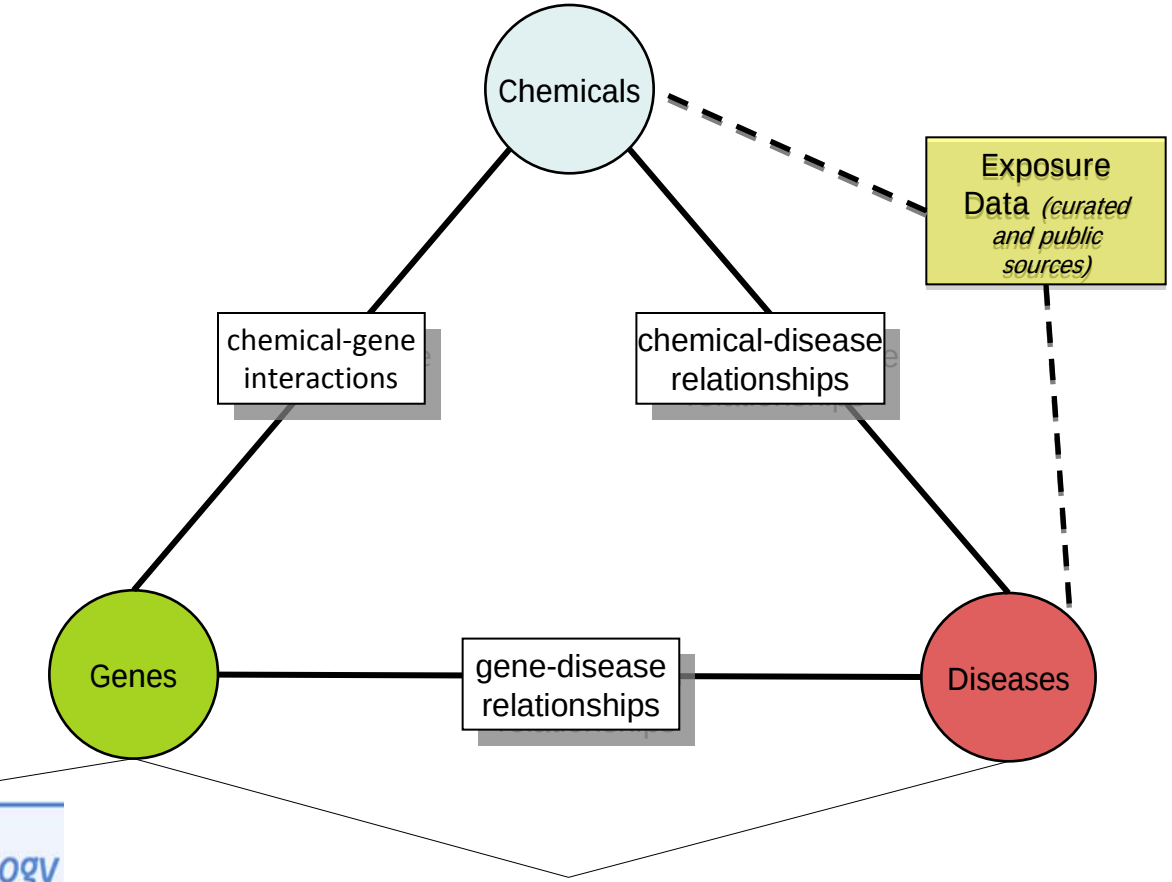
"Facilitating the centralization and integration of exposure data through exposure ontology development and expanded accessibility to exposure studies." Carolyn Mattingly, Mount Desert Island Biological Laboratory – LRI funded research

- Specific aim 1. Develop an exposure data ontology that will expand the capacity for exposure data integration, centralization, curation and analysis – test by curating exposure manuscripts in CTD
- Specific aim 2. Enable public access to a seminal exposure data set conducted and compiled by the Silent Spring Institute (SSI; the Household Exposure Studies) to begin facilitating integration and centralization of exposure data for the research community
- To further develop and test exposure ontology, Tom McKone, LBNL, will lead a small related project to map the Exposome considering Value of Information approach.

Pilot Curation of Exposure Data into CTD



the Gene Ontology

functional annotations

KEGG

pathway data

ctd

CTD advances understanding of the effects of environmental chemicals on human health.

The Comparative Toxicogenomics Database™

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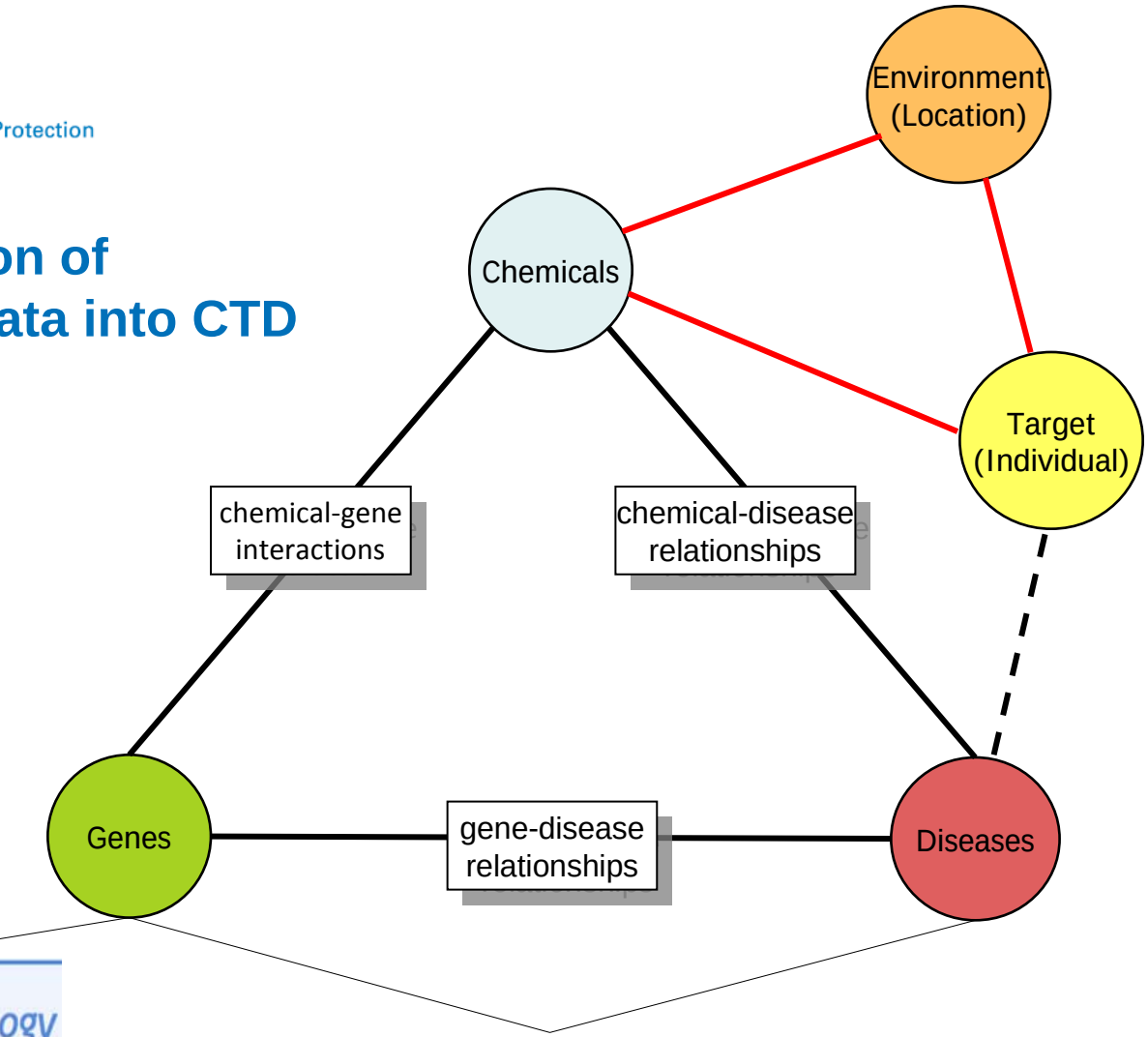
Pilot Curation of Exposure Data into CTD



the Gene Ontology

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KEGG Kyoto Encyclopedia of Genes and Genomes

R

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Consideration of Exposure for Green Design and Sustainable Use

- **A transformation in the framework for design, manufacture and management of chemicals is occurring to address society's need for safe and effective chemicals (Anastas, 2009).**
  - Principles of green chemistry require holistic consideration of integrated environmental, economic, and social factors.
  - Prediction of potential exposures across the product lifecycle for all chemical classes and use scenarios is required under green engineering principles to minimize potential health risks to all vulnerable groups.

- **Exposure research questions**
  - What key metrics describe potential for exposure along the chemical/product lifecycle?
  - How can these metrics of exposure potential be linked with key attributes of chemicals to evaluate safety of chemical/material alternatives?

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Disclaimer

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