Evaluating MoE and its Uncertainty and Variability for Food Contaminants

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OUTLINE

- Introduction
  - Some definitions
- MoEs for Chemicals that are Genotoxic and Carcinogenic
  - An example, and lessons
  - Exposure assessment is hard
  - Evaluation of the urgency of an MoE depends on the exact definition
- A model to evaluate variability and uncertainty of MoEs
- The greater uncertainty – thousands of chemicals with virtually no health effects or exposure information
  - Steps towards rapid computation of MoEs using *in vitro* and *in silico* methods.

MoE: Margin of Exposure

The ratio of two factors which assesses for a given population the dose at which a small but measurable adverse effect is first observed and the level of exposure to the substance considered. (EFSA)

$$\text{MoE} = \frac{\text{Health-related dose (e.g., BMDL}_{10}\text{)}}{\text{Exposure-related dose (e.g., population median dose)}}$$

Example

BMDL_{10} = 10 mg/kg/day

Target (human) population median dose = .01 mg/kg/day

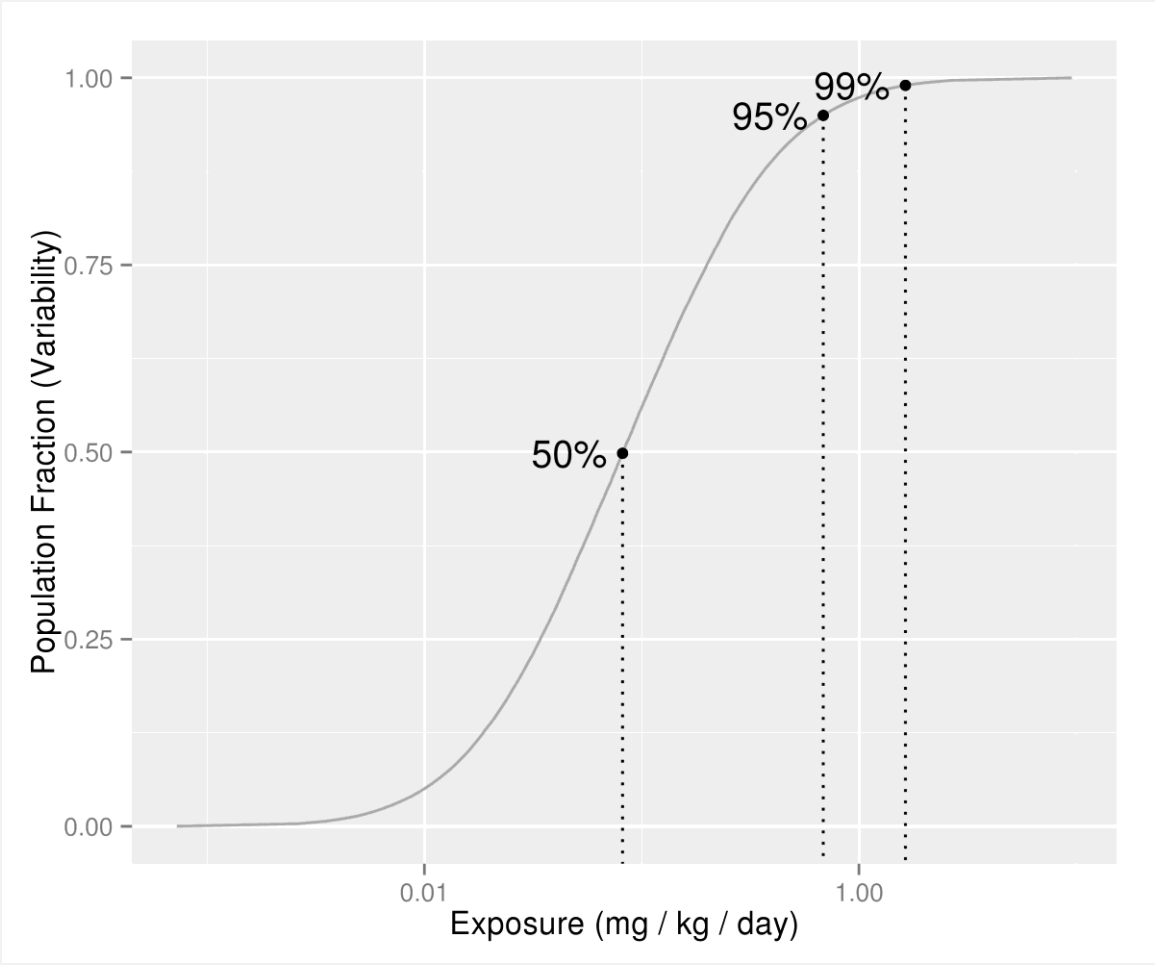
$$\text{MoE} = \frac{10 \text{ mg/kg/day}}{0.01 \text{ mg/kg/day}} = 1000$$

Target (human) population 99th percentile dose = .2 mg/kg/day

$$\text{MoE} = \frac{10 \text{ mg/kg/day}}{0.2 \text{ mg/kg/day}} = 50$$

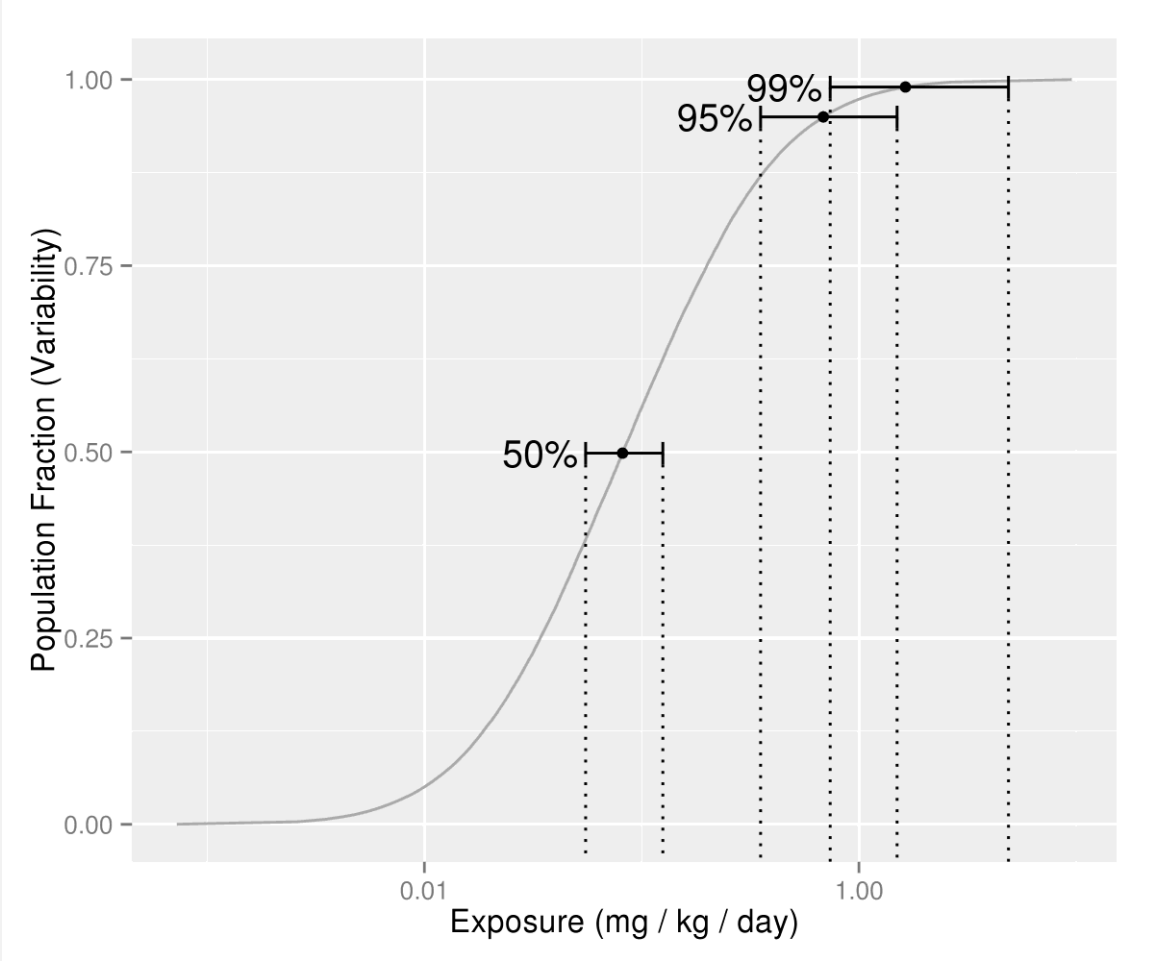
Variability

Differences among entities or states of an entity attributable to heterogeneity. Variability is an inherent property of nature and may not be reduced by measurement. (US EPA)

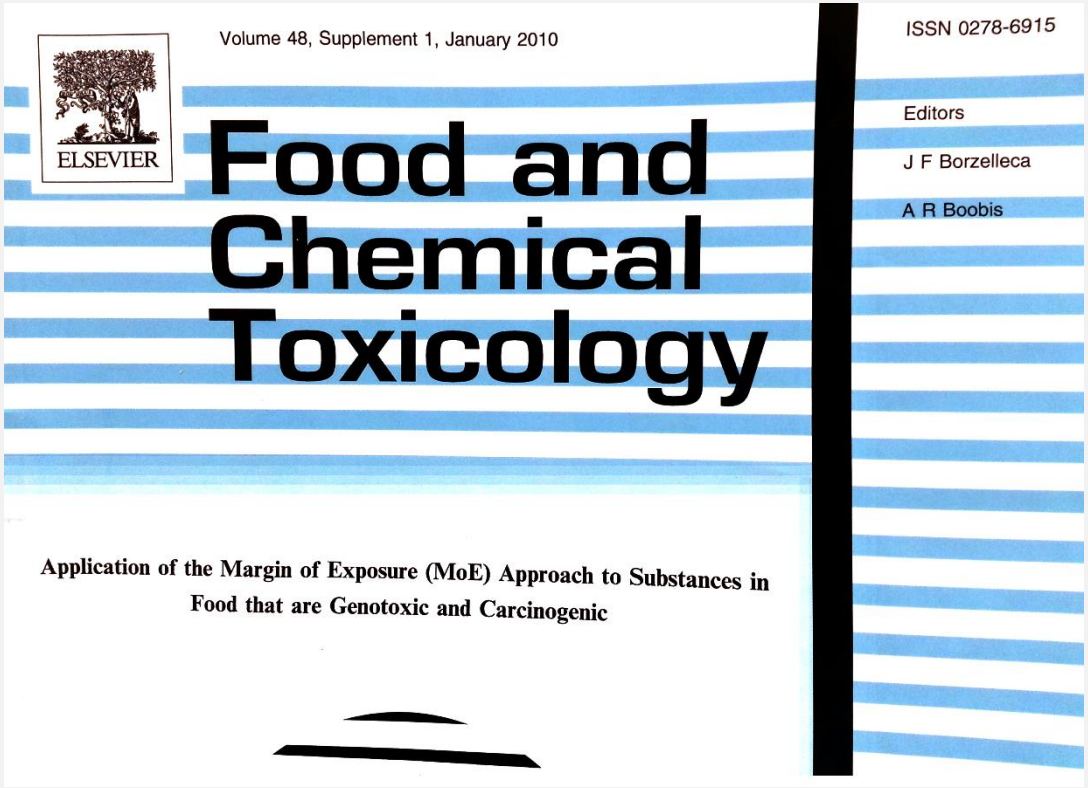


Uncertainty vs Variability

Lack of knowledge concerning an event, state, model, or parameter. Uncertainty, unlike variability, may be reduced by research or observation. (US EPA)



MOEs for CHEMICALS that are GENOTOXIC and CARCINOGENIC



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Under the responsibility of the ILSI Europe risk Assessment of Genotoxic Carcinogens Task Force

Chemicals Evaluated

1,3-Dichloro-2-propanol
1 Methylcyclopropene impurities
Acrylamide
Aflatoxin B1
BaP in PAHs
Benzene
Ethyl carbamate
Furan
Leucomalachite green
Methyleugenol
PhIP
Sudan I

MoE Components

Health-related dose = $BMDL_{10}$ for cancer endpoints deemed relevant to humans.

Uncertainties:

- *Statistical*:
  - Estimation error, given a model
  - What is the right model?
- *Biological*
  - Which cancer endpoints are relevant to humans?

Chemical	Endpoint	Exposure Scenario	MoE
1,3-Dichloro-2-propanol	Combined kidney carcinomas and adenomas male rats	average	100,000
1 methylcyclopropene impurities	Nasal carcinoma in male rats	Scenario A, average	600,000
Acrylamide	Peritesticular mesothelioma	Average	1000
Aflatoxin B1	Hepatocellular carcinomas	low	600
BaP	Total tumor-bearing mice	average	20,000
Benzene	Female rat zymbal gland carcinoma	beverage	2,000,000
		High-end food	400,000
Ethyl carbamate	Alveolar/bronchiolar adenoma and carcinoma in mice	Mean from food (no alcohol)	20,000
Furan	Male rat hepatocellular adenoma and carcinoma	Average (50%)	4300
Leucomalachite green	Female mouse hepatocellular carcinomas	average	4,000,000
Methyleugenol	Male rat combined hepatocellular carcinomas	average	800
PhIP	Prostate ventral carcinoma	average	80,000
Sudan I	Male rat hepatocellular carcinoma	France, max	3,000
		Germany, max	500
		Middle Africa, max	30

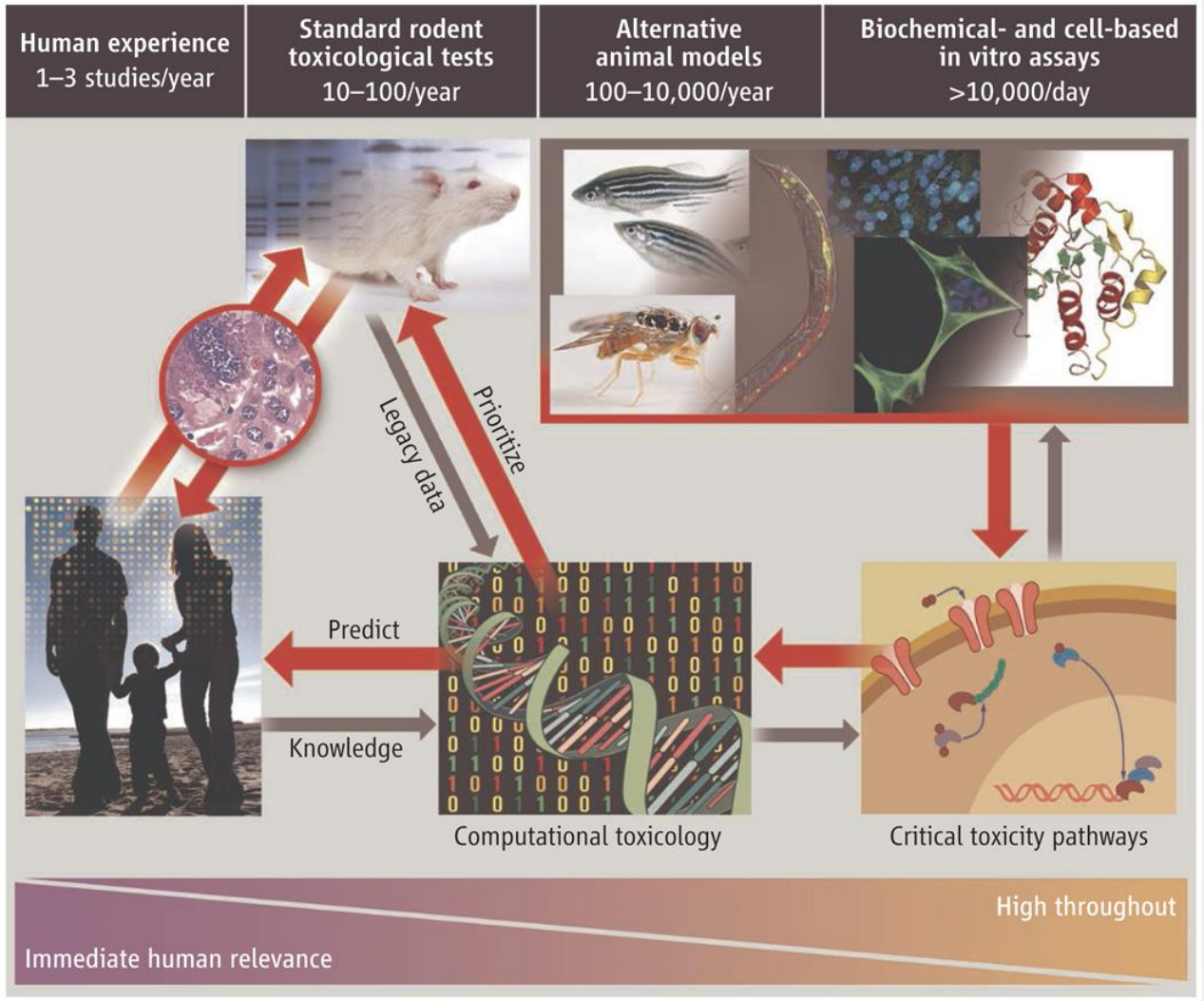

EPA
United States
Environmental Protection
Agency

Specifics of the MoE Definition Matter

EPA United States Environmental Protection Agency

HIGH-THROUGHPUT CHARACTERIZATION OF MoEs

Vision: Transforming Toxicity Testing



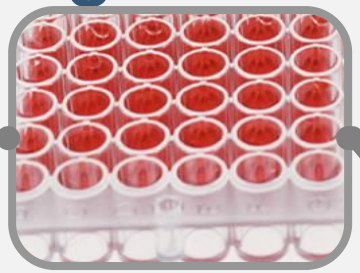
Citation: Science. 2008 Feb 15;319(5865):906-7.
Toxicology. Transforming environmental health protection.
Collins FS, Gray GM, Bucher JR.
Source
National Human Genome Research Institute (NHGRI), National Institutes of Health, Bethesda, MD 20892, USA.

Goals for High Throughput Exposure

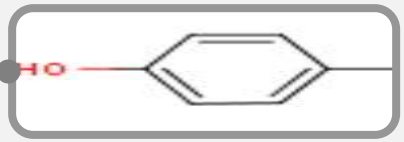
- Incorporate multiple models into consensus predictions for 1000s of chemicals
- Evaluate/calibrate predictions with available measurement data across many chemical classes
- Empirically estimate uncertainty in predictions

How it Works: ToxCast Innovative Screening

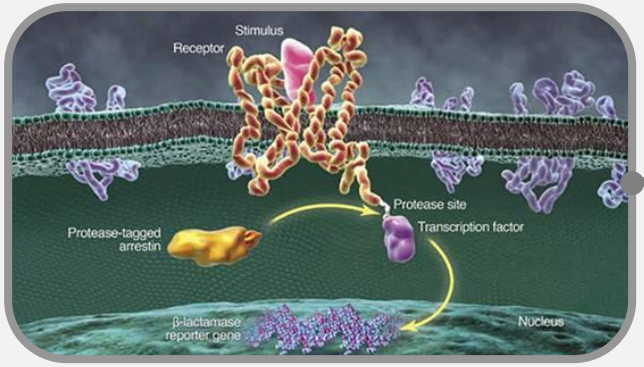
Technology



Uses 96-, 384-, 1536 Chemical Well Plates



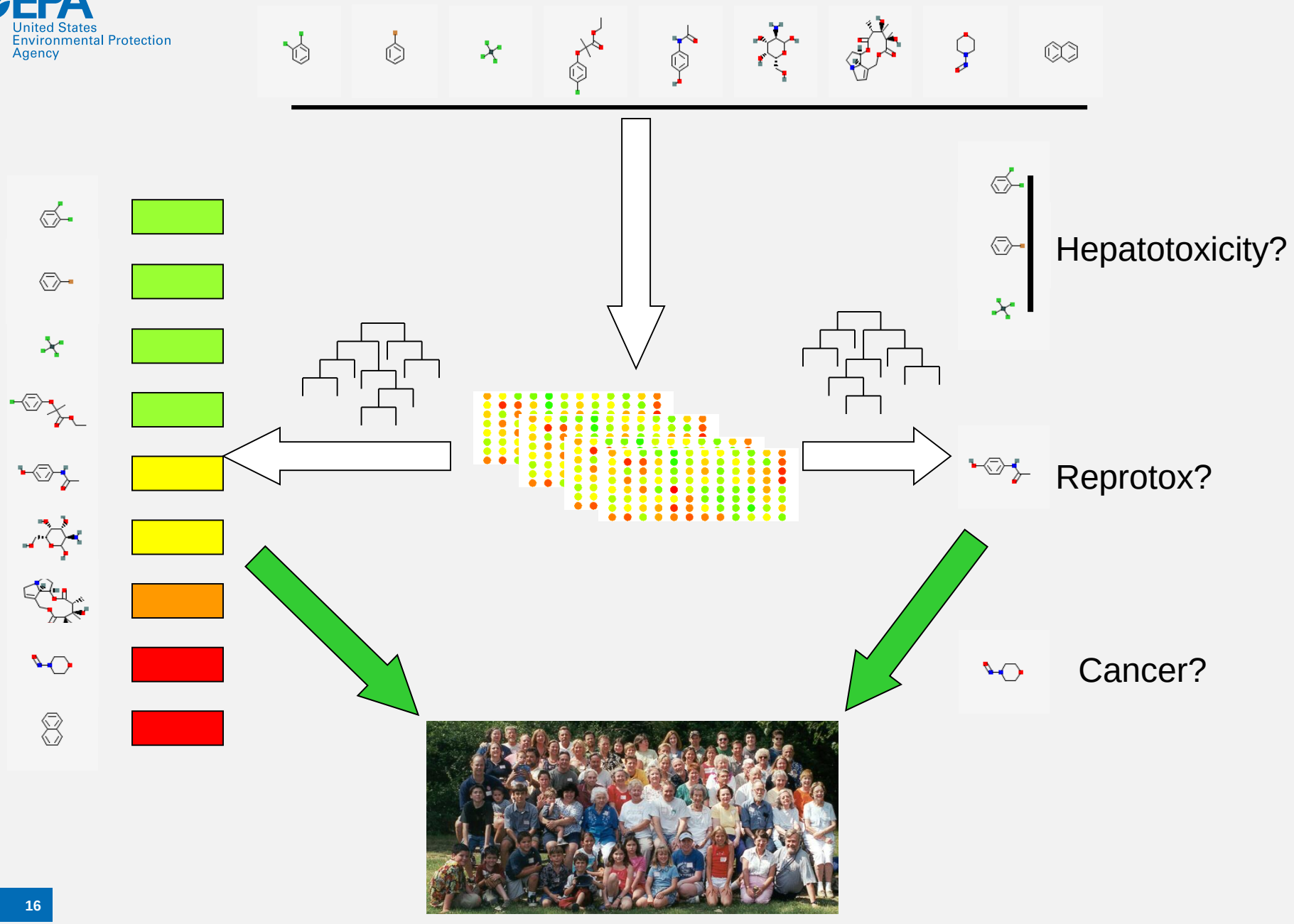
Hundreds of chemicals put on well plate



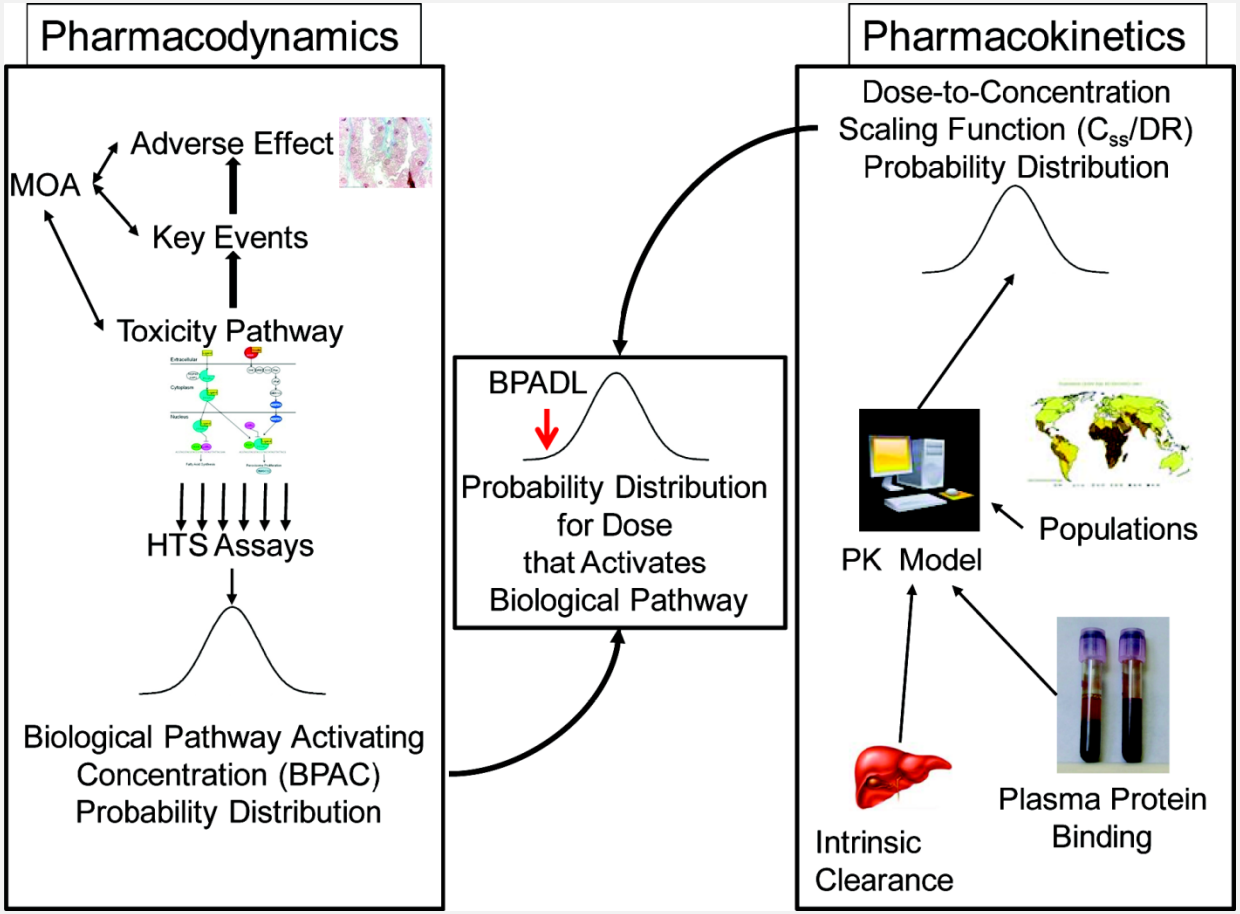
Human cells are put on wells with chemicals to determine potential interactions with biological processes

Which of the chemicals being screened have the highest potential for certain toxicity (ie: Disrupting the endocrine system)

HTS: High Throughput Screening

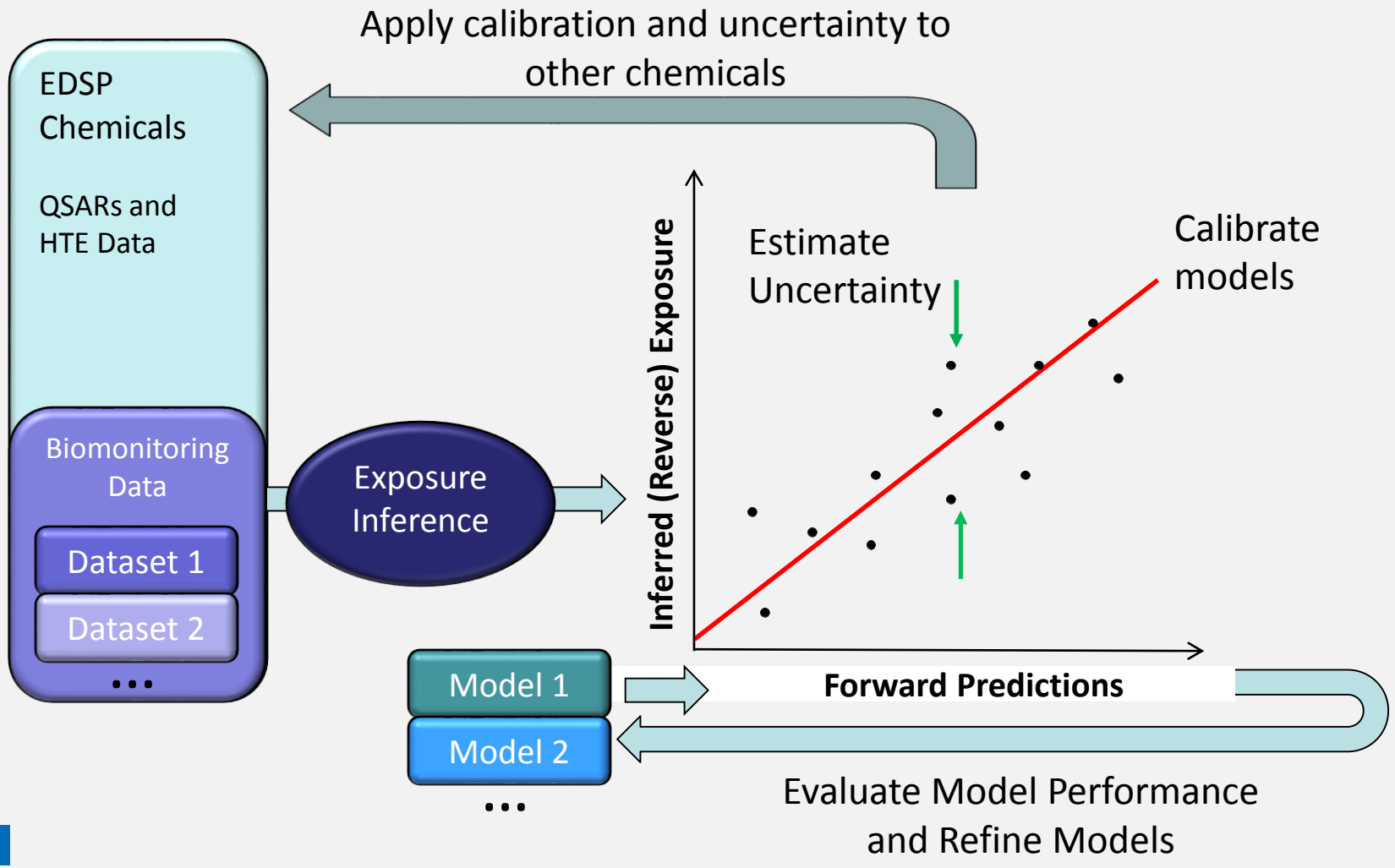

Hepatotoxicity?
Reprotox?
Cancer?

BPAD: HT Effects Component for Screening & Prioritization

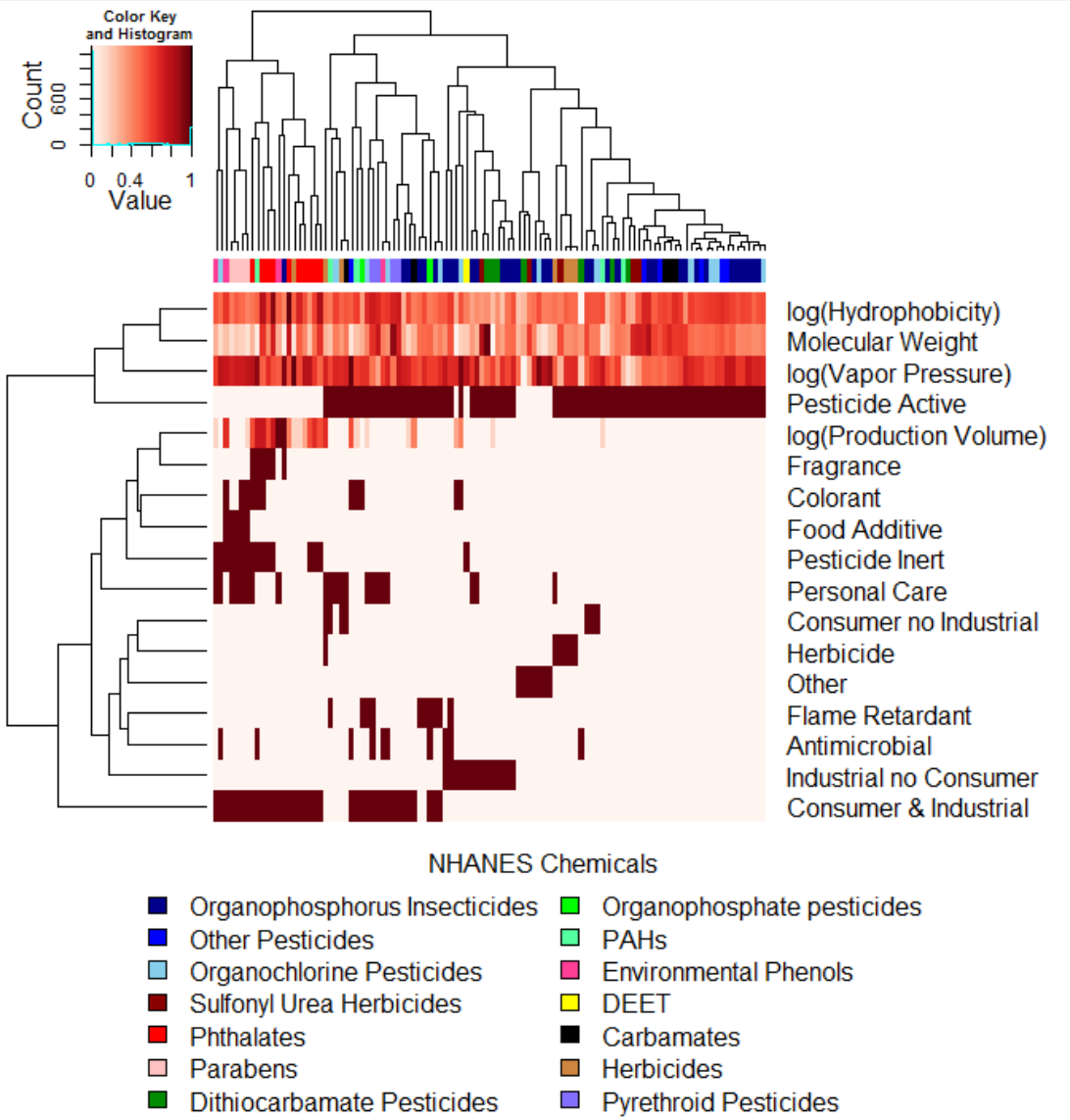


Judson, et al. 2011

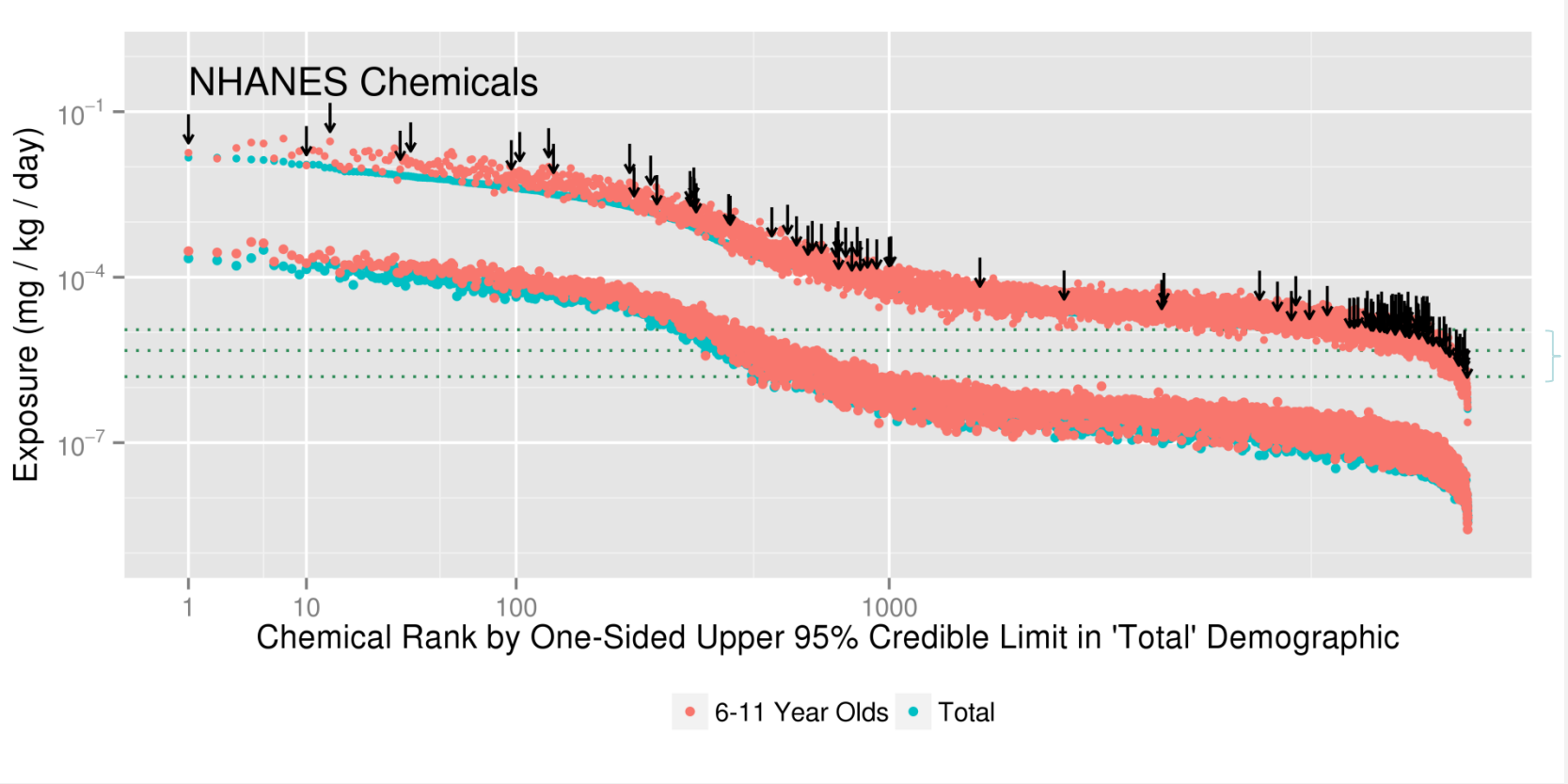
The SEEM Framework



High Throughput Descriptors for NHANES



Exposure Predictions for 7968 EDSP Chemicals



- Chemicals currently monitored by NHANES are distributed throughput the predictions
- Chemicals with the first and ninth highest 95% limit are monitored by NHANES

Summary

- MoE definition
  - Numerator and denominator definition and level of concern derivation are co-dependent
  - Uncertainty includes:
    - Ambiguity of definition
    - Statistical uncertainty of numerator and denominator
    - The “usual” uncertainties about health effects and exposure assessments.
- Conventional Application
- Rapid Assessment
  - Effects assessed through high-throughput assays, modeling
  - Assess exposure through chemical use & occurrence data, modeling,

United States Environmental Protection Agency

Extra Slides

Definitions

- **MoE, Margin of Exposure:**

  ratio of two factors which assesses for a given population the dose at which a small but measurable adverse effect is first observed and the level of exposure to the substance considered. (EFSA)

- **Variability:**

  Differences among entities or states of an entity attributable to heterogeneity. Variability is an inherent property of nature and may not be reduced by measurement. (US EPA)

- **Uncertainty:**

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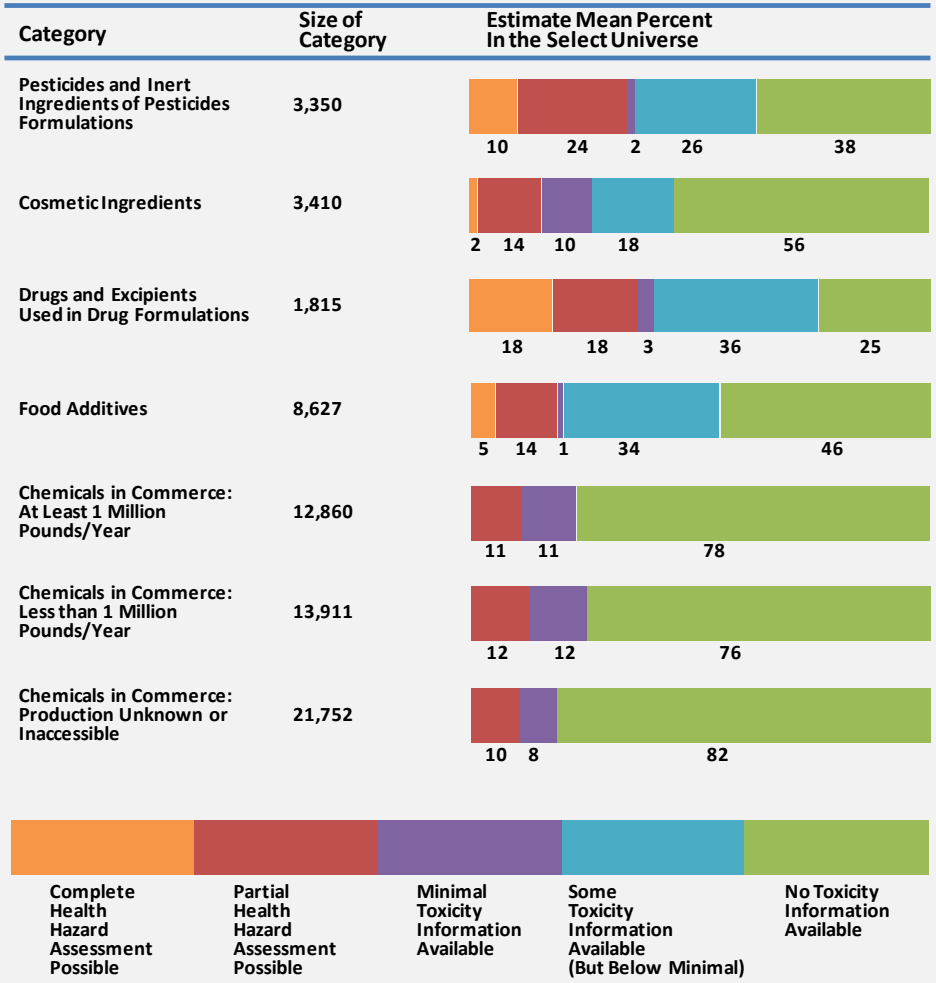
Risk Assessment and the Chemical Universe

- US NRC report
- Major challenge is too many chemicals and not enough data
- Total = 65725
- No tox data = 46,000

US National Research Council, 1984



Risk Assessment and the Chemical Universe

- Since 1984 not much progress has been made
- TSCA Inventory = 75,000
- REACH Inventory = 150,000
- US & Canadian estimates of about 30 thousand substances in commercial use

Judson et al (2009) estimated that there are ~10,000 high priority chemicals

For these high priority chemicals most lack adequate studies