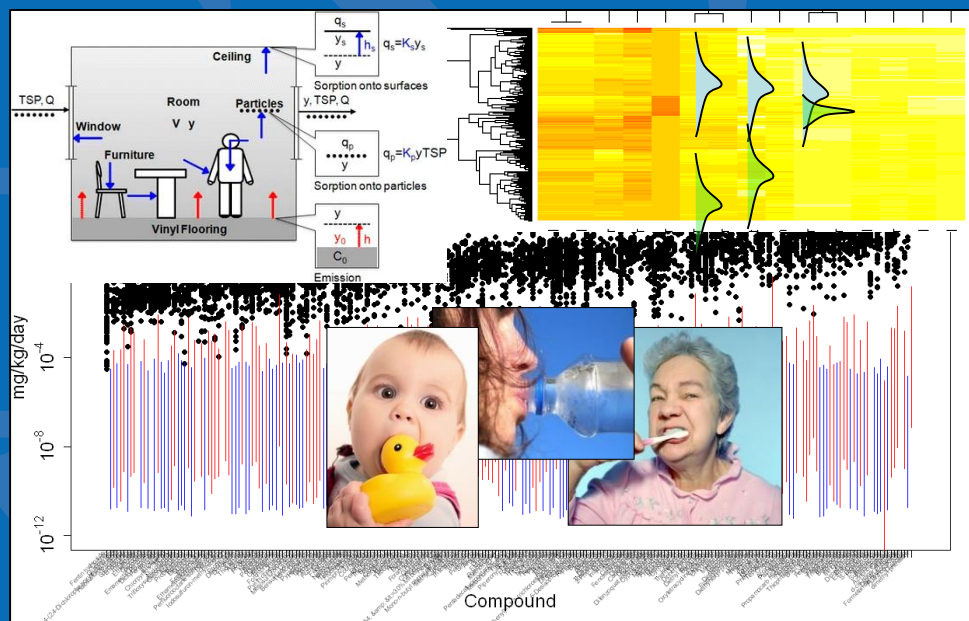


# Non-Targeted Analysis Challenge

*John Wambaugh*

*National Center for Computational Toxicology*

*U.S. EPA, Office of Research and Development*



**ADVANCING NON-TARGETED ANALYSES OF XENOBIOTICS  
IN ENVIRONMENTAL AND BIOLOGICAL MEDIA**

**August 18-19, 2015**

# Opportunity

- The timely characterization of the human and ecological risk posed by thousands of existing and emerging commercial chemicals is a critical challenge
- While advances have been made in HT toxicity screening, exposure methods applicable to 1000s of chemicals are needed



*"I'm searching for my keys."*

- With non-targeted/suspect screening we now have the tools to provide monitoring data greatly beyond the "lamp post"
- Further, opportunities now exist to rapidly incorporate new data into some aspects of chemical decision making

# Endocrine Disrupter Screening Program (EDSP)

## **1996 Federal Food, Drug and Cosmetic Act, section 408(p)**

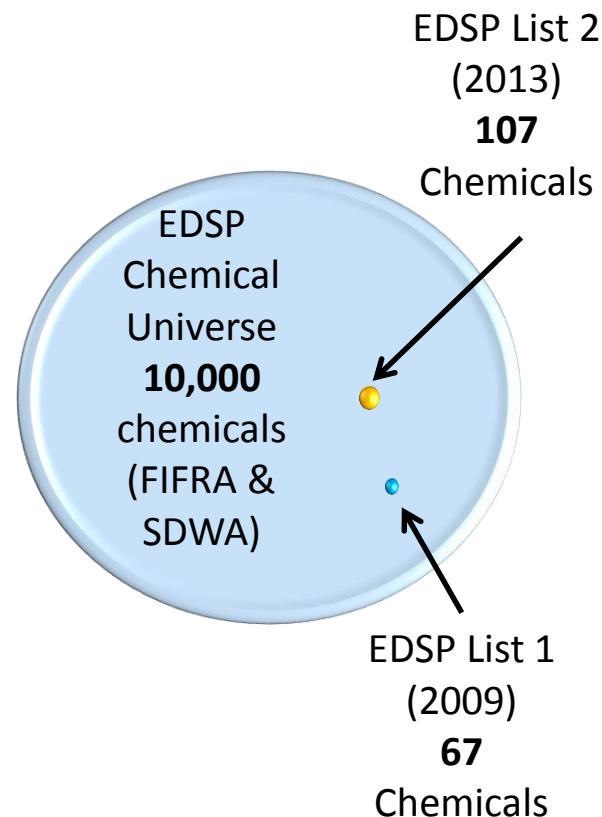
Requires the U. S. EPA to develop a screening program using appropriate validated test systems and other scientifically relevant methods to determine whether certain substances may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effect as the Administrator may designate.

## **1996 Safe Drinking Water Act Amendments, section 1457**

Testing of chemical substances that may be found in sources of drinking water, if substantial human populations may be exposed.

# EDSP Universe of Chemicals

Chemical List	Number of Compounds
Conventional Active Ingredients	838
Antimicrobial Active Ingredients	324
Biological Pesticide Active Ingredients	287
Non Food Use Inert Ingredients	2,211
Food Use Inert Ingredients	1,536
Fragrances used as Inert Ingredients	1,529
Safe Drinking Water Act Chemicals	3,616
<b>TOTAL</b>	<b>10,341</b>



So far 67 chemicals have undergone testing  
and an additional 107 are being tested

# Toxicity Screening Studies

	Estrogen Receptor	Androgen Receptor	Thyroid Receptor	Steroidogenesis
<i>In vitro</i>	*	X		X
<i>In vivo</i>	*	X	X	X

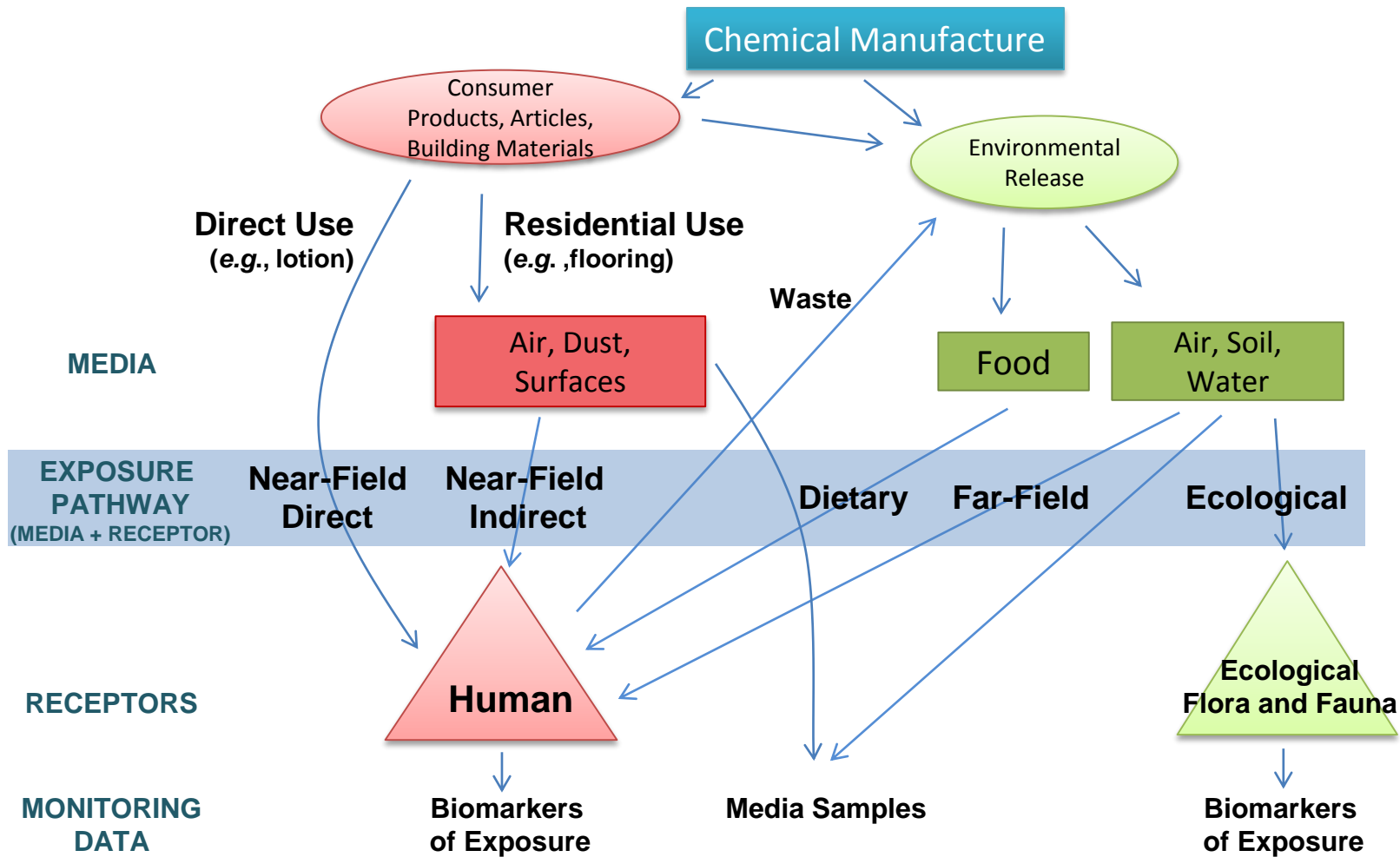
- Initial assays (*in vitro* and *in vivo*) were relatively low throughput, **but:**
- \*Federal Register (June 19, 2015): **Use of High Throughput Assays and Computational Tools; Endocrine Disruptor Screening Program** – high throughput ToxCast screening assays for estrogen receptor allow 1000s of chemicals to be screened
- Is EATS (Estrogen/Androgen/Thyroid/Steroidogenesis) the whole picture?
  - 20–30 % of infertile couples remain childless without identifiable causes, according to the routinely used tests – unknown molecular and functional causes of male and female infertility? (Esteves *et al.*, 2015)

# New methods for Exposure Forecasting (ExpoCast)

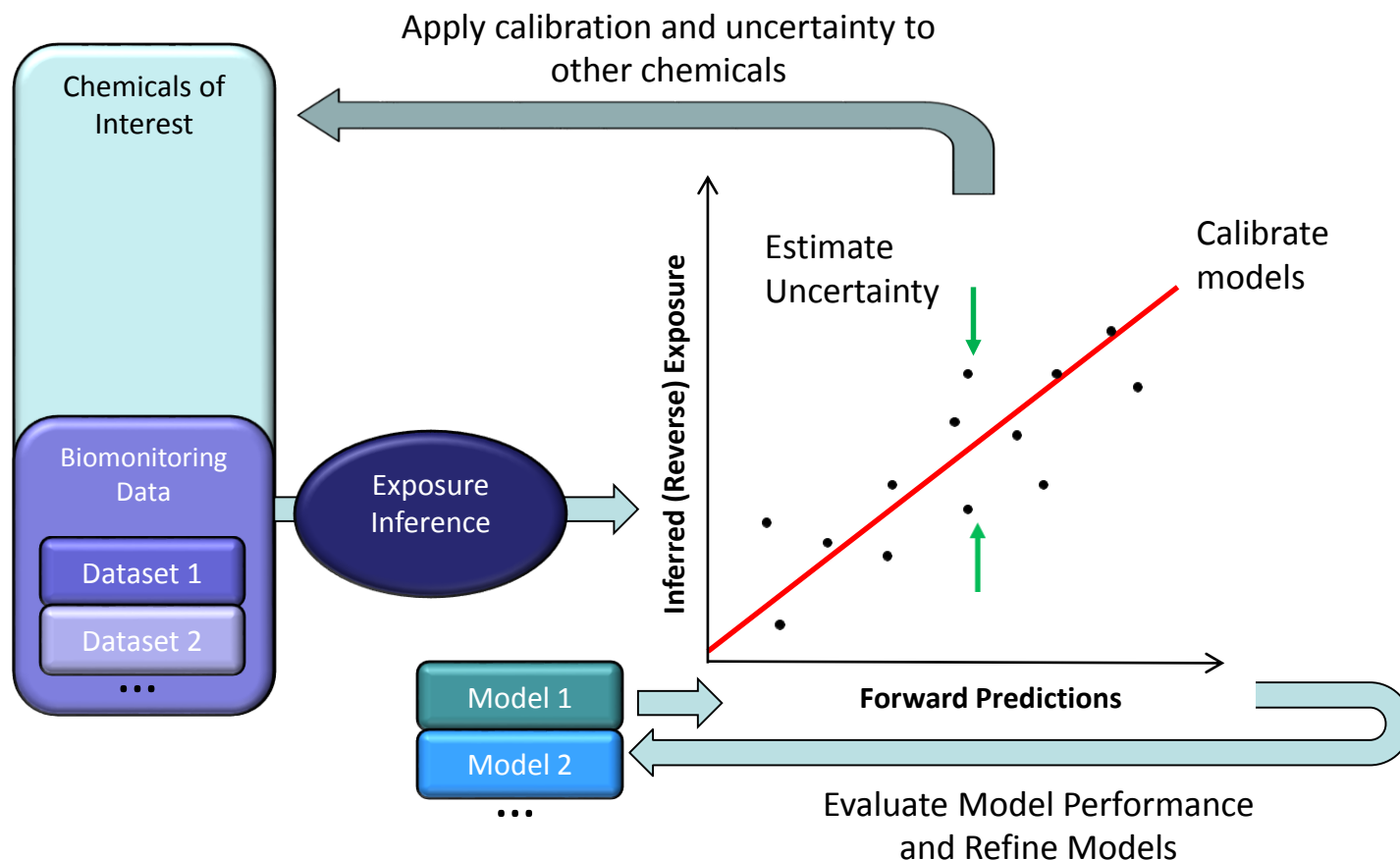
Data and  
Models



Data and  
Models

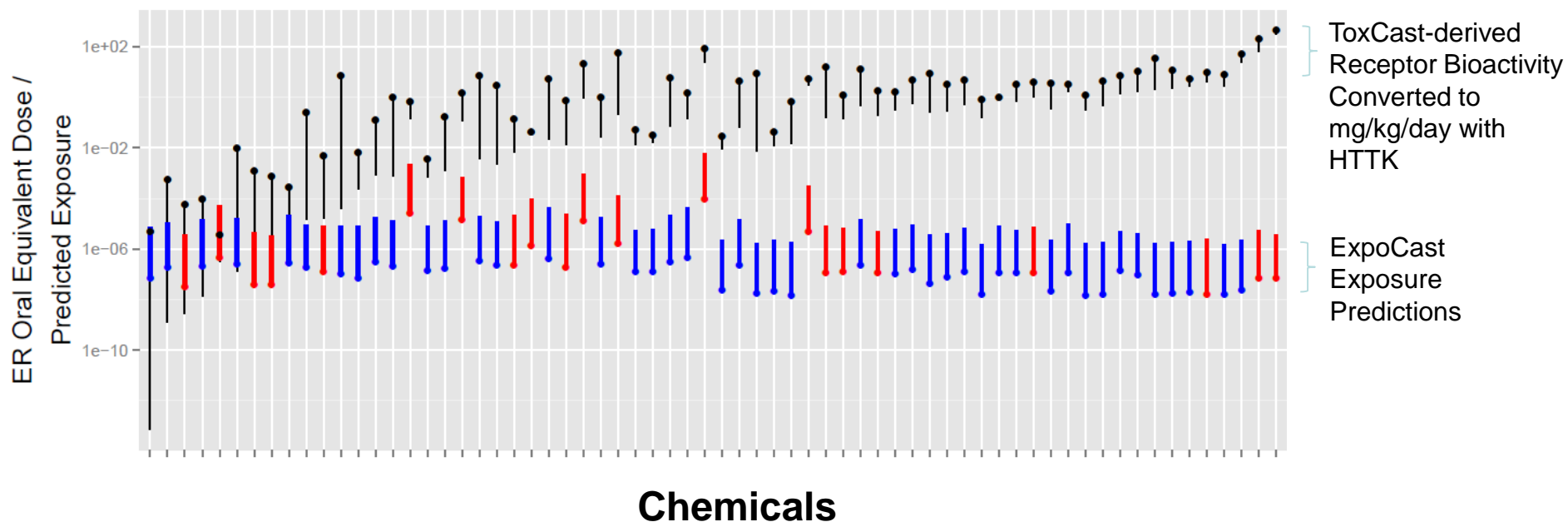


# Systematic Empirical Evaluation of Models (SEEM)



So far we have used exposure rates inferred from NHANES urine for 106 chemicals to evaluate our models (Wambaugh et al., 2014)

# Risk-based Prioritization for additional Testing

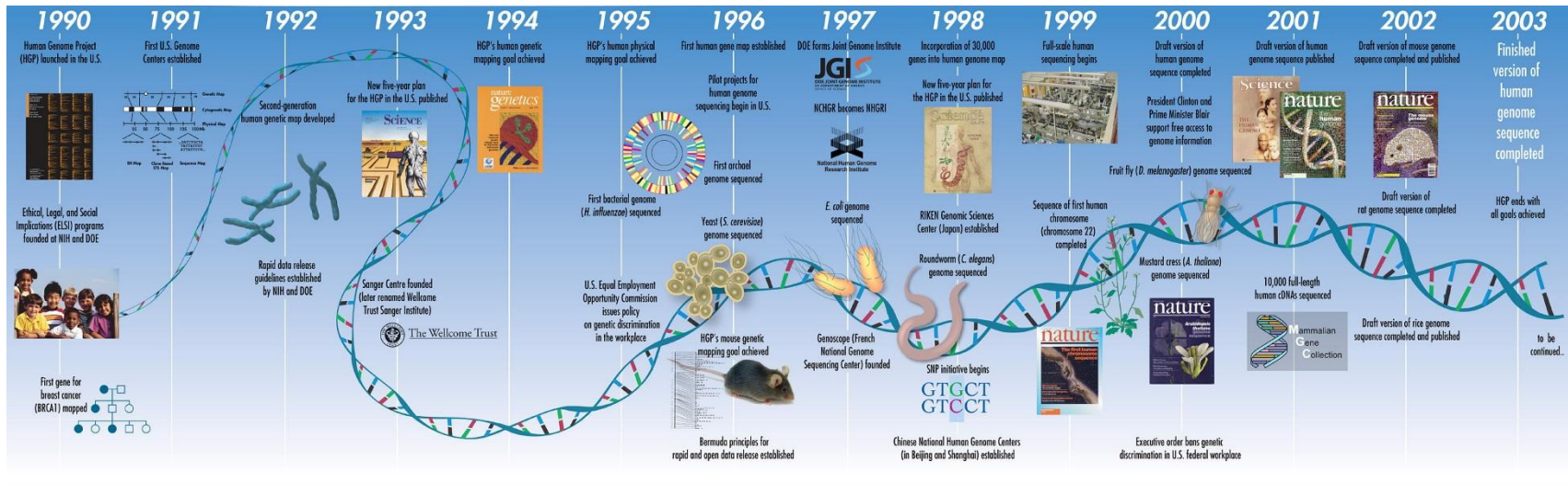


Prioritization as in  
Wetmore *et al.*  
(2012) Bioactivity,  
Dosimetry, and  
Exposure Paper

So far we have used exposure rates inferred from NHANES  
urine for 106 chemicals to evaluate our models



# “Sequencing” an Exposome



- Human genome project took 13 years, but we already have the tools in hand
- Initial progress of ExpoCast project and successful regulatory review hinged on the broad response received to an initial challenge to make “high throughput” predictions for the same 50 chemicals

# ExpoCast Model Challenge



ELSEVIER

Contents lists available at [SciVerse ScienceDirect](#)

Science of the Total Environment

journal homepage: [www.elsevier.com/locate/scitotenv](http://www.elsevier.com/locate/scitotenv)



Comparison of modeling approaches to prioritize chemicals based on estimates of exposure and exposure potential

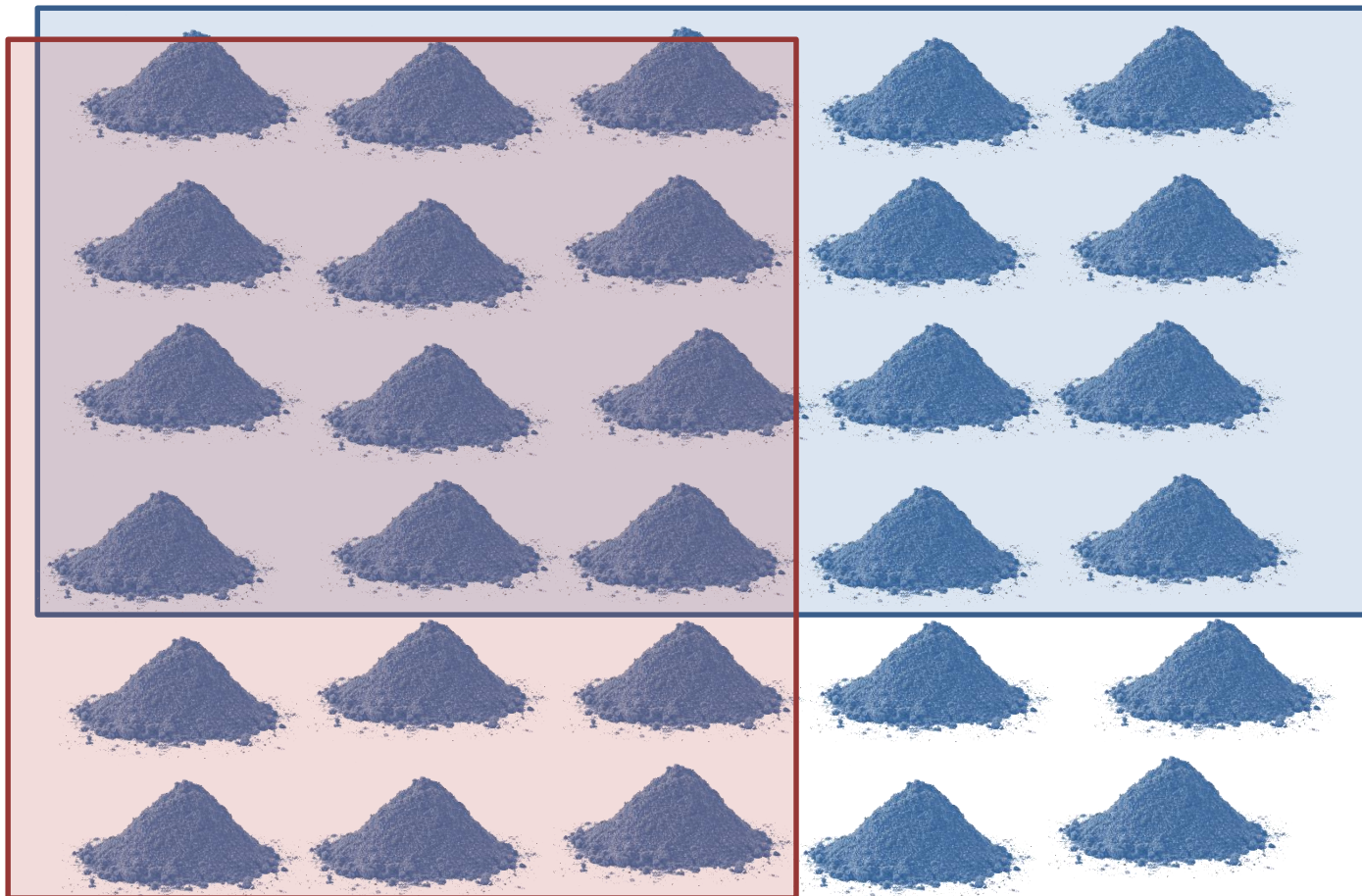


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RAIDAR  
MENTOR  
GEXFRAME  
SHEDS  
E-FAST

# Suspect-Screening Challenge

## The Chemical Universe



### Method 1

EPA has mechanisms to provide reference samples for 1000's of chemicals for cross-lab evaluation

EPA has team devoted to developing and maintaining public databases

### Method 2



# Discussion Questions

- What sample(s) are we going to “sequence”?
- Can we jointly develop libraries/databases of chemical-specific methods and signatures?
  - EPA has team devoted to developing and maintaining public databases
- This is evaluation, not validation!
  - No wrong answers, but a sincere interest in strengths and any blind-spots for various methodologies
- EPA has mechanisms to provide references for 1000's of chemical for cross-lab evaluation
  - 20 mM solutions in DMSO the easiest but others are possible
- Direct opportunity to impact chemical safety assessment
- What else?



## Chemical Safety for Sustainability (CSS) Rapid Exposure and Dosimetry (RED) Project

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