Addressing Population Variability in Risk Assessment: Challenges and Opportunities

SRP Risk e-Learning Webinar
31 May 2018

Weihsueh A. Chiu, PhD
Texas A&M University

Conflict of Interest Statement

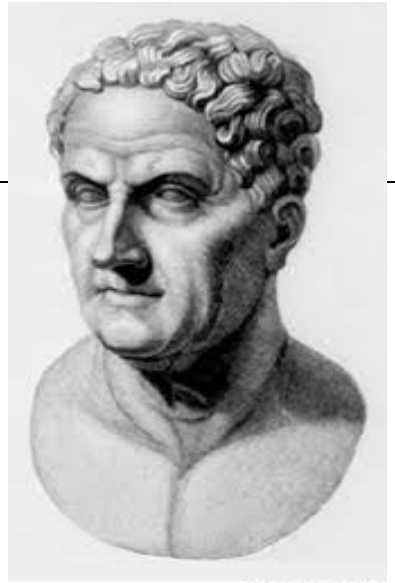
Neither myself nor any of my coauthors, including members of our immediate families, have any financial interest or affiliation with a commercial organization that has a direct or indirect interest in the subject matter of my presentation.

Outline

- Motivation for addressing population variability and susceptibility
- Opportunities using emerging population-based in vivo, in vitro, and in silico approaches
  - Hazard identification and mechanisms of toxicity
  - Dose-Response Assessment
- Challenges in risk characterization

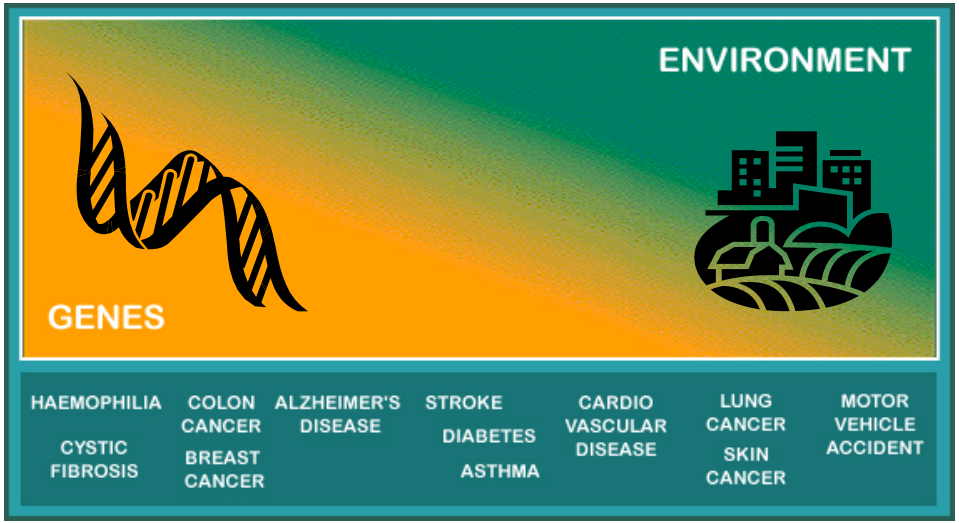
Claudius Galenus (Galen of Pergamum)

129-217 AD



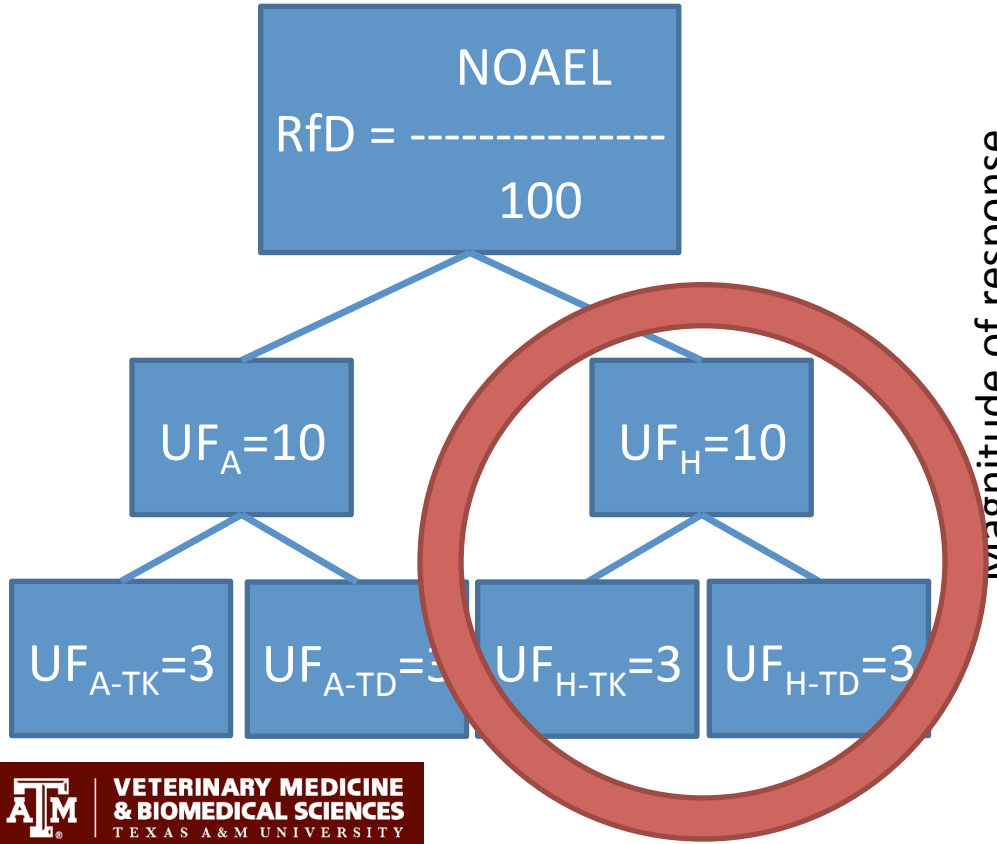
Library of Congress

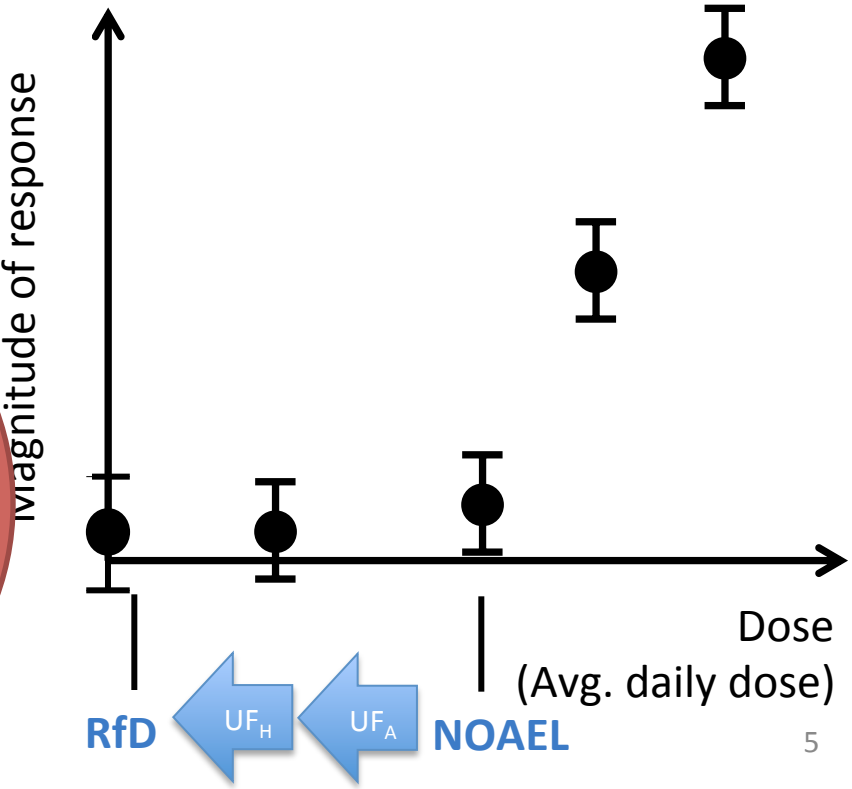
"But remember throughout that no external cause is efficient without a predisposition of the body itself. Otherwise, external causes which affect one would affect all."



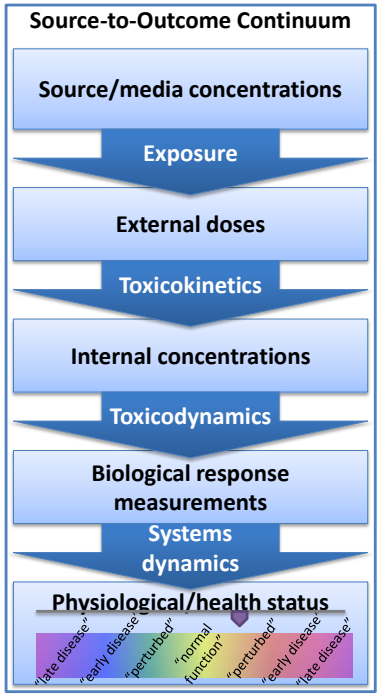
Slide courtesy of D. Threadgill

“Uncertainty” or “Safety” Factors





How well can we characterize variability?



Epidemiologic & clinical studies

- Available for relatively few chemicals (~100).
- **Limited power to examine population variability/susceptibility.**
- **Generalizing from occupational/patient cohorts to the population.**

Animal bioassays

- Available for relatively few chemicals (<1000).
- Uncertain interspecies differences.
- **Homogeneous (genetics, diet, etc.) experimental animals.**

TK models

- Available for relatively few chemicals (~100 PBPK; <1000 total).
- **Few examples analyzing population variability or uncertainty.**

In vitro assays, Toxicity pathways

- Available for more chemicals (~10,000).
- Uncertain relationship to health risk.
- **Genetically homogeneous in vitro systems.**

Adverse Outcome Pathways

- Available for only a few endpoints (~10?).
- Qualitative, not quantitative.
- Most are artificially linear constructs.
- **Variability/susceptibility not included.**

Toxicity values and risk characterization

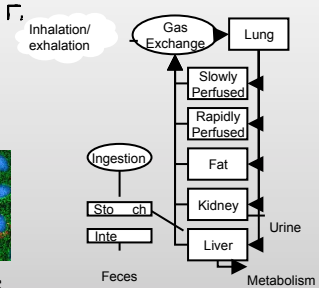
- Available for relatively few chemicals (<1000).
- **Do not adequately address uncertainty, variability, susceptibility (10-fold factor).**
- In most cases, do not explicitly estimate risk.

Population Variability in Susceptibility Remains a Risk Assessment Challenge

Animals, *in vitro*, or *in silico* data → **Humans**

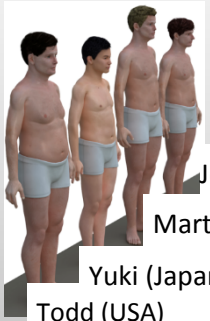
B6C3F1 Hybrid Mice

HeLa cells



PBPK models

Predictions for an Average Male (or Female)



Jérémy (France)
Martijn (Holland)
Yuki (Japan)
Todd (USA)

J. HAMBLIN *The Atlantic* (Oct 10, 2013)

?

Predictions for a Variable Population

Individual → **Population**

See review Chiu & Rusyn (2018) doi:10.1007/s00335-017-9731-6

New Population-Based Approaches and Tools

- Genetically diverse mouse populations
  - Diversity Panel
  - Collaborative Cross, Diversity Outbred
- Populations of human cells
  - Cell lines
  - Inducted pluripotent stem cells
- Computational modeling of populations

All involve studying populations instead of individuals in an experimental and/or computational setting.

Challenges for Hazard Identification

Animals, *in vitro*, or *in silico* data → **Humans**

B6C3F1 Hybrid Mice

?

Predictions for an Average Male (or Female)

J. HAMBLIN *The Atlantic* (Oct 10, 2013)

Individual

- **Human relevance of single strain rodent (positive and negative findings)**
- **No information about human population variability**

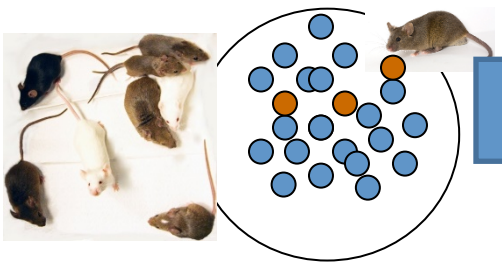
Predictions for a Variable Population

Population

Hazard Identification: Why Use Population-Based Models?

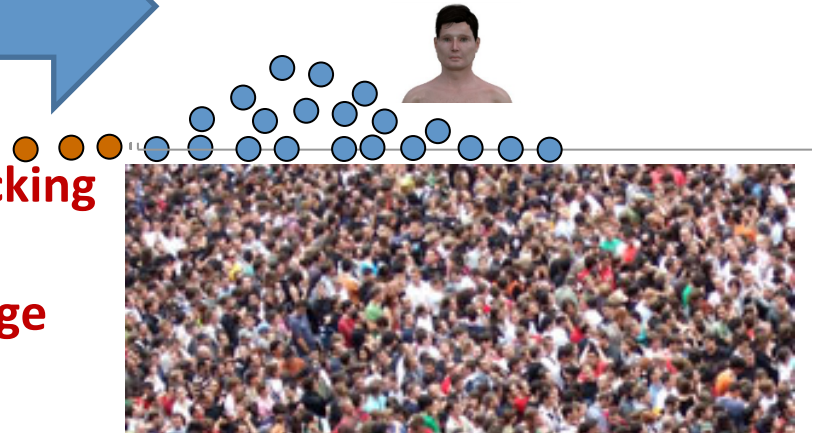
Mouse

- Poor models of humans
- Good models of humans



Extrapolation

Range of Human Responses



- **Reduce chances of being "unlucky" and picking a strain that is a "poor" model of humans**
- **Obtaining information about potential range of population variability**

Mouse Diversity Panel (MDP)

- Comprised of dozens of conventional inbred strains
- Each line is genetically distinct
- Many strains have a high degree of genetic relatedness between them, potentially limiting degree of genetic diversity across strains

Strain Selection

Founder Strains: A/J, C57BL/6J, 129S1/SvImJ, NOD/ShiLtJ, NZO/H1LtJ, CAST/EiJ, PWK/PhJ, WSB/EiJ

F1 Diallel Cross→F1 Crosses

Establish Inbreeding Funnels

Collaborative Cross (CC)

- >100 RI lines available
- Each RI line is genetically distinct
- Within each RI line, all mice are genetically identical

Initiation: Interbred 144 segregating CC lines between G2:F4 and G2:F12 generations

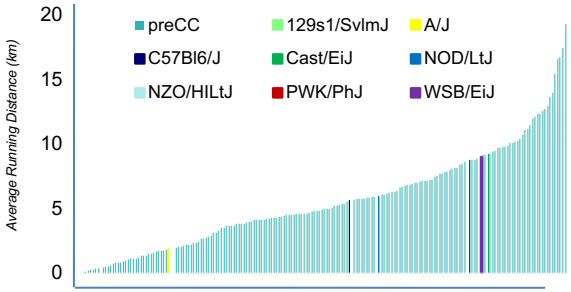
Diversity Outbred (DO)

- Large population of genetically unique individuals
- High level of genomic heterozygosity
- Each individual animal is genetically unique

Harrill & McAllister (2018) https://doi.org/10.1289/EHP1274

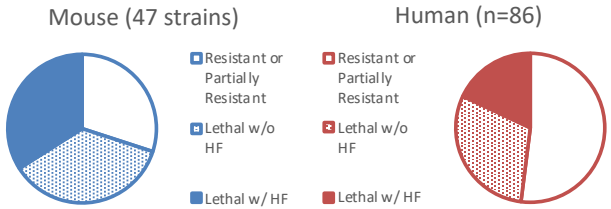
Extreme Transgressive Variation

Average Daily Running Distance



AJP - Endocrinology and Metabolism, 2011

Mouse and Human Response Phenotypes to Ebola Virus Infection



Sources: Rasmussen et al. 2014 (mouse), McElroy et al. 2014 (human)

VETERINARY MEDICINE & BIOMEDICAL SCIENCES
TEXAS A&M UNIVERSITY

Hazard Identification:

Proof of Principle Using Population-Based Mouse Models

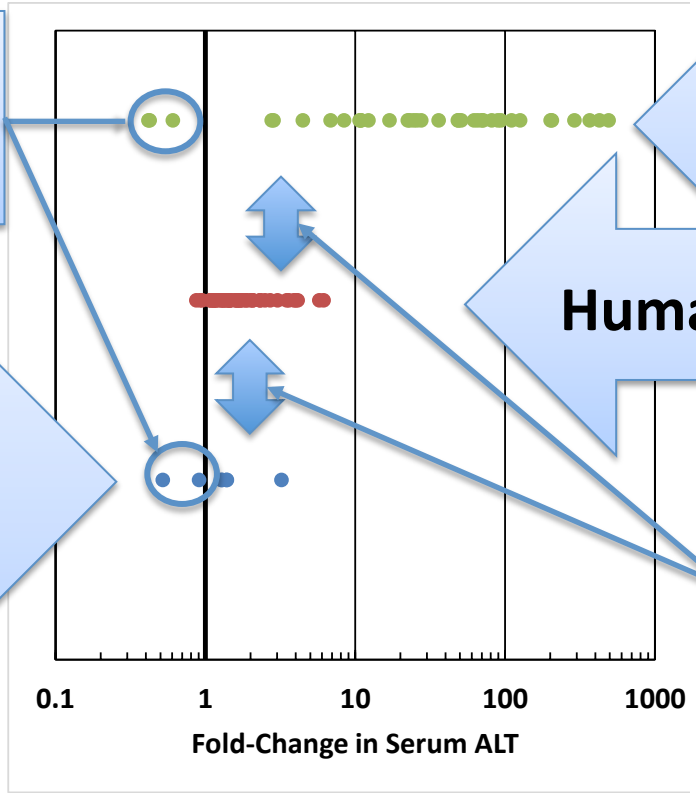
Might miss hazard if only testing one of these strains

37 different inbred mouse strains

Humans

6 different inbred mouse strains (lower dose)

Distributions of responses overlap



Alison H. Harrill et al. Genome Res. 2009;19:1507-1515

Challenges for Characterizing Mechanisms of Toxicity and Susceptibility

Animals, *in vitro*, or *in silico* data → **Humans**

Individual → **Population**

B6C3F1 Hybrid Mice

?

Predictions for an Average Male (or Female)

J. HAMBLIN *The Atlantic* (Oct 10, 2013)

?

Predictions for a Variable Population

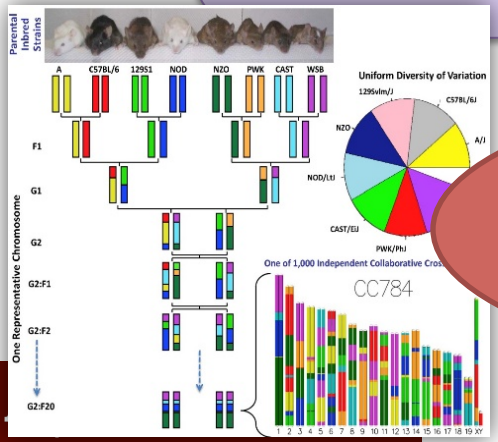
- **Knockout studies probe one gene at a time**
- **Difficult to distinguish inter- and intra-species susceptibility differences**

Population-Based Models to Investigate Mechanisms of Toxicity and Susceptibility

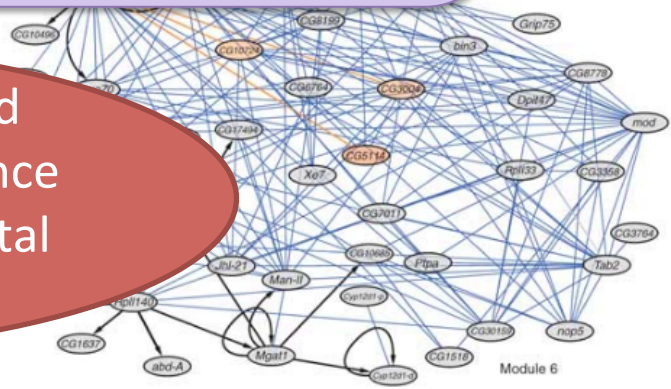
Experiments with Genetically Diverse Populations

Environ. Factors → Toxicity

Genes

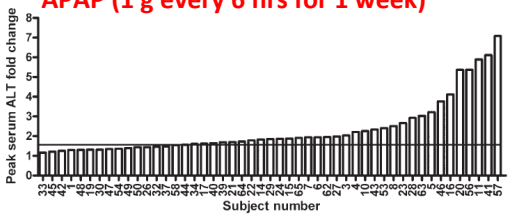


Genes/pathways associated with susceptibility or resistance to toxicity from environmental factors

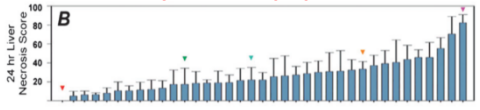


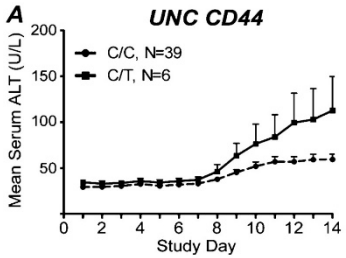
Mechanisms of Toxicity and Susceptibility:
Proof of Principle Using Population-Based Mouse Models

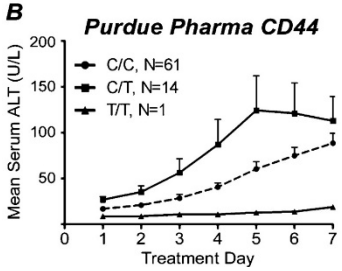
Liver toxicity: Humans
APAP (1 g every 6 hrs for 1 week)



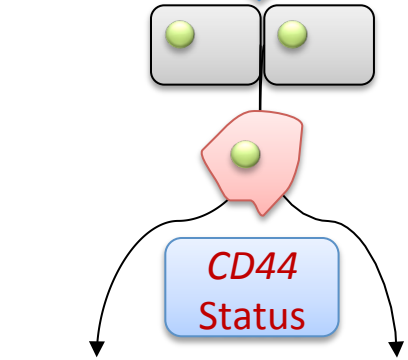
Liver toxicity: Mouse population



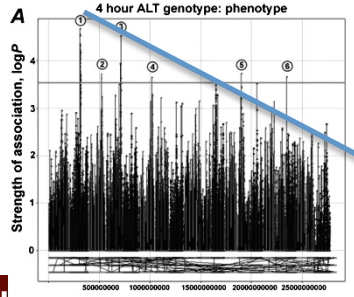




Insights into mechanism of toxicity



GWAS in mice



Confirmed in human cohorts

CD44 Candidate Susceptibility Gene

Alison H. Harrill et al. Genome Res. 2009;19:1507-1515

Challenges for Dose-Response Assessment

Animals, *in vitro*, or *in silico* data → **Humans**

Individual ↓ **Population**

B6C3F1 Hybrid Mice

÷10

Predictions for an Average Male (or Female)

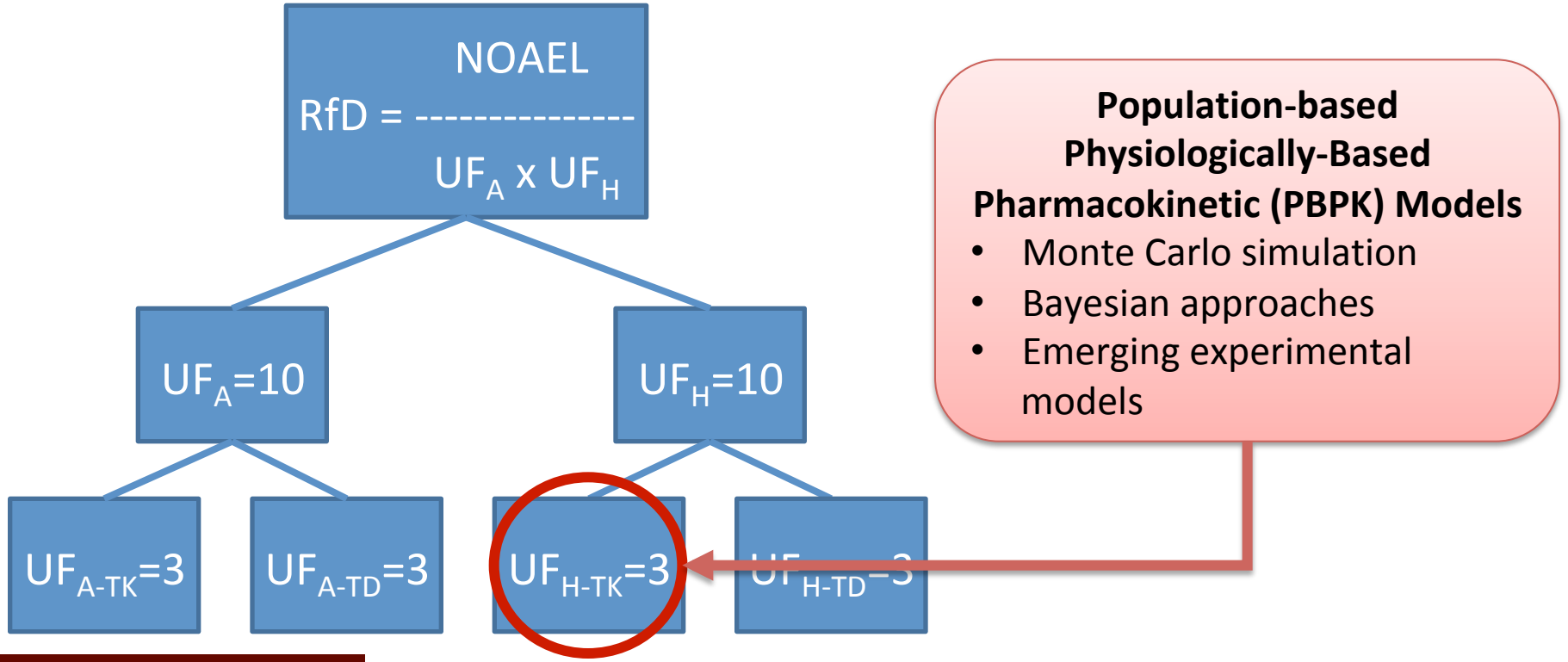
J. HAMBLIN *The Atlantic* (Oct 10, 2013)

÷10

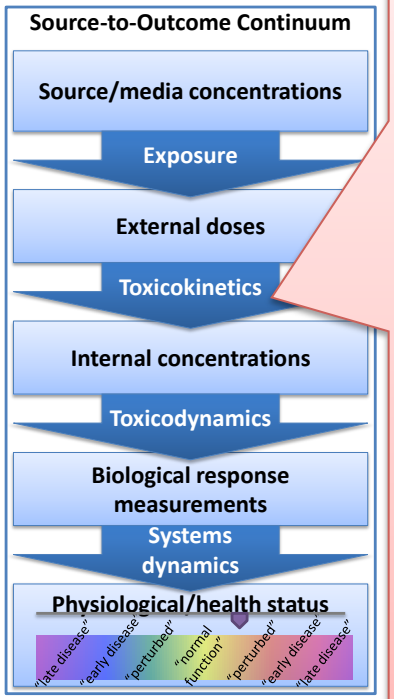
Predictions for a Variable Population

- **Single strain dose-response assumed to be representative of population**
- **10-fold inter- and intra-species factors assumed to be adequate (conservative?)**

Population Variability in Toxicokinetics

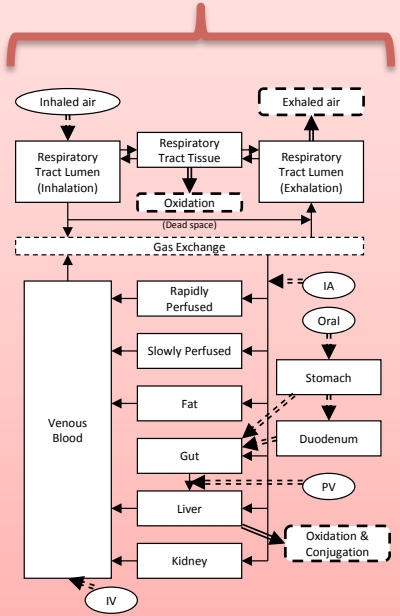


Human population variability of trichloroethylene pharmacokinetics



Bayesian Population PBPK Model

parameters vary by individual [~50 individuals total]

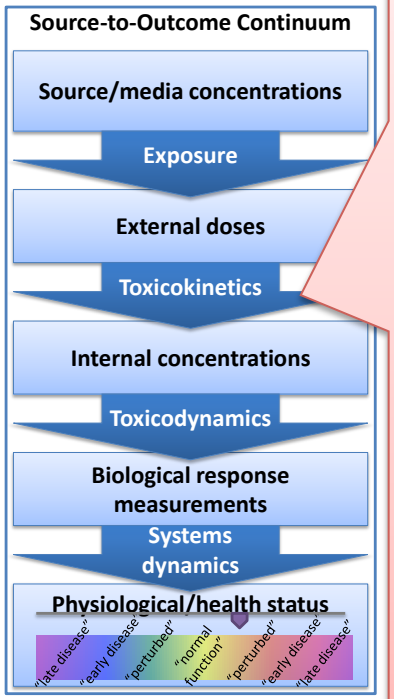


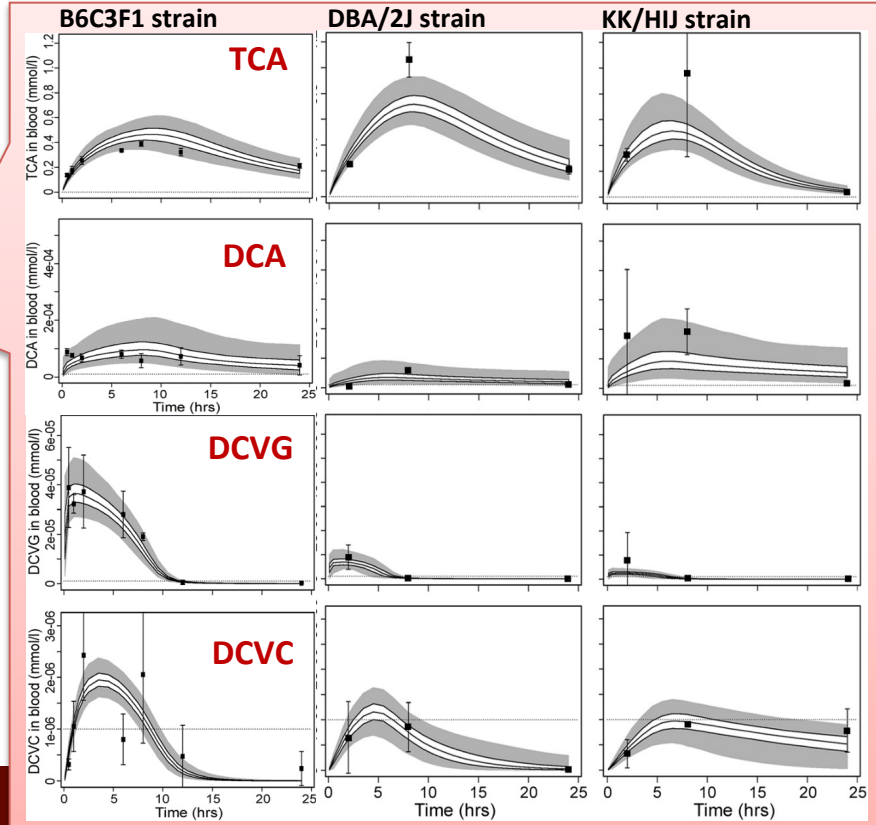
	Ratio of 95th percentile/ 50th percentile individual
	Human inter-individual variability
TCE oxidized by P450	**1.11** (1.05, 1.22)
Total TCA produced	**2.09** (1.81, 2.51)
TCE conj. with GSH	**6.61** (3.95, 11.17)

Depending on the toxic moiety (which may be different for different effects), humans could have very low or very high variability.

Source: Chiu et al., 2009

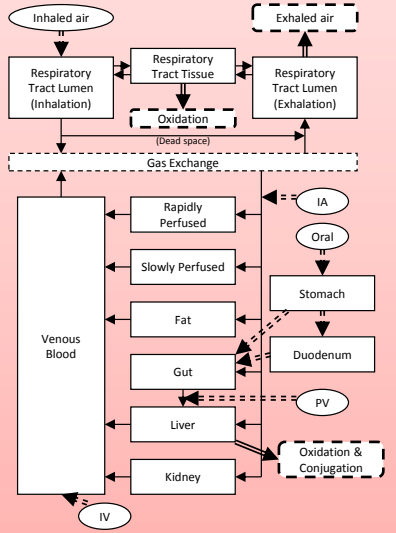
Using a population of mouse strains to address TCE toxicokinetic variability





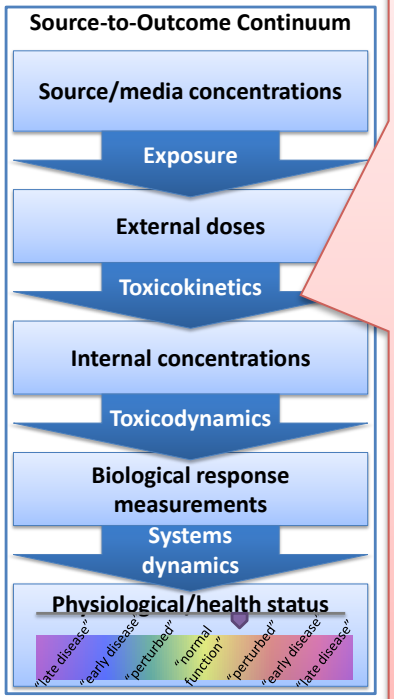
Bayesian Population PBPK Model

parameters vary by strain [17 strains total]



Source: Chiu et al., 2014

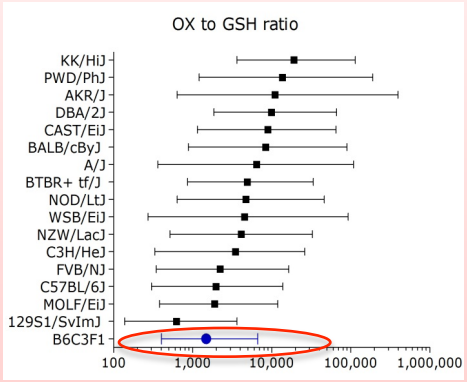
Using a population of mouse strains to address TCE toxicokinetic variability

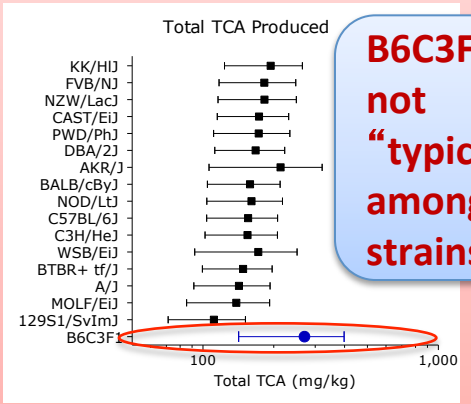


	Ratio of 95th percentile/50th percentile individual or strain*	
	Human inter-individual variability	**Mouse** inter-strain variability
TCE oxidized by P450	**1.11** (1.05, 1.22)	**1.05** (1.01, 1.27)
Total TCA produced	**2.09** (1.81, 2.51)	**1.77** (1.36, 2.99)
TCE conj. with GSH	**6.61** (3.95, 11.17)	**7.12** (3.43, 20.7)

*Median and 95% CI

Estimates of mouse population variability from multi-strain experiments are consistent with estimates of human population variability from controlled human exposure studies.

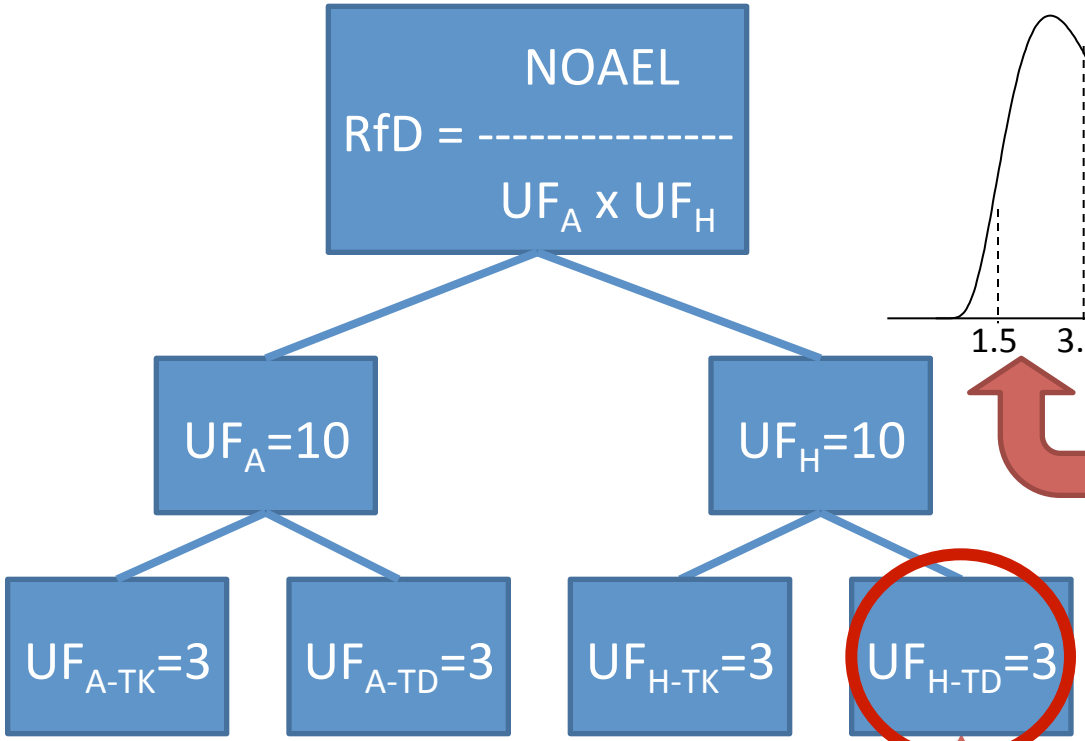


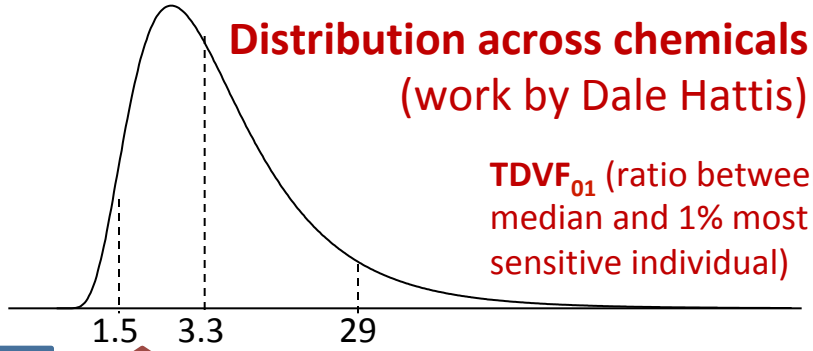


B6C3F1 is not "typical" among strains

Source: Chiu et al., 2014

Population Variability in Toxicodynamics





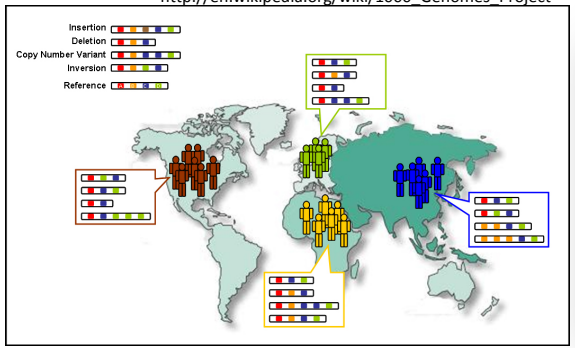
Distribution across chemicals
(work by Dale Hattis)

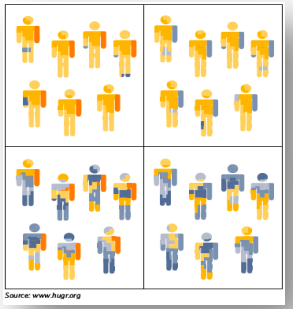
$TDVF_{01}$ (ratio between median and 1% most sensitive individual)

- Some idea as to the **range** of possible toxicodynamic variability, based on existing data mostly from drugs.
- **Virtually no other examples** for chemical-specific estimates of toxicodynamic variability.

Genetically diverse human population

http://en.wikipedia.org/wiki/1000_Genomes_Project



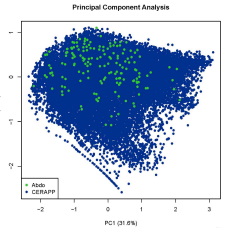


Genetically defined sample of population

High throughput *in vitro* model system

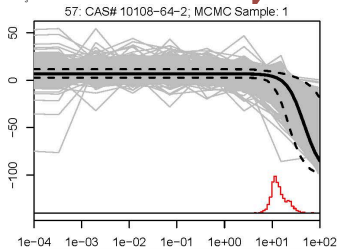
~1000 individuals cytotoxicity screening

Structurally diverse chemical population

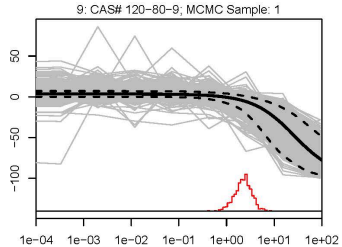


~170 compounds

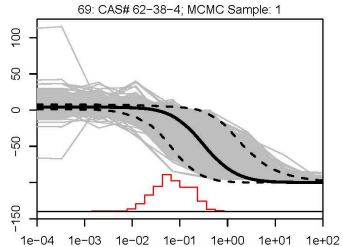
Chemical-Specific TD Variability Factor ($TDVF_{01}$):
The factor estimated to protect up to the most sensitive 1% for human toxicodynamic variability for a chemical

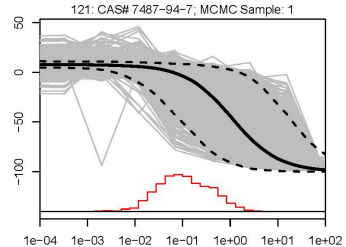


Cadmium Chloride ~2-fold



Catechol ~3-fold



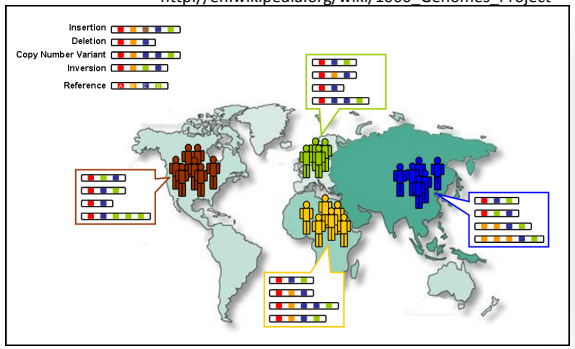


Organic and inorganic mercury compounds >8-fold

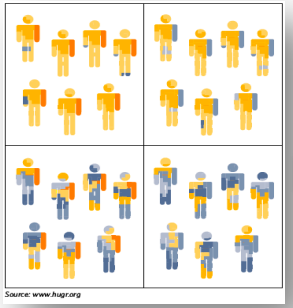
Abdo et al., 2015
Chiu et al., 2017
https://doi.org/10.14573/altex.1608251

Genetically diverse human population

http://en.wikipedia.org/wiki/1000_Genomes_Project



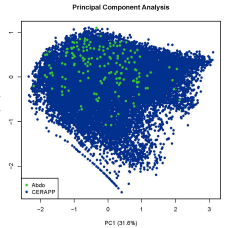
Genetically defined sample of population



High throughput *in vitro* model system

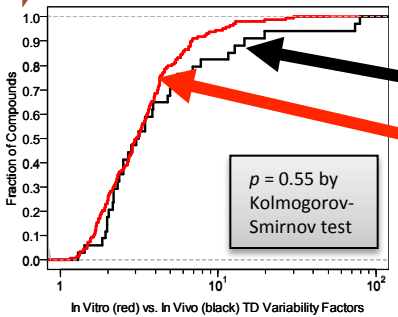
~1000 individuals cytotoxicity screening

Structurally diverse chemical population



~170 compounds

Chemical-Specific TD Variability Factor ($TDVF_{01}$):
The factor estimated to protect up to the most sensitive 1% for human toxicodynamic variability for a chemical



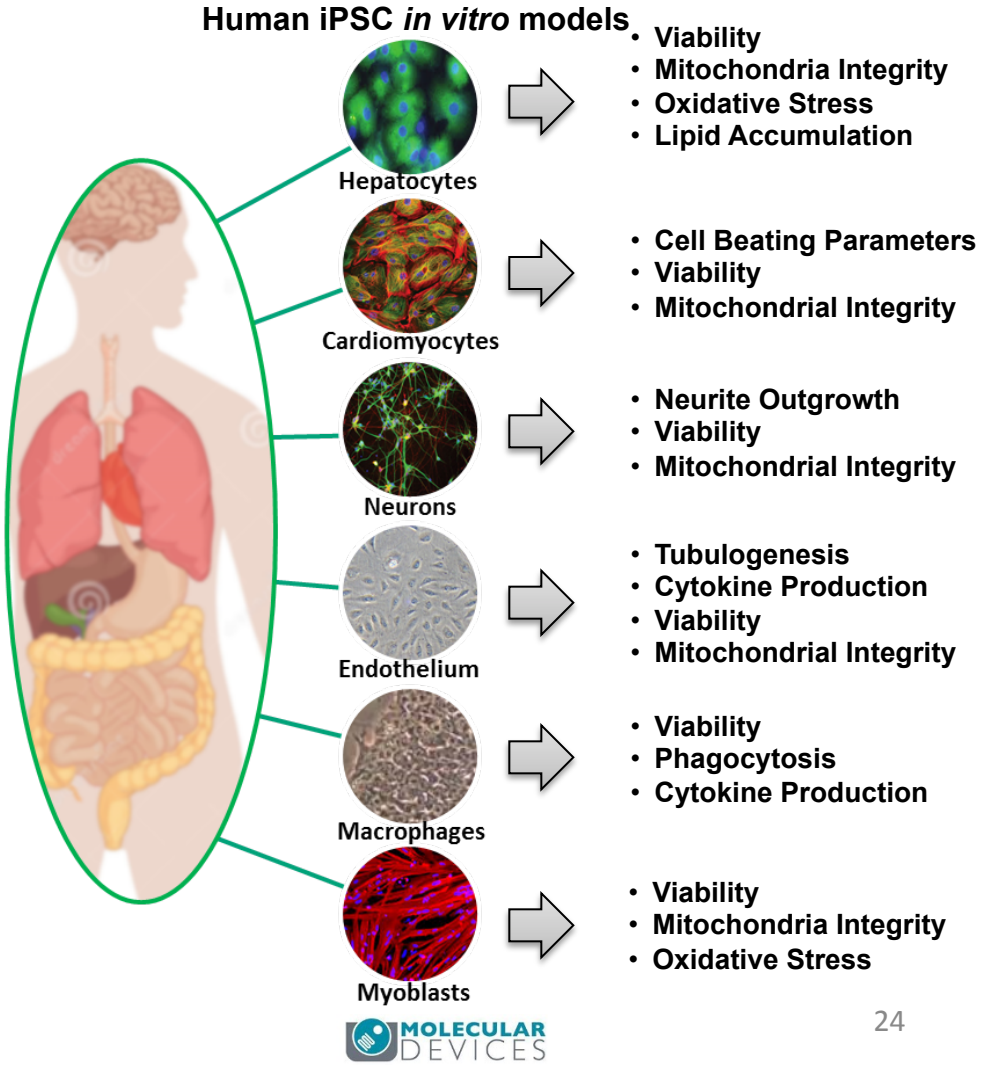
Consistent estimates of toxicodynamic variability in vitro and in vivo.

	Human In vitro	Human in vivo
TD variability factor*	3.04 (1.33, 12.6)	3.10 (1.40, 74.3)

Abdo et al., 2015
Chiu et al., 2017
https://doi.org/10.14573/altex.1608251

Next Step: Other Cell Types and Phenotypes

- Induced pluripotent stem cells (iPSC)
  - Multiple cell types, eventually from multiple individuals
  - Cell-type-specific measures of function/ toxicity

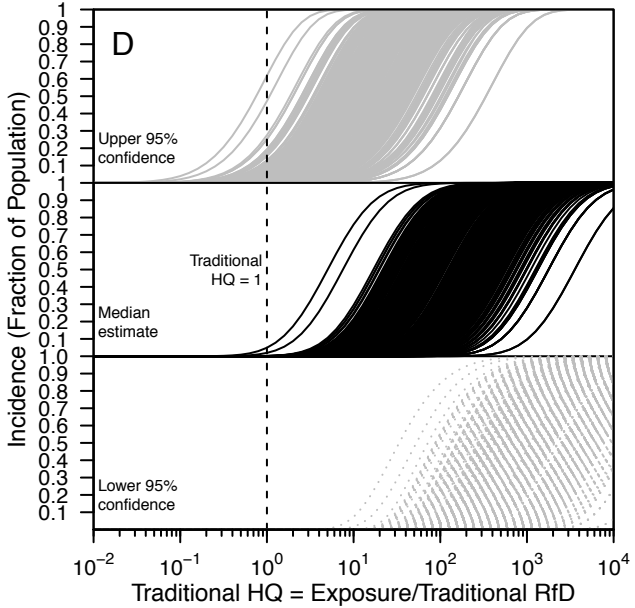


Challenges to Risk Characterization

Acknowledging that "safe" exposures are **not risk-free**.

- Uncertainty – can never achieve 100% certainty
- Variability – can never ensure 100% of population is protected

What is the risk at the RfD?



- Applied WHO/IPCS probabilistic framework to >1500 endpoints for >600 chemicals
- Exposure at the RfD implies upper 95% confidence bound population incidence of several percent.
- Noted that there is wide range of severity of the associated effects, from clinical chemistry to mortality (!).

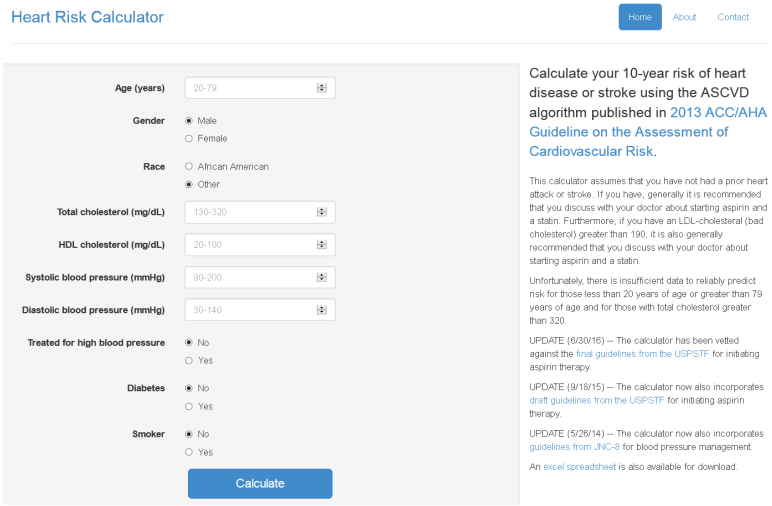
Confirmation that the RfD is not 100% risk-free!

Chiu et al. 2018 (EHP, accepted)

Challenges to Risk Characterization

Emerging data and methods have the potential to identify **who** may remain at risk.

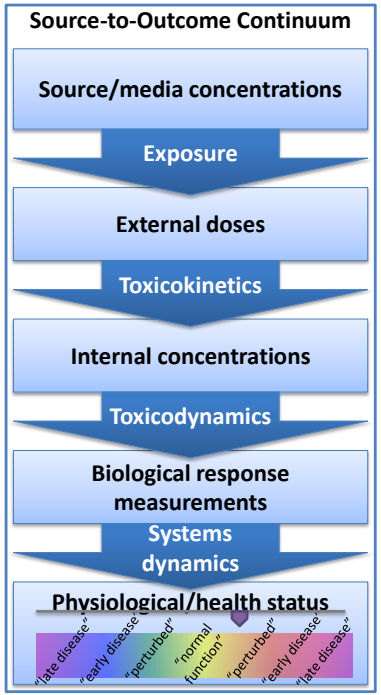
- Risk-based policies presume individuals are unidentifiable.
- Precedent in cardiovascular health for calculating individual risk profiles.
- What if toxicity testing were done on each individuals' cells?



23andMe

And Beyond…

Summary and Conclusions: Addressing Population Variability and Susceptibility



- **Hazard identification: Multiple opportunities for improvement**
  - Population-based experimental models are more likely to overlap with human population responses
  - Genetic-based analyses of experimental populations have potential to identify mechanisms of toxicity and susceptibility
- **Dose-Response Assessment: Multiple opportunities for improvement**
  - Population PBPK modeling of toxicokinetic variability facilitated by new population-based in vivo and in vitro data
  - Emerging genetically diverse cell-based systems, including iPSC-based technologies, for assessing toxicodynamic variability
  - Potential for directly estimating population dose-response experimentally in toxicity testing using genetically diverse populations
  - Probabilistic dose-response modeling necessary to integrate population-based data for characterizing risk
- **Risk Characterization: Challenges to communication and policy**