Advancing Risk Assessment with Population-Based Experimental Resources

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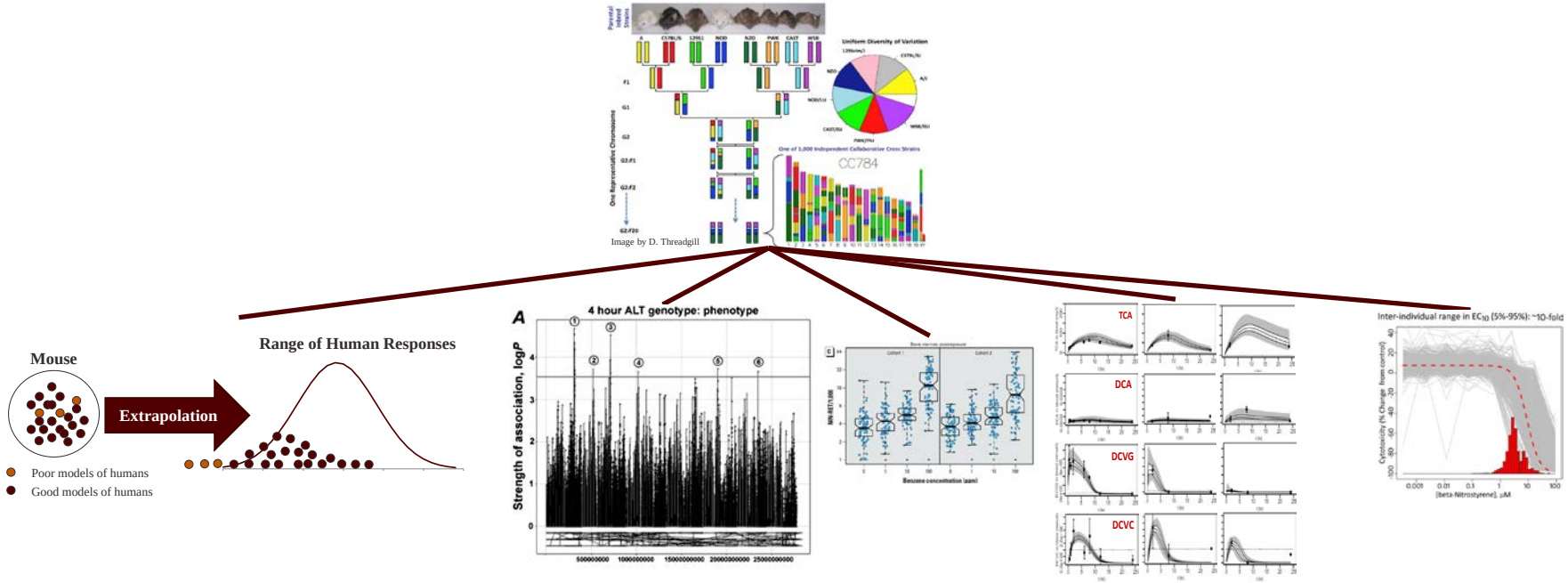

Hazard Identification

Mechanisms of Toxicity and Susceptiblity

Characterizing Human Variability in Dose-Response

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Colleagues

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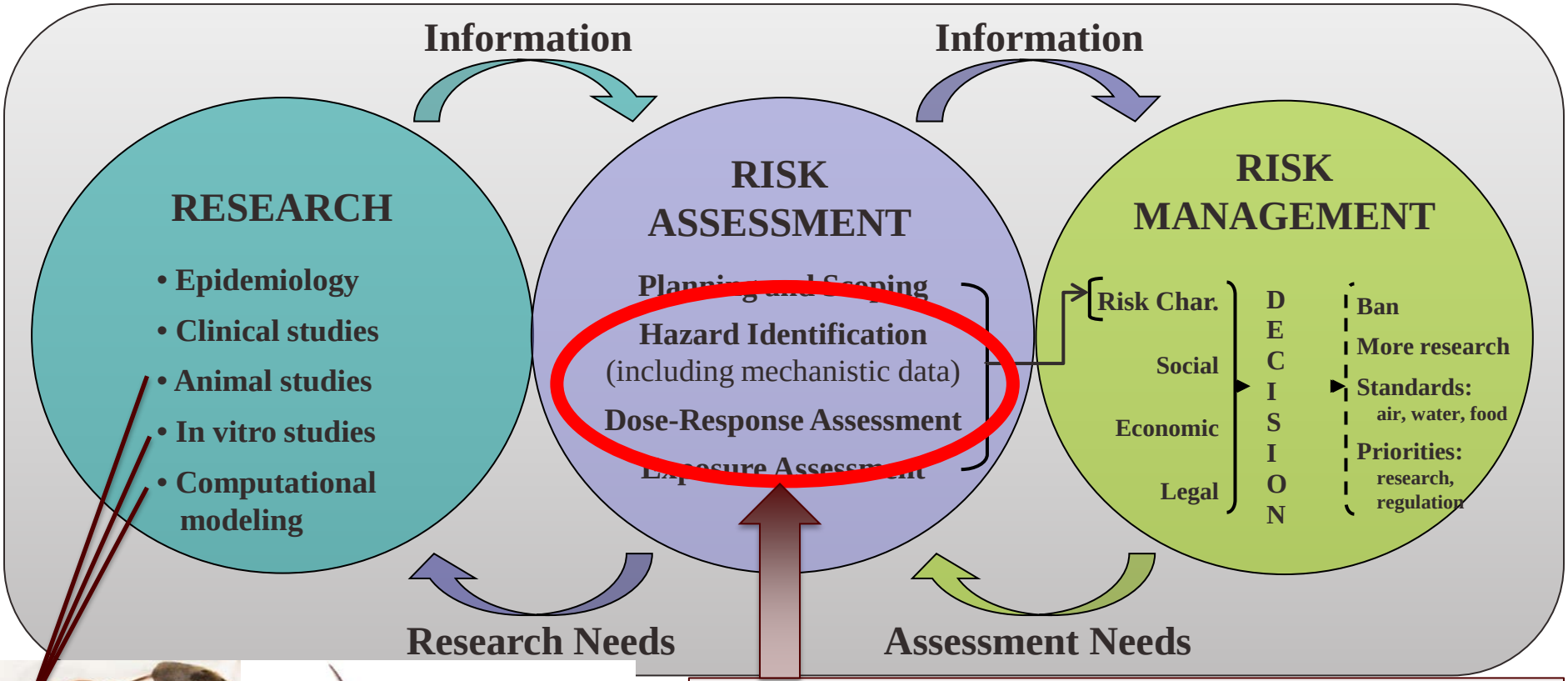
Outline

- Risk Assessment Context
- Improving Hazard Identification
- Identifying Mechanisms of Toxicity and Susceptibility
- Improving Dose-Response Assessment
- Opportunities and Challenges Ahead

Risk Assessment Context



New experimental systems <u>can</u> incorporate genetic diversity:

while still controlling most variables in terms of age, treatment, etc., one can be using populations with

defined genetic heterogeneity

Hazard Identification

"the process of determining whether exposure to an agent can cause an increase in the incidence of a health condition … [including] characterizing the nature and strength of the evidence of causation"

NRC (1983)

Animal data almost exclusively from inbred rodent strains

1 = established
2A = probably
2B = possibly
3 = unclassifiable
4 = probably not

		Animals			
		Sufficient	Limited	Inadequate	Suggesting lack
Humans	Sufficient	1	1	1	1
	Limited	2A (1)	2B (2A)	2B (2A)	2B (2A)
	Inadequate	2B (1, 2A, 3)	3 (2B)	3	3 (4)
	Suggesting lack	3 (1)	3	3	4

International Agency for Research on Cancer Monograph Program

Hazard Identification:
Challenges to Using Single Rodent Strains

B6C3F1

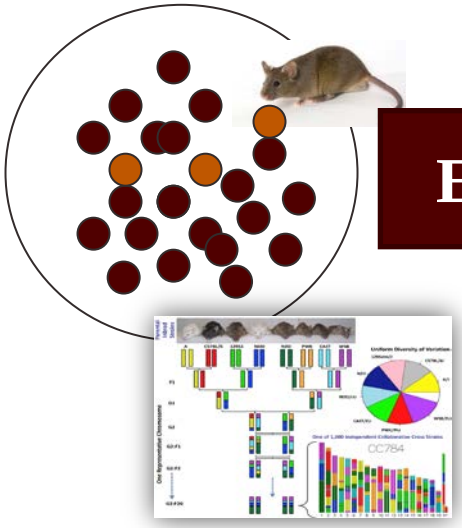
"Todd"

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

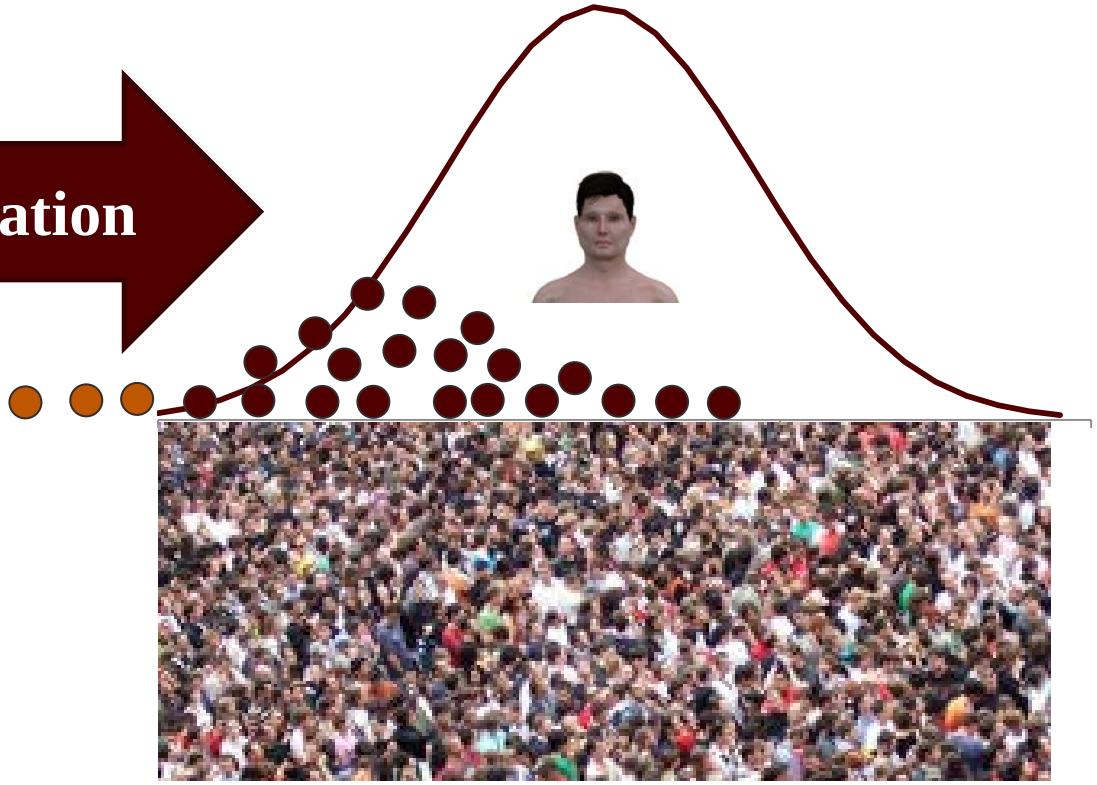
Hazard Identification:
Adding Population Variability

Range of Human Responses

Mouse



Extrapolation

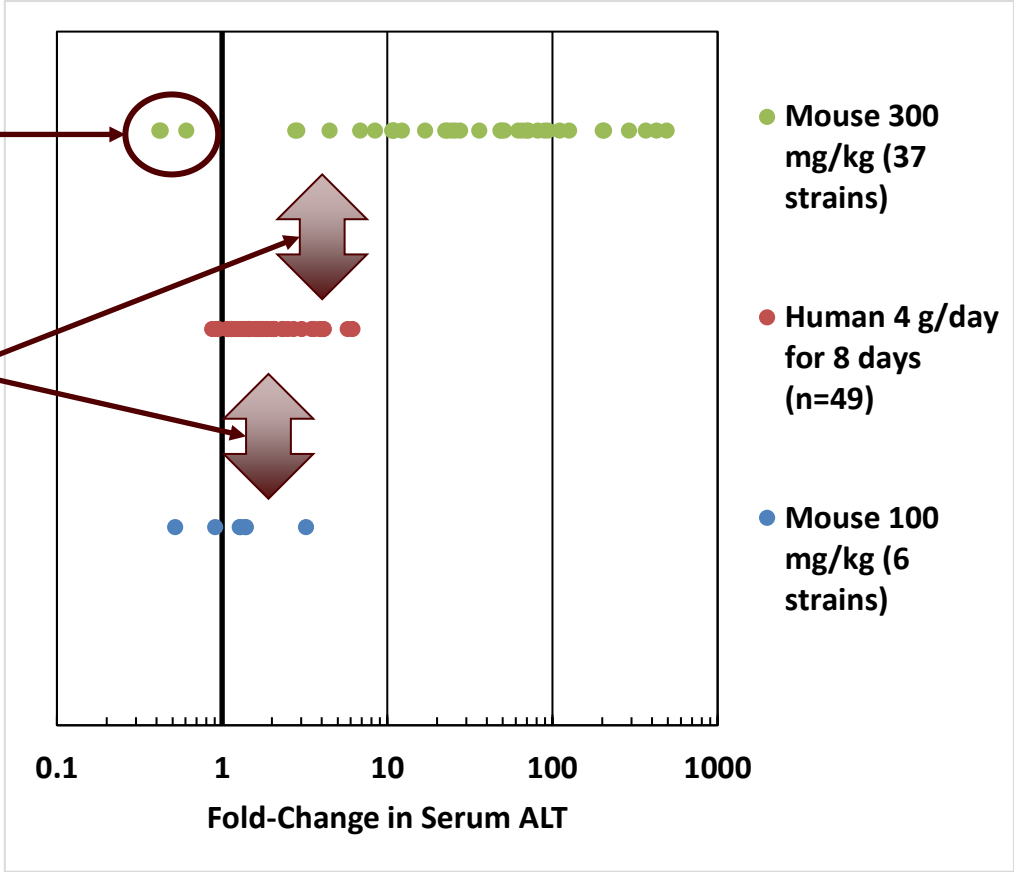


- Poor models of humans
- Good models of humans

Hazard Identification:
Proof of Principle

Might miss hazard if only testing one of these strains

Distributions of responses overlap



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

Hazard Identification:
Improvements Using Population-Based Rodent Resources

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?

"Todd"

Hazard Identification

Population-Based Rodent

Opportunities and Challenges to Using Population-Based Models

Hazard Identification	Mechanisms of Toxicity and Susceptibility	Dose-Response Assessment
Opportunities: • Higher probability of overlapping with range of human responses • Directly informing population variability		
Challenges: • Optimizing data analysis/statistical modeling approaches • Understanding when, on a fixed budget, a population-based model has more power to identify a hazard		

Mechanisms of Toxicity and Susceptibility

Uses of mechanistic (mode of action) data:

- Assess the **relevance** of laboratory animal results to human environmental exposures
- Provide insight into whether the dose-response curve is likely to be **linear or nonlinear** at low doses
- Identify **susceptible populations** and **lifestages**
- Quantify the **relative sensitivity of laboratory animals and human populations**

–U.S. EPA (2005) Guidelines for Carcinogen Assessment

If human data are less than "sufficient":

- Can "upgrade" based on strong evidence that mechanism operates in humans
- Can "downgrade" based on strong evidence the mechanism does not operate in humans

- **Animal data almost exclusively from inbred rodent strains**
- **Human data often difficult to obtain**

1 = established
2A = probably
2B = possibly
3 = unclassifiable
4 = probably not

		Animals			
		Sufficient	Limited	Inadequate	Suggesting lack
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International Agency for Research on Cancer Monograph Program

Mechanisms of Toxicity and Susceptibility: Challenges to Using Single Rodent Strains

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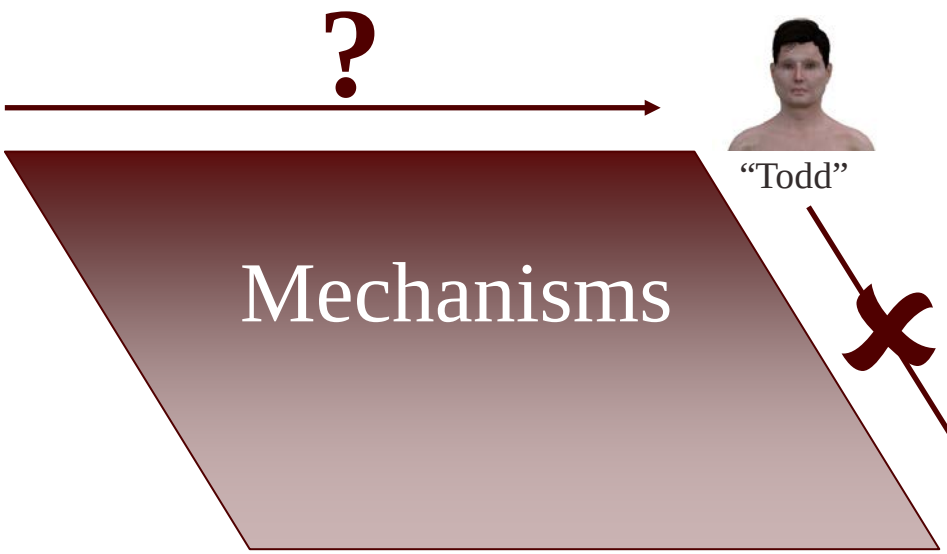

"Todd"

- Human relevance of single strain rodent (positive and negative findings)
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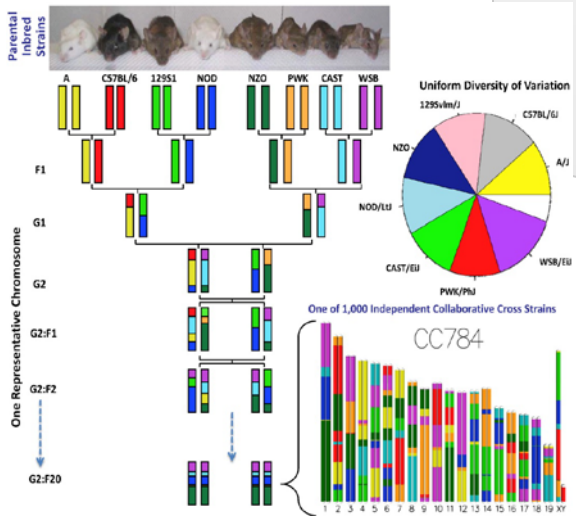
Mechanisms of Toxicity and Susceptibility:
Adding Population Variability to Identify Pathways

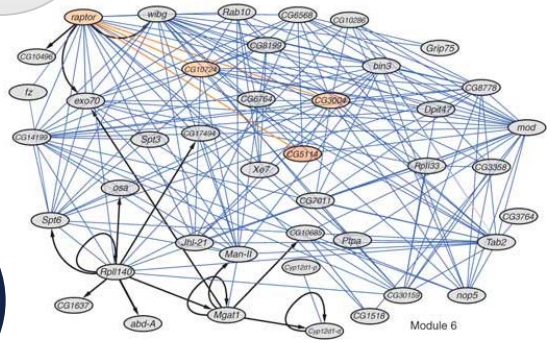
Experiments with Genetically Diverse Populations

Environ. Factors → Toxicity

Genes → Toxicity



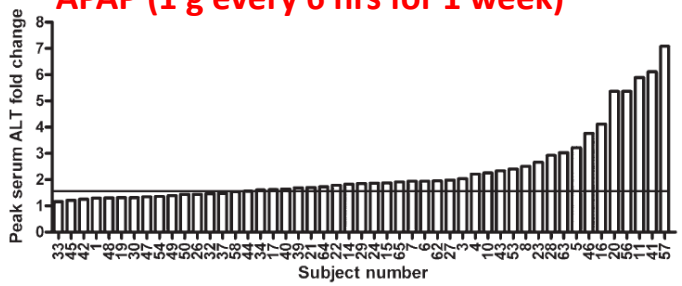
Genes/pathways associated with susceptibility or resistance to toxicity from environ. factors



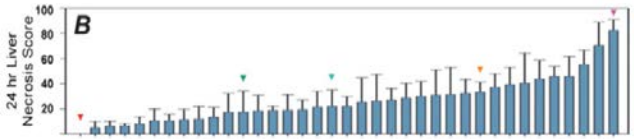
Mechanisms of Toxicity and Susceptibility:
Proof of Principle

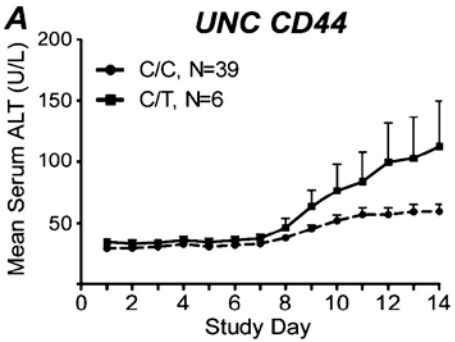
Liver toxicity: Humans

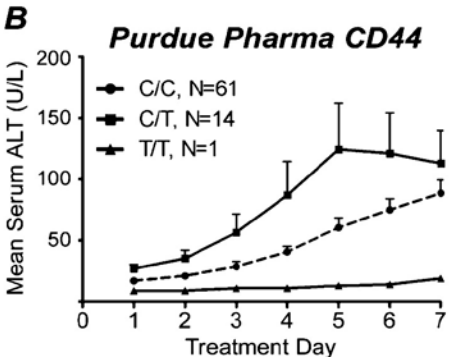
APAP (1 g every 6 hrs for 1 week)



Liver toxicity: Mouse population

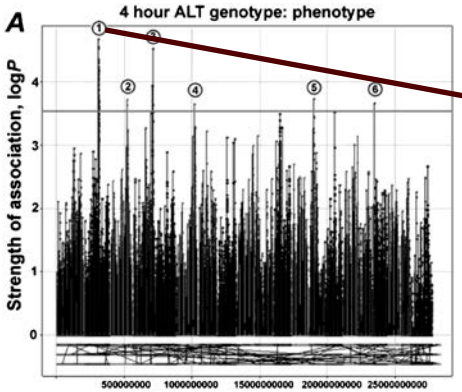






Confirmed in human cohorts

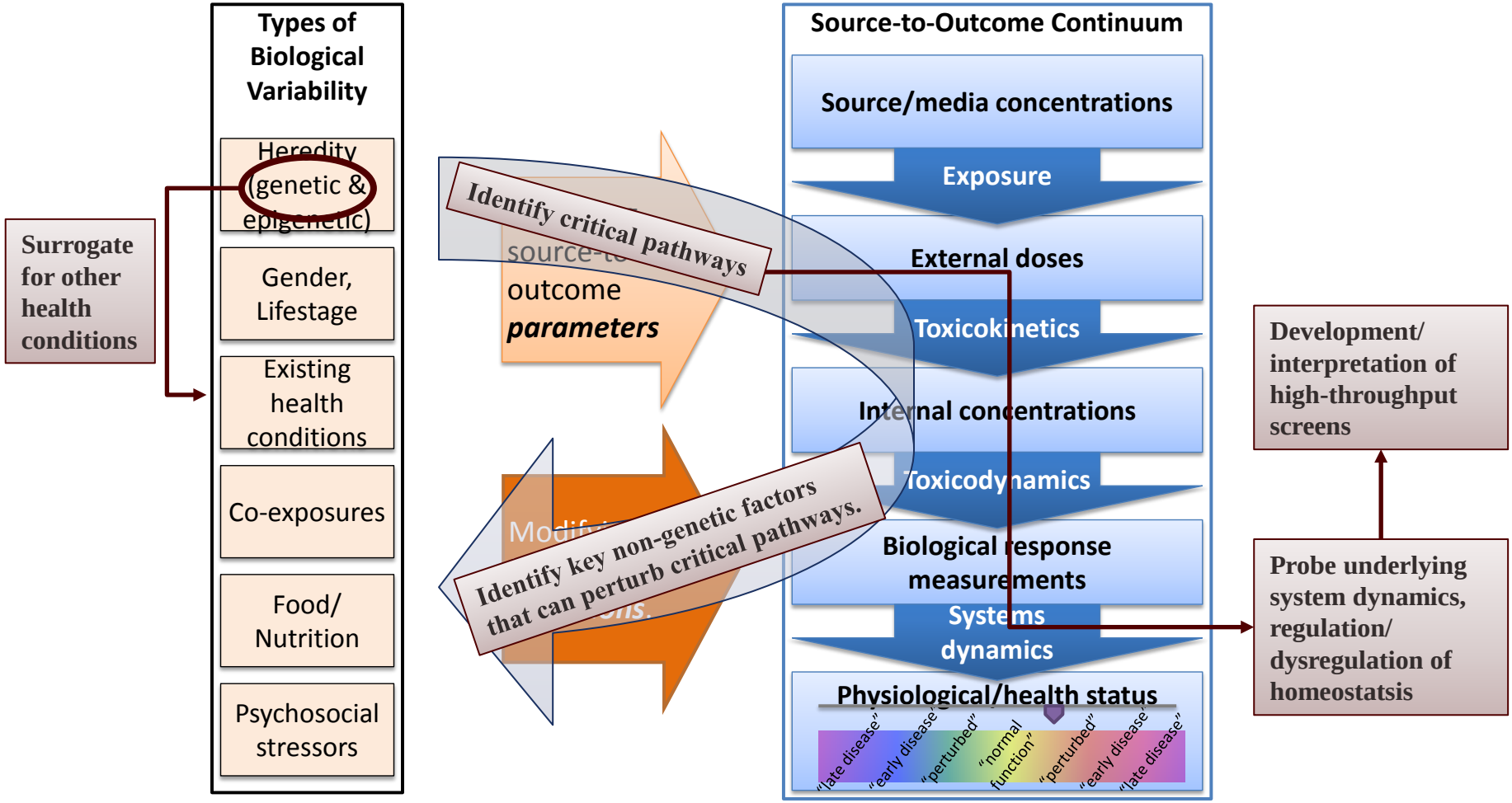
GWAS in mice



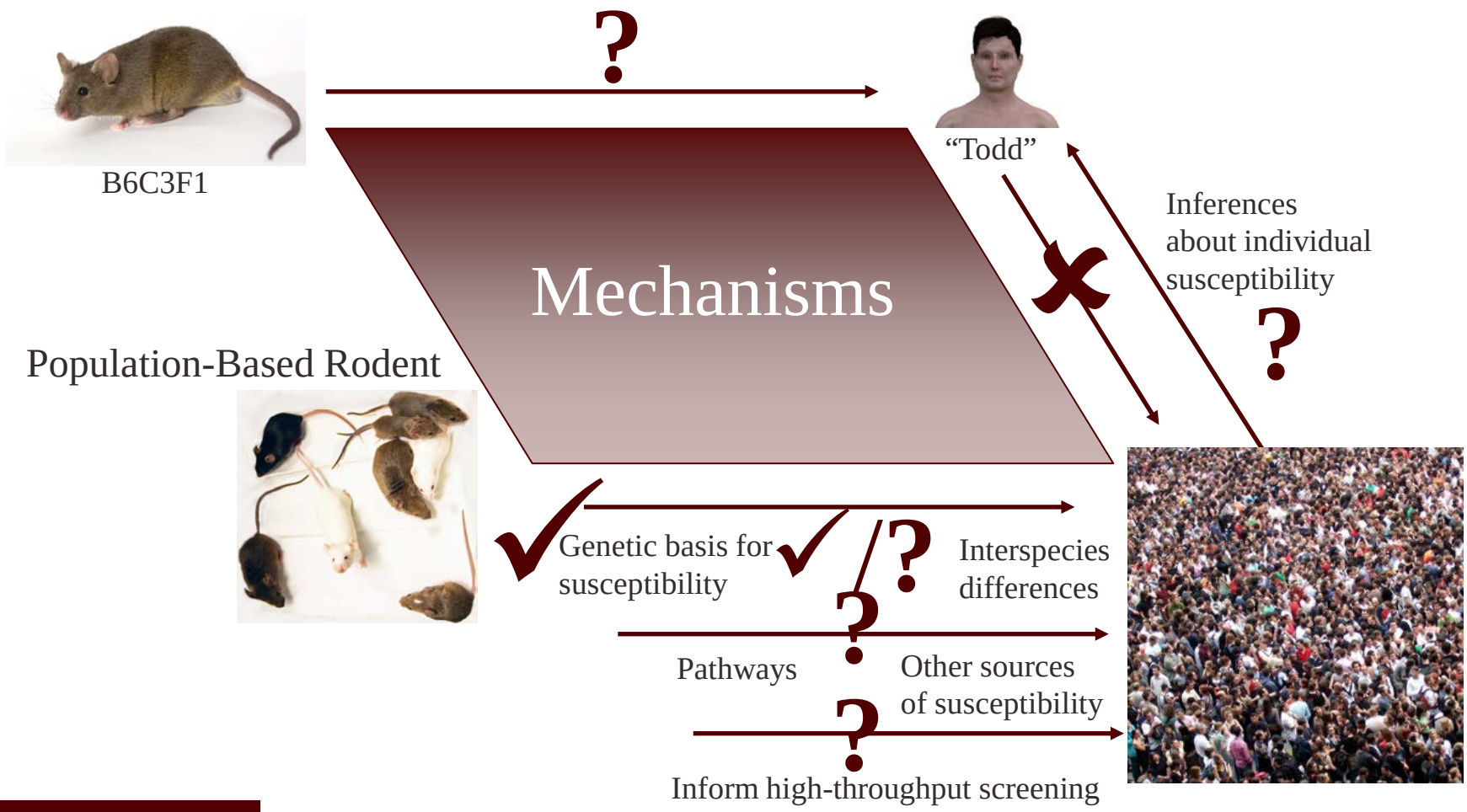
CD44 Candidate Susceptibility Gene

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

Mechanisms of Toxicity and Susceptibility:
Extending Beyond Genetic Variability



Mechanisms of Toxicity and Susceptibility: Improvements Using Population-Based Rodent Resources



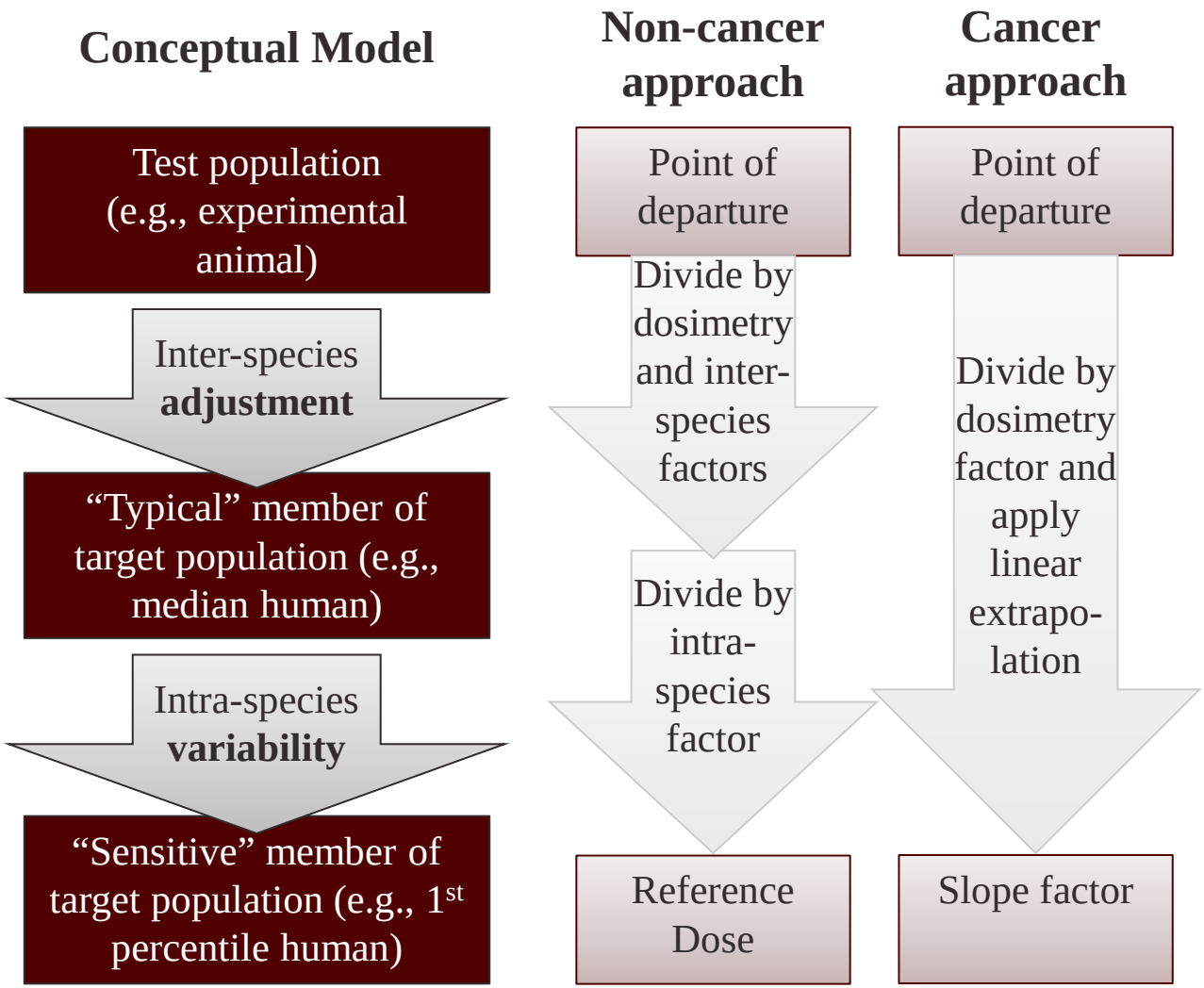
Opportunities and Challenges to Using Population-Based Models

Hazard Identification	Mechanisms of Toxicity and Susceptibility	Dose-Response Assessment
Opportunities: • Higher probability of overlapping with range of human responses • Directly informing population variability	**Opportunities:** • Identifying genetic basis for susceptibility • Interspecies extrapolation/ confirmation in humans (?) • Informing HTS • Personalized risk assessment (?)	
Challenges: • Optimizing data analysis/statistical modeling approaches • Understanding when, on a fixed budget, a population-based model has more power to identify a hazard	**Challenges:** • Characterizing polygenic susceptibilities • Non-genetic sources of variability	

Dose-Response Assessment

"the process of characterizing the relation between the dose of an agent administered or received and the incidence of an adverse health effect … as a function of human exposure to the agent."

NRC (1983)



Dose-Response Assessment:
Challenges of Using Single Rodent Strains

B6C3F1

? 10-fold

"Todd"

Dose-Response Assessment

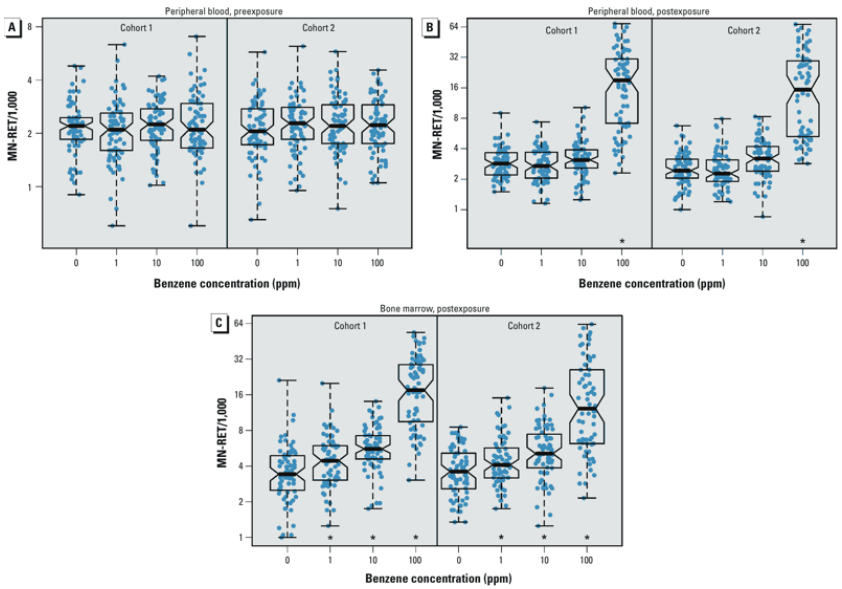
? 10-fold

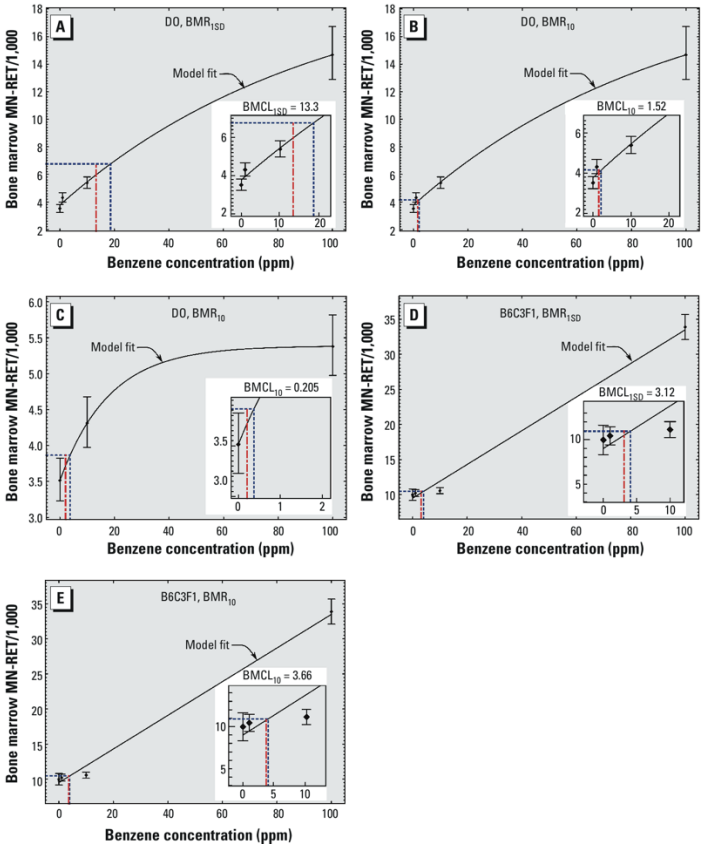
Is the single strain dose-response representative of the population?
Is the generic interspecies factor appropriate for the selected strain?
10-fold for variability assumed to be adequate (conservative?), but:

- Does it apply to <u>all</u> chemicals and end points? 90%? 95%? 99%?
- What percent of the population is being protected? 90%? 95%? 99%?
- How might the appropriate value differ from 10? 2? 5? 25?

Dose-Response Assessment:

Proof of Principle – Population Dose-Response

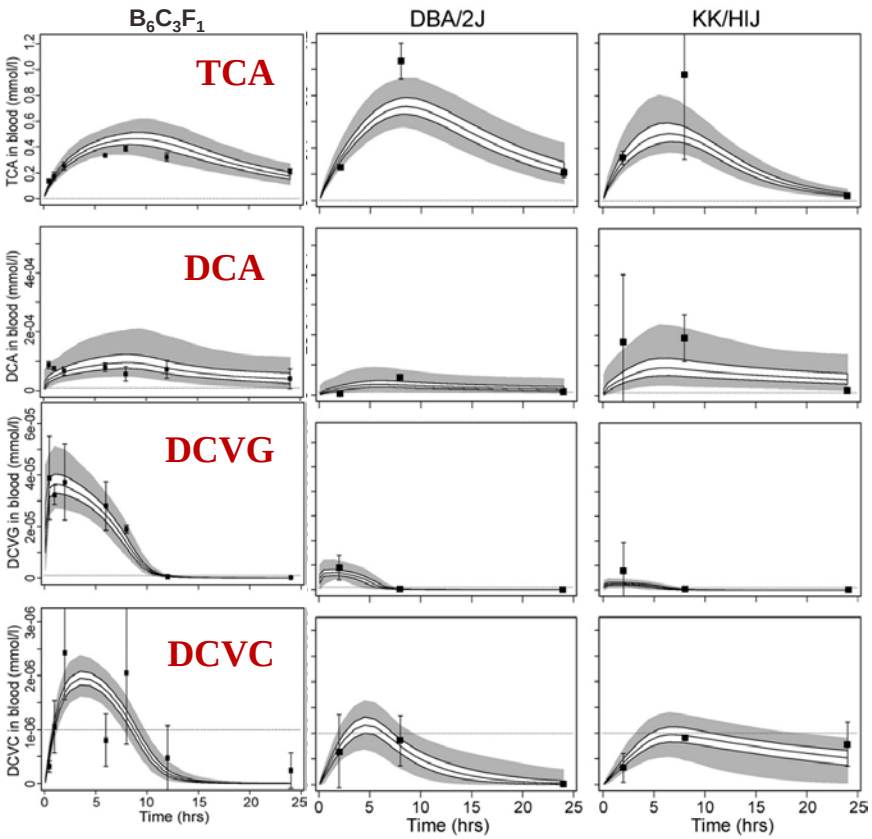




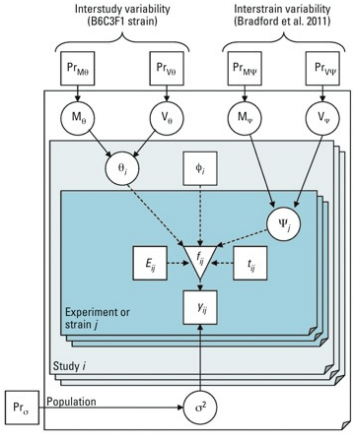
Note: EPA Benchmark Dose Software was not designed for population data

Source: French et al., 2015

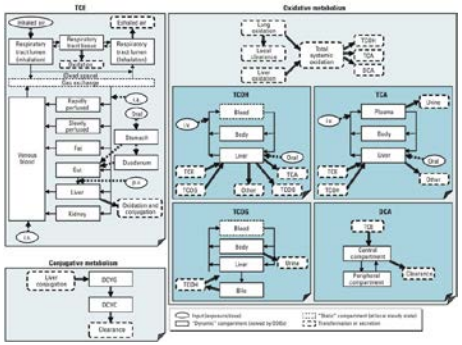
Dose-Response Assessment:
Proof of Principle – Toxicokinetic Variability



Source: Chiu et al., 2014



Bayesian Population Model
+
Physiologically-Based Pharmacokinetic Model



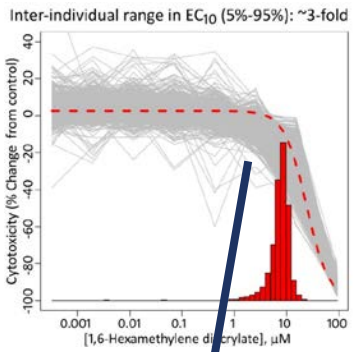
Consistent estimates of toxicokinetic variability from mice and humans.

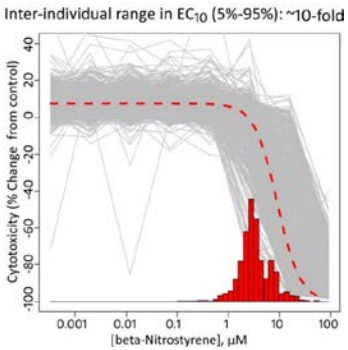
	Mouse inter-strain variability*	Human inter-individual variability*
TCE oxidized by P450	**1.05** (1.01, 1.27)	**1.11** (1.05, 1.22)
Total TCA produced	**1.77** (1.36, 2.99)	**2.09** (1.81, 2.51)
TCE conj. with GSH	**7.12** (3.43, 20.7)	**6.61** (3.95, 11.2)

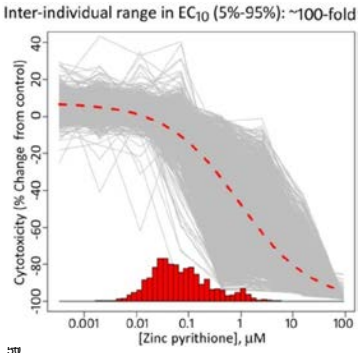
*Ratio of 95th percentile to 50th percentile individual or strain, expressed as **median** (95% confidence interval).

Dose-Response Assessment:

(Partial) Proof of Principle – Toxicodynamic Variability

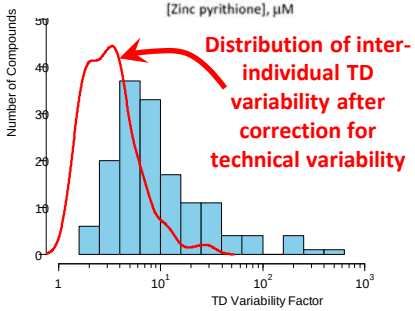






Cytotoxicity across 1086 **human** cell lines

Repeat with 179 compounds

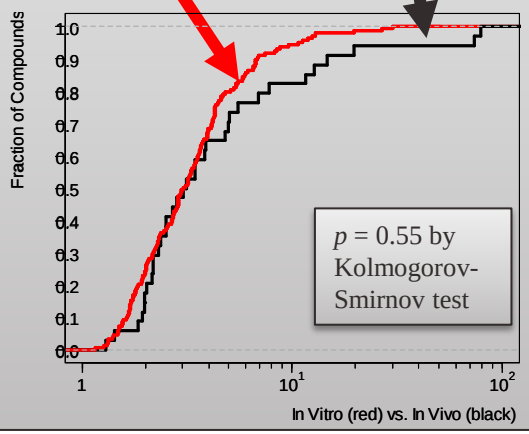


Source: Abdo et al., 2015

Consistent estimates of toxicodynamic variability in vitro and in vivo.

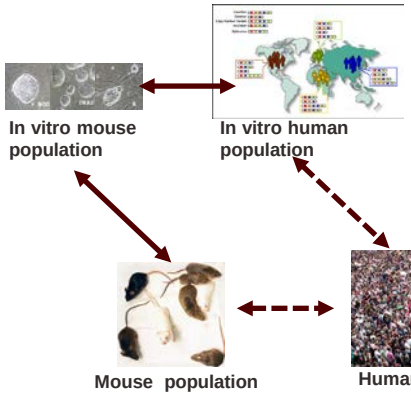
	Human In vitro	Human in vivo
TD variability factor*	3.04 (1.33, 12.6)	3.10 (1.40, 74.3)

*Ratio of 99th percentile to 50th percentile individual expressed as **median** (95% confidence interval) across chemicals.



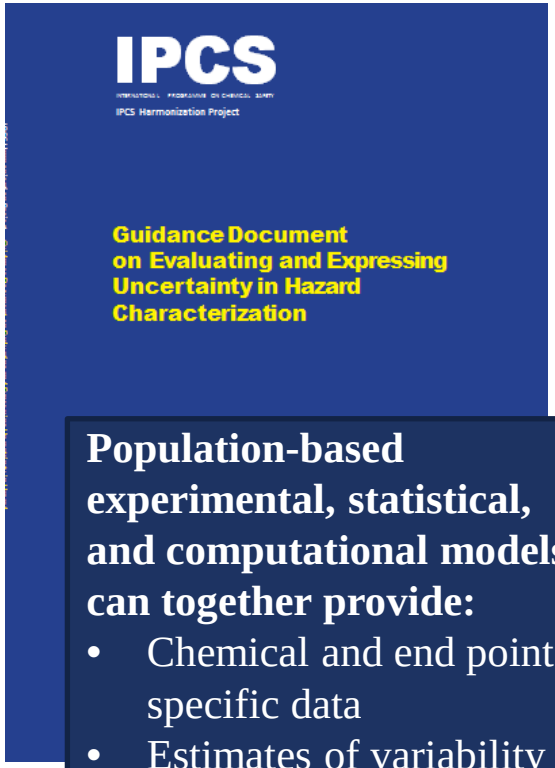
Can population rodent resources help to better characterize:

- **Extrapolation from *in vitro* to *in vivo*?**
- **Interspecies differences?**



Dose-Response Assessment

Adapting Current Approaches to Incorporate Variability Data



Population-based experimental, statistical, and computational models can together provide:

- Chemical and end point-specific data
- Estimates of variability for any percentile of the population (e.g. 95%, 99%)
- Confidence intervals that convey uncertainty

Conceptual Model

Test population (e.g., experimental animal)

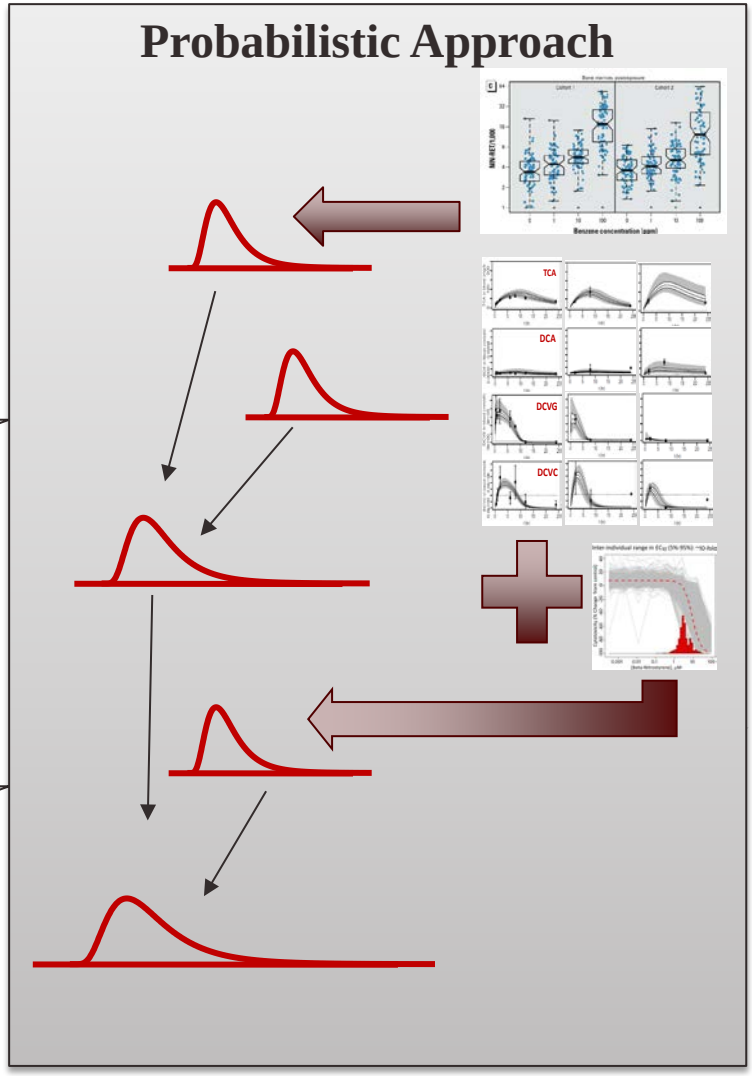
Inter-species **adjustment**

"Typical" member of target population (e.g., median human)

Intra-species **variability**

"Sensitive" member of target population (e.g., 1st percentile human)

Probabilistic Approach



Dose-Response Assessment: Improvements Using Population-Based Rodent Resources

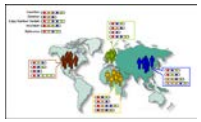
B6C3F1

? 10-fold

"Todd"

Dose-Response Assessment

? 10-fold



? In vitro-in vivo

Population-Based Rodent

✓ Population dose-response

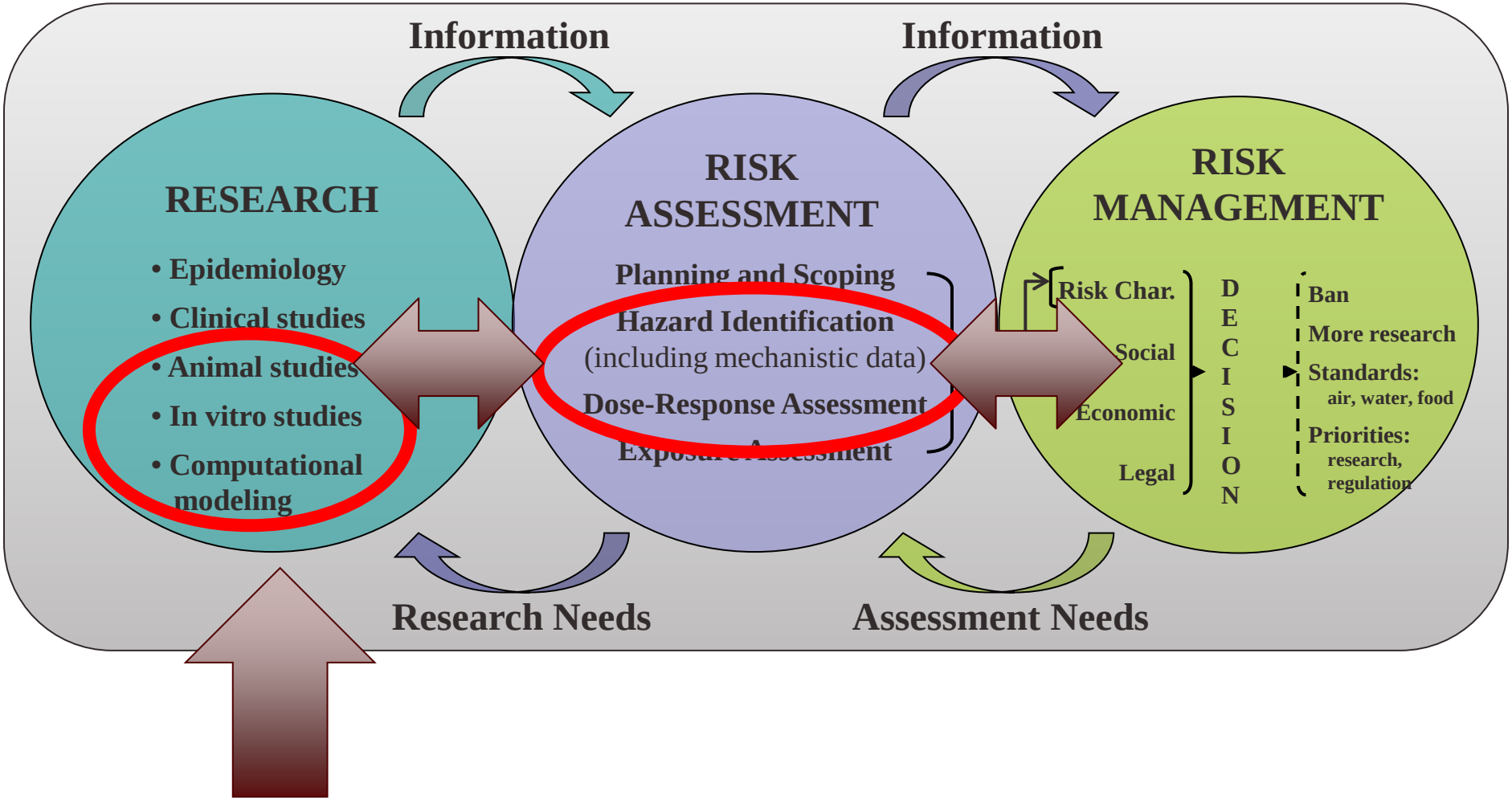
✓ ✓/?

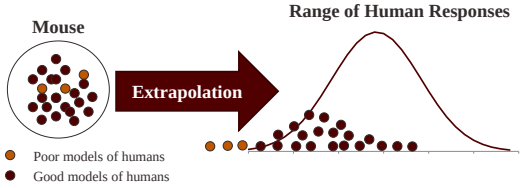
Toxicokinetics Toxicodynamics

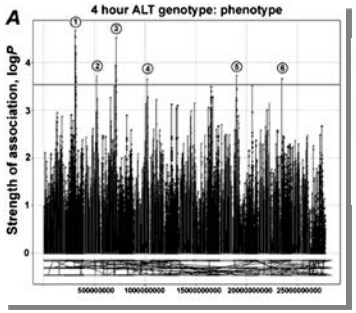
? Interspecies

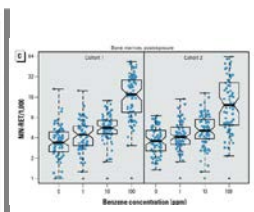
Opportunities and Challenges to Using Population-Based Models

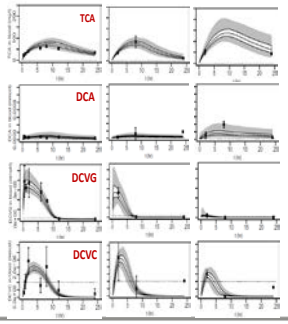
Hazard Identification	Mechanisms of Toxicity and Susceptibility	Dose-Response Assessment
Opportunities: • Higher probability of overlapping with range of human responses • Directly informing population variability	**Opportunities:** • Identifying genetic basis for susceptibility • Interspecies extrapolation/ confirmation in humans (?) • Informing HTS (?) • Personalized risk assessment (?)	**Opportunities:** • Population-level dose-response data • Chemical-/endpoint-specific estimates of human variability. • Interspecies and *in vitro-in vivo* extrapolation (?)
Challenges: • Optimizing data analysis/statistical modeling approaches • Understanding when, on a fixed budget, a population-based model has more power to identify a hazard	**Challenges:** • Characterizing polygenic susceptibilities • Non-genetic sources of variability	**Challenges:** • Incorporating probabilistic, population-based statistical and computational models • Engagement and communication among researchers, risk assessors, and risk managers.

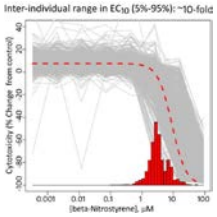

Information
Information
RESEARCH
• Epidemiology
• Clinical studies
• Animal studies
• In vitro studies
• Computational modeling
RISK ASSESSMENT
Planning and Scoping
Hazard Identification
(including mechanistic data)
Dose-Response Assessment
Exposure Assessment
RISK MANAGEMENT
Risk Char.
Social
Economic
Legal
DECISION
Ban
More research
Standards:
air, water, food
Priorities:
research, regulation
Research Needs
Assessment Needs


Mouse
Extrapolation
Range of Human Responses
Poor models of humans
Good models of humans


A
4 hour ALT genotype: phenotype
Strength of association, logP




TCA
DCA
DCVG
DCVC


Inter-individual range in EC10 (5%-95%): ~10-fold
Cytotoxicity (% Change from control)
[beta-Nitrostyrene], µM