Advancing Risk Assessment with Population-Based Experimental Resources

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Mouse

Extrapolation

Range of Human Responses

Hazard Identification

Mechanisms of Toxicity and Susceptibility

Characterizing Human Variability in Dose-Response
Acknowledgments

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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

**Research Needs**
- 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

**Assessment Needs**

**RISK MANAGEMENT**
- Risk Char.
- Social
- Economic
- Legal
  - Ban
  - More research
  - Standards: air, water, food
  - Priorities: research, regulation

New experimental systems can 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
Hazard Identification:
Challenges to Using Single Rodent Strains

- Human relevance of single strain rodent (positive and negative findings)
- No information about human population variability
Hazard Identification: Adding Population Variability

Mouse

- Poor models of humans
- Good models of humans

Range of Human Responses

Extrapolation
Hazard Identification: Proof of Principle

Might miss hazard if only testing one of these strains

Distributions of responses overlap

Mouse 300 mg/kg (37 strains)

Human 4 g/day for 8 days (n=49)

Mouse 100 mg/kg (6 strains)

Hazard Identification:
Improvements Using Population-Based Rodent Resources

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Population-Based Rodent

Hazard Identification

“Todd”

+
# Opportunities and Challenges to Using Population-Based Models

<table>
<thead>
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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**


**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

<table>
<thead>
<tr>
<th>1 = established</th>
<th>2A = probably</th>
<th>2B = possibly</th>
<th>3 = unclassifiable</th>
<th>4 = probably not</th>
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<tr>
<td><strong>Animals</strong></td>
<td><strong>Humans</strong></td>
<td><strong>Sufficient</strong></td>
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<td><strong>Inadequate</strong></td>
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<tr>
<td>Sufficient</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Limited</td>
<td>2A (1)</td>
<td>2B (2A)</td>
<td>2B (2A)</td>
<td>2B (2A)</td>
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<tr>
<td>Inadequate</td>
<td>2B (1, 2A, 3)</td>
<td>3 (2B)</td>
<td>3</td>
<td>3 (4)</td>
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<tr>
<td>Suggesting lack</td>
<td>3 (1)</td>
<td>3</td>
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International Agency for Research on Cancer Monograph Program
Mechanisms of Toxicity and Susceptibility: Challenges to Using Single Rodent Strains

- Human relevance of single strain rodent (positive and negative findings)
- No information about human population variability
Mechanisms of Toxicity and Susceptibility: Adding Population Variability to Identify Pathways

Experiments with Genetically Diverse Populations

Genes

Environ. Factors → 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

GWAS in mice

CD44 Candidate Susceptibility Gene

Confirmed in human cohorts

Mechanisms of Toxicity and Susceptibility: Extending Beyond Genetic Variability

Types of Biological Variability
- Heredity (genetic & epigenetic)
- Gender, Lifestage
- Existing health conditions
- Co-exposures
- Food/Nutrition
- Psychosocial stressors

Source-to-Outcome Continuum
- Source/media concentrations
- Exposure
- External doses
- Toxicokinetics
- Internal concentrations
- Toxicodynamics
- Biological response measurements
- Systems dynamics
- Physiological/health status

Identify critical pathways
- Surrogate for other health conditions
- Identify key non-genetic factors that can perturb critical pathways.
- Modify baseline conditions
- Development/interpretation of high-throughput screens
- Probe underlying system dynamics, regulation/dysregulation of homeostasis
Mechanisms of Toxicity and Susceptibility: Improvements Using Population-Based Rodent Resources

- Genetic basis for susceptibility
- Interspecies differences
- Pathways
- Other sources of susceptibility
- Inform high-throughput screening

Inferences about individual susceptibility

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## Opportunities and Challenges to Using Population-Based Models

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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)

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)

Non-cancer approach

Point of departure

Divide by dosimetry and inter-species factors

Divide by intra-species factor

Reference Dose

Cancer approach

Point of departure

Divide by dosimetry factor and apply linear extrapolation

Slope factor
Dose-Response Assessment: Challenges of Using Single Rodent Strains

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 all 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

Source: French et al., 2015

Note: EPA Benchmark Dose Software was not designed for population data
Dose-Response Assessment: Proof of Principle – Toxicokinetic Variability

Consistent estimates of toxicokinetic variability from mice and humans.

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<th>Mouse inter-strain variability*</th>
<th>Human inter-individual variability*</th>
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<tr>
<td>TCE oxidized by P450</td>
<td>1.05 (1.01, 1.27)</td>
<td>1.11 (1.05, 1.22)</td>
</tr>
<tr>
<td>Total TCA produced</td>
<td>1.77 (1.36, 2.99)</td>
<td>2.09 (1.81, 2.51)</td>
</tr>
<tr>
<td>TCE conj. with GSH</td>
<td>7.12 (3.43, 20.7)</td>
<td>6.61 (3.95, 11.2)</td>
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*Ratio of 95th percentile to 50th percentile individual or strain, expressed as median (95% confidence interval).

Source: Chiu et al., 2014
Dose-Response Assessment: (Partial) Proof of Principle – Toxicodynamic Variability

Inter-individual range in EC$_{50}$ (5%-95%): ~3-fold
Inter-individual range in EC$_{10}$ (5%-95%): ~10-fold
Inter-individual range in EC$_{50}$ (5%-95%): ~100-fold

Cytotoxicity across 1086 human cell lines

Repeat with 179 compounds

Can population rodent resources help to better characterize:
- Extrapolation from *in vitro* to *in vivo*?
- Interspecies differences?

Consistent estimates of toxicodynamic variability in *in vitro* and *in vivo*.

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<th>Human In vitro</th>
<th>Human In vivo</th>
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<td>TD variability factor*</td>
<td>3.04 (1.33, 12.6)</td>
<td>3.10 (1.40, 74.3)</td>
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*Ratio of 99th percentile to 50th percentile individual expressed as median (95% confidence interval) across chemicals.

$p = 0.55$ by Kolmogorov-Smirnov test

Source: Abdo et al., 2015
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

Non-cancer approach Conceptual Model
Divide by intra-species factor

Point of departure

Slope factor

Cancer approach
Divide by dosimetry factor and apply linear extrapolation

Probabilistic Approach

TCA
DCA
DCVG
DCVC
Dose-Response Assessment: Improvements Using Population-Based Rodent Resources

Population dose-response

Toxicokinetics

Toxicodynamics

Interspecies

B6C3F1

“Todd”

10-fold

In vitro

In vivo
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<td>• Engagement and communication among researchers, risk assessors, and risk managers.</td>
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Mouse

Poor models of humans
Good models of humans

Range of Human Responses

Extrapolation

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 Characterization
- Social
- Economic
- Legal
- Decision
- Ban
- More research
- Priorities: research, regulation
- Standards: air, water, food

Research Needs

Assessment Needs

Research Needs Assessment Needs

Ban
More research
Standards:
air, water, food
Priorities:
research, regulation

VETERINARY MEDICINE & BIOMEDICAL SCIENCES
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