

# Day 2 Breakout Session: Topic 1 – Modeling Mixture Toxicity

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# Priority Matrix

Degree of Impact	High		
	Low		
		Short	Long
		Time scale	

Short timeframe < 3 years, Long timeframe > 3 years

Low impact will only incrementally advance a limited area of mixtures research, high impact will advance the field significantly

# High Impact/Short Timeframe

- Testing interaction threshold
  - High Throughput Screening (HTS) approach
  - Many mixtures, many endpoints
  - Fixed ratio ray design studies
- MCR hypothesis (maximum cumulative ratio)
  - Are toxic mixtures dominated by 1 or 2 components?
  - HTS of many mixtures using many endpoints
- Build database identifying interactions
  - Analyze mechanisms related to interactions
  - Look to drug-drug interactions for beginning

# High Impact/Short Timeframe

- Behavior-based exposure modeling for cumulative exposure
- Statistics methods development
  - Clustering techniques
  - Prioritization methods
  - Multivariate dimension reduction
  - Principle components
- Sufficient similarity
  - Chemical analysis comparison
  - Toxicity data (endpoints, sequence), *in vitro*
  - Herbals, petroleum mixtures, stored farm products
  - Systematic library of PAHs in different scenarios (e.g. high exposure)

# High Impact/Long Timeframe

- *In vitro to in vivo* linkage
- *In vitro* (HTS battery, -omics) <-> animal <-> epidemiology
  - Defined mixtures (occupational?)
    - Same or different pathway
  - Mirror 4-lab study with another mixture
  - Sufficient similarity of research mixture to epidemiological exposure
- Multi-route mixtures cumulative effect
  - *In vivo*
  - Modeling
- Systems biology models/prediction
  - PBPK/PD – biochemical reaction network modeling

# Last thoughts

- Most projects listed can be separated into short-term and long-term components
- Most projects would benefit from a proof-of-concept demonstration project
- Model development requires mathematical and statistical efforts, sometimes new procedures
- Need NIEHS Mixture Study Section (with strong biomathematical expertise)

# Discussants

John Bailer

Lyndsey Darrow

Mike DeVito

Gregg Dinse

Chris Gennings

L. Earl Gray

Bethany Hannas (rapporteur)

Richard Hertzberg  
(chairperson)

Paul Price

Glenn Rice

Cynthia Rider

James Rusling

Raymond Yang