Current State and Directions of Animal Toxicity Testing

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Drivers of Toxicity Testing

- History of toxicity testing
  - Unexpected adverse health events in workers and general population
  - Society of Toxicology founded 1961
- Key regulatory initiatives (1970's & beyond)
  - FIFRA (pesticides)
  - TSCA (industrial chemicals & pollutants)
  - REACH (Europe; industrial chemicals)
- Product stewardardship
  - "knowing your products"

Animal Toxicity Tests: Standard Battery

- Acute (single dose, oral, skin, inhalation)
- Genetic Toxicity (*in vitro* and *in vivo*)
- Immunotoxicity/Sensitization
- Subchronic dose (28-90 days; organ injury)
- Chronic Toxicity & Cancer (lifetime)
- Developmental Toxicity (birth defects)
- Two-generation Reproductive Toxicity
- Adult Neurotoxicity
- Developmental Neurotoxicity

Animal Toxicity Testing: The Issues

- Costly (~ $3-5MM for full battery)
- Large numbers of animals required (> 12,000 for full battery)
- Low through-put (> 4 yr to complete battery)
  - Full battery required only for pesticides
  - Thousands of non-pesticide chemicals in development and in commerce
- Animal-to-human extrapolation uncertainties
  - Impacts of: cross-species, age, genetic variations, etc.?
  - Accounted for with use of conservative risk assessment defaults
  - “Mode-of-Action” assessments used to reduce uncertainty

Reducing demands for full battery testing: Tier-based toxicity testing strategies

Toxicity tests grouped into three tiers

Tier I	Tier II	Tier III
Acute toxicity	*In vivo* cytogenetics	Chronic toxicity/ oncogenicity
Genetic toxicity	Immunotoxicity	Developmental neurotoxicity
Subchronic toxicity (28 or 90 days)	Neurotoxicity screening battery	
Prenatal developmental toxicity	2-Generation reproduction study	
Reproductive toxicity		

From: Becker et.al. Fd.Chem.Toxicol. 45: 2454-2469, 2007

Refining Animal Toxicity Testing: Ongoing Emphases

- Exposure-Dose considerations ("margins of exposure")
  - Understand "delivered dose" to test animals (how much and what gets in?)
  - Relationships of animal test doses to real-world human exposures:
    - Better understanding of: human uses, production volumes, human biomonitoring, exposure modeling, etc.
- Structure-Activity-Relationships ("predictive" toxicology)
- "Mode of Action" information
  - Human relevance of animal test findings
- "Combination" test protocols
  - Extracting more "bang-for-buck" effects information from consolidated test protocols