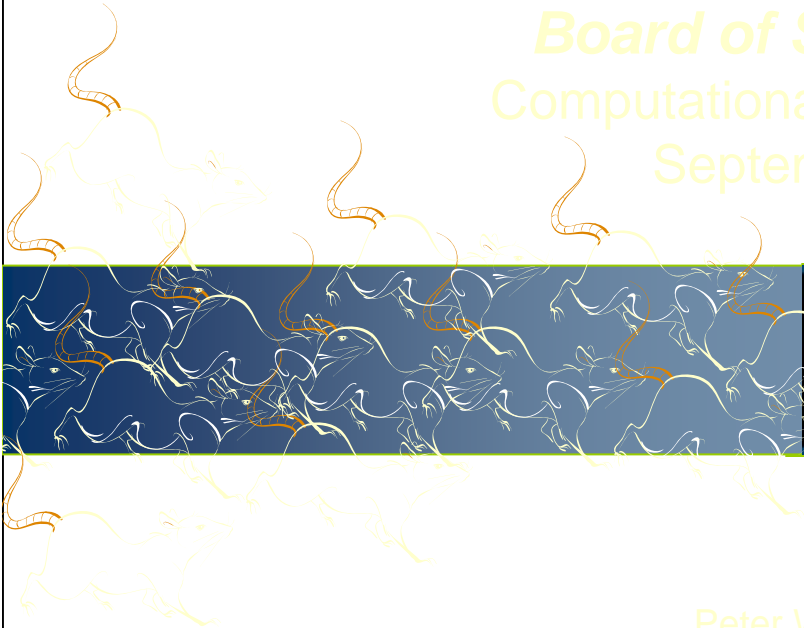




Presentation for the
Board of Scientific Counselors'
Computational Toxicology Subcommittee
September 29 and 30, 2009



COMPUTATIONAL
TOXICOLOGY

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Human Health Risk Assessment is:

- Fundamental to U.S. EPA's approach to analysis of potential risk from exposure to environmental contaminants
- Essential for U.S. EPA regulatory decision-making
- Evolving in the face of new understandings about uncertainty, mode of action, metabolism, susceptibility, etc.
- Addressing emerging science and new science challenges





Current Approach

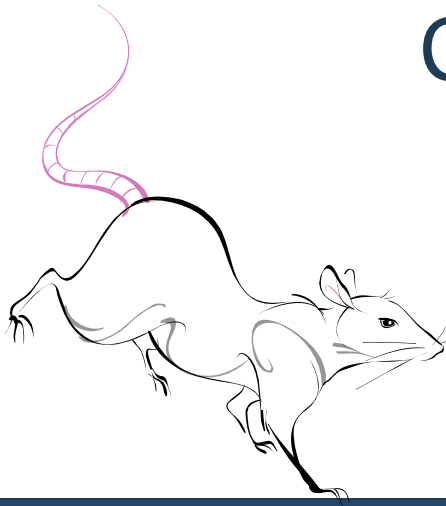
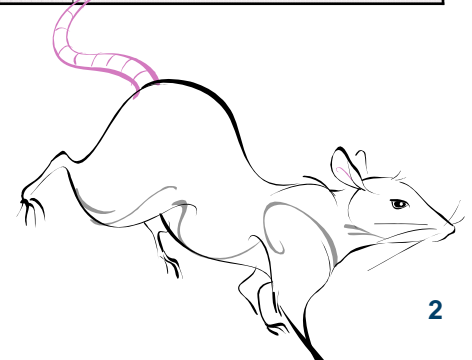


Table 4-31. Noncancer effects in animals repeatedly exposed to chemical x by the oral route

Reference/species	Exposure (mg/kg-day)	NOAEL	LOAEL	Effect
		(mg/kg-day)		
Burek et al., 1980 F344 rat, M&F	0, 0.05, 0.2,	0.2	1	Degenerative nerve changes Degenerative nerve changes Hindlimb foot splay Decreased body weight Atrophy of testes & skeletal muscle
	1, 5,	1	5	
	or 20	5	20	
			20	
			2	Degenerative nerve changes (L) Hindlimb foot splay Decreased body weight Early mortality after 24 weeks Other nonneoplastic lesions
			ND	
			2	
			ND	
			2.0(M)	degenerative nerve changes (L) Decreased body weight (8–9%) Early mortality after 60 weeks Other nonneoplastic lesions
			3.0(F)	
			ND	
			ND	

- Large number of animals
- Low throughput
- Expensive
- Time consuming
- Pathology endpoints
- Dose response extrapolations over a wide range
- Application of uncertainty factors
- Little focus on mode of action and biology
- Few epidemiology studies





Human Health Risk Assessment

Issues:

- There are tens of thousands of chemicals that are untested and lack assessment of potential for human toxicity.
- Current toxicology testing methods are too expensive, too slow, and can cope with too few chemicals.
- Toxicology approaches are evolving away from reliance on *in vivo* testing of laboratory animals
- Current approaches to risk analysis need to be significantly modified to deal with more chemicals; innovative approaches
 - *Screening application*
 - *Human health disease-related approach*



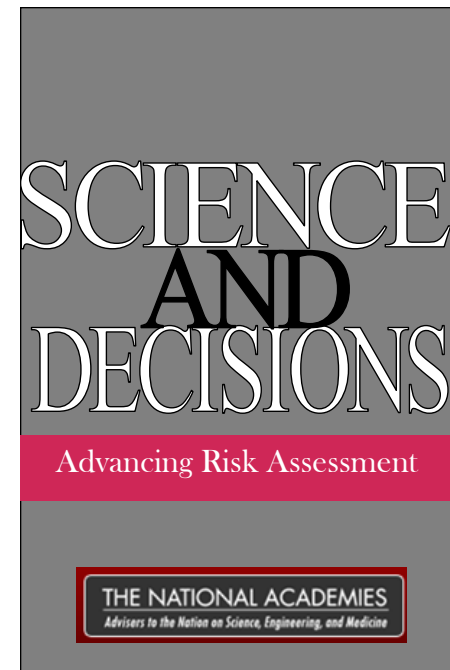
Human Health Risk Assessment: *Transforming to address emerging science and new science challenges*

- Risk assessment approaches are being discussed that can use the generation of new data types and arrays that are being developed in ORD's *Computational Toxicology Research Program*
- The environmental health community needs to develop next generation of risk assessment tools, approaches, and practices
- ORD's *Human Health Assessment Program* and the *Computational Toxicology Research Program* are in close partnership to move human health risk assessment forward and develop...
- **NexGen risk assessment**



U.S. EPA Consulted with the U.S. National Academy of Sciences on Future of Human Health Risk Assessment

- Risk assessment data needs cannot be met using the current testing methodologies
- Broader problem conceptualization can better reflect environmental risks, e.g. cumulative risks, families of similar chemicals, biofuels
- Current risk assessment practices do not fully utilize 21st century data and systems biology approaches to understand environmentally-induced disease
- Incorporation of data and insights from scientific advancements for intra- and inter-species extrapolation is a priority
- Estimates of risk should be refined to include the probability of harm
- Cumulative risk assessment for mixtures should focus primarily on physiologic consequences, resulting in the same common adverse outcomes, rather than structurally or mechanistically related chemicals
- The transformation of risk assessment that must occur will be best addressed through the joint efforts of stakeholders





NexGen Assessments:

From Now Until the Future

- In addition to challenges identified by the National Academy of Sciences, there are other issues that need to be addressed
- Techniques and knowledge to improve throughput still in the future
- More importantly, maybe we need to think differently about risk.
- Three approaches under consideration
 - *Create high priority list and streamlined process*
 - *Broaden scope of assessments.*
 - *Develop better methods for current assessments*
- ORD's Human Health Risk Assessment Program and the Computational Toxicology Research Program are working together to address these issues.



NexGen Assessments:

Strategy for the Future

- The intent of this possible strategy is to thoughtfully position environmental health assessors for the future, and contribute to meaningful change within the larger risk assessment/risk management community.
- ORD is embarking on an exploration of new science, methods and policies that could be incorporated into currently emerging and future risk assessments.
- The goal of this draft strategy is to map a course forward, focusing on creating prototype NexGen risk assessments, learning from these efforts and, then, refining the next versions based on this new knowledge.
- This possible strategy focuses on development of:
 1. *A pilot implementation of a new approach for risk based decision-making, including characterization of risk management needs, policy relevant questions and implications for NexGen risk assessments;*
 2. *An operational scale knowledge mining, creation and management system to support risk assessment work and interface with gene environment data bases.*
 3. *Prototype examples of increasingly complex assessments responsive to the risk context and refined through discussions with scientists, risk managers, and stakeholders.*



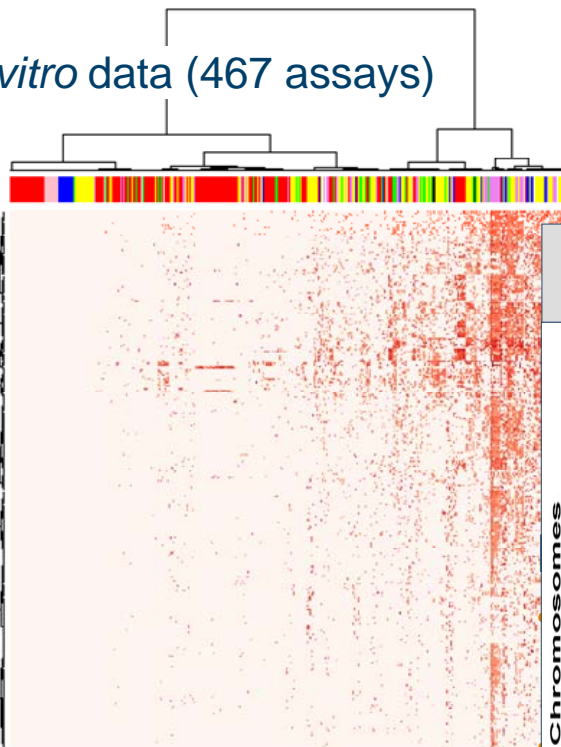
Computational Toxicology and NexGen Human Health Risk Assessment: *Partnering for a Changing Future*

- HHRA Program and CTR Program are exchanging scientific staff to learn the needs and capabilities of each organization
- Staffs are becoming familiar with HHRA approaches and CTR methodologies
- Development of case studies are underway to explore the use of computational toxicology data in human health assessments
- Case studies focus on assessments where there are an abundance of “traditional “data, as well as new computational toxicology data
 - Combine the two data sources and characterize the health effects
 - Assess the capability of the new data to help address science issues, increase speed and decrease costs

ToxCast *in vitro* data (467 assays)

- Cell Free HTS
- Multiplexed TF
- Human BioMap
- HCS
- qNPAs
- XMEs
- Impedance
- Genotoxicity

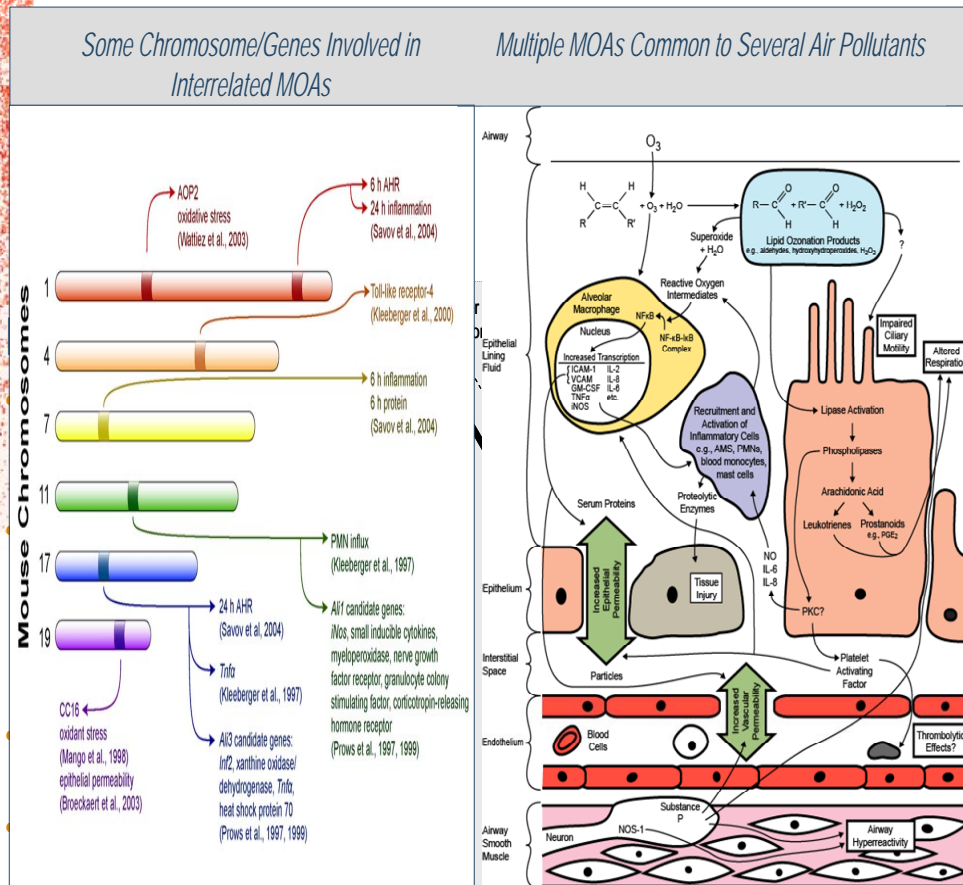
Chemicals



>200,000 dose response experiments

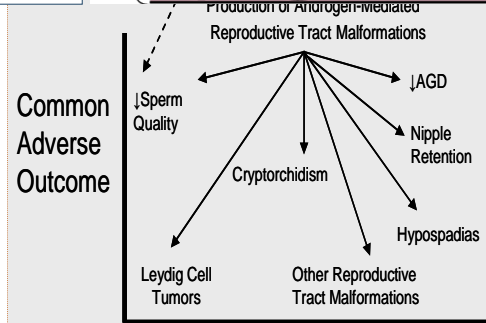
Case Study: *Phthalates* Case Study: *Ozone*

As an example, several air pollutants (family) are thought to act via common MOAs to cause similar respiratory disease (cumulative effects)



hypothesized testicular dysgenesis syndrome in humans and observed effects due to androgen insufficiency in humans and animals.

Source: NAS Report, *Phthalates and Cumulative Risk Assessment*, December 2008





The Changing Landscape of Human Health Risk Assessment

- ORD's Human Health Risk Assessment Program and the Computational Toxicology Research Program are partners in the future of human health risk assessment
- EPA is building a risk assessment program that will eventually be centered around the research products coming from the ORD's Computational Toxicology Research Program

