



The Future of Toxicity Testing

American Chemical Society/Society of Toxicology
Congressional Briefing
December 10, 2009

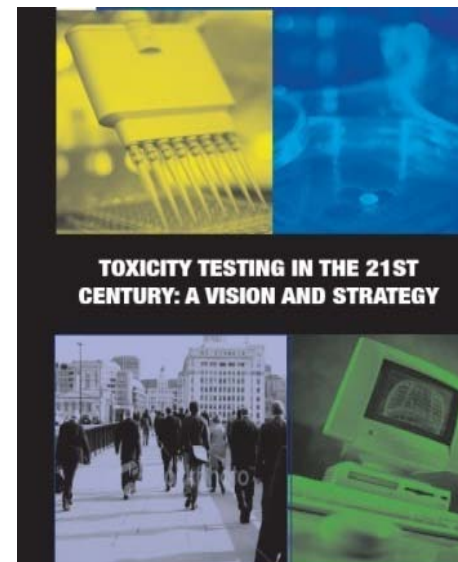
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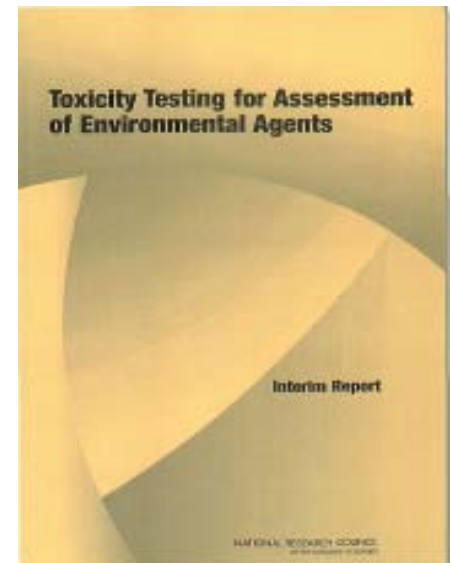
Research Triangle Park, NC USA

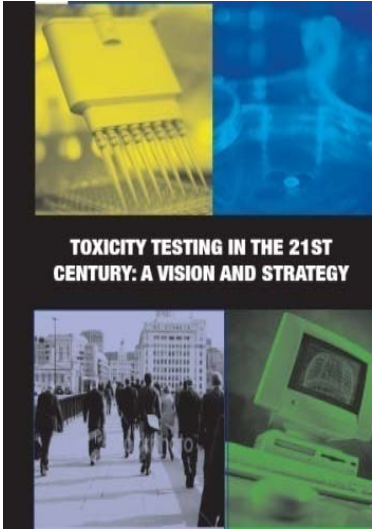
mandersen@thehamner.org



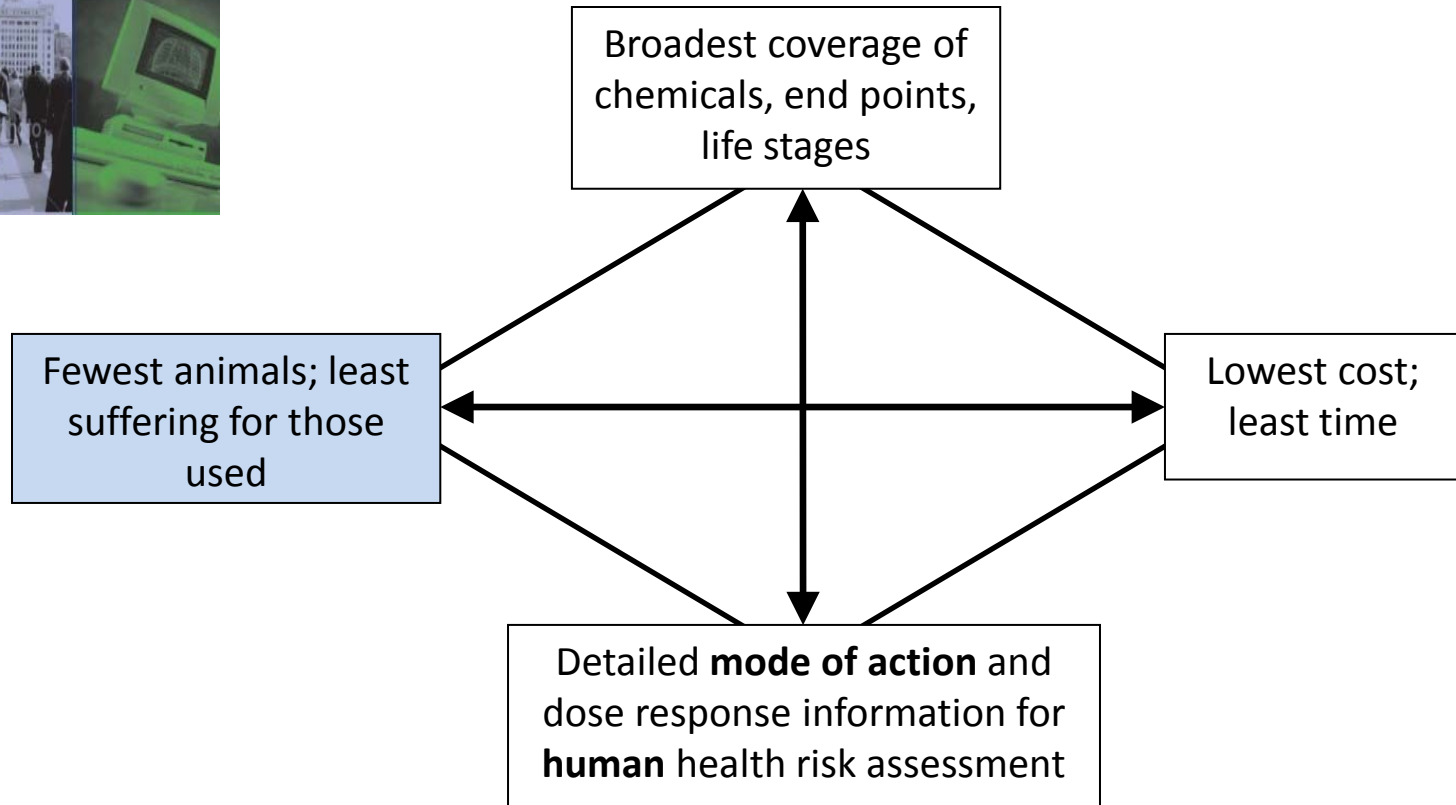
Status quo - 2005

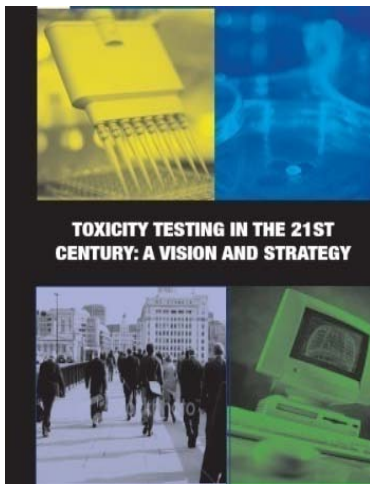
- Dates back to 1930's
- Low throughput; expensive
- Conservative extrapolations
- **Questionable relevance to humans**
- **Little use of modern biology, mode of action**
- Exorbitant in use of animals





Toxicity Testing of Environmental Agents needs to consider key Design Criteria



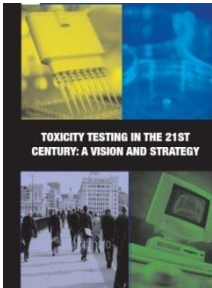
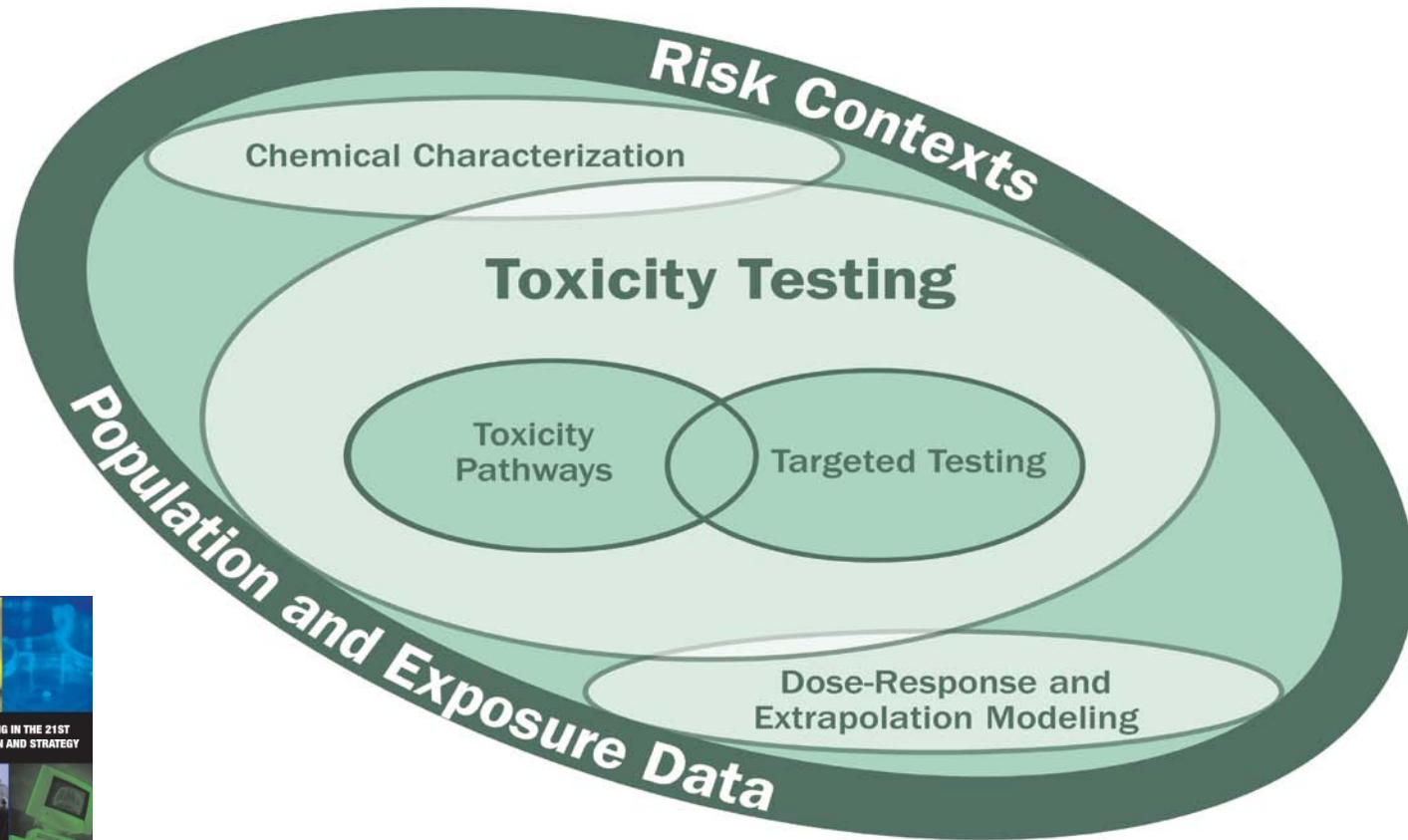


Vision

... routine toxicity testing will be conducted in human cells *in vitro* by evaluating perturbations of cellular responses in a suite of toxicity pathway assays.

Andersen and Krewski (2009). Toxicity Testing in the 21st Century: Bringing the Vision to Life. *Tox. Sci.*, 107, 324-330.

Components – Toxicity Pathways



In the new testing approach,

- Toxicity pathways reflect human biology and modes of action
- Increased speed and throughput; decreased costs and animal usage
- Move away from interpretation of human risks from high dose animal studies, but
- **Now we must interpret human risks/safety from studies with cells**

Organizing Results for Risk/Safety Assessment

Coverage of chemical
activity by diverse
toxicity pathway assays



Evaluating dose response in
the cell based toxicity
pathway



Going from human cells in
test tubes to real people



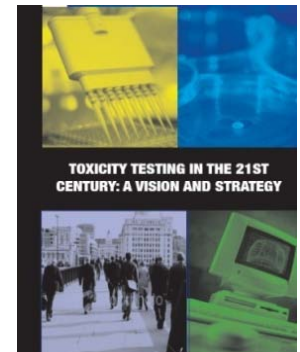
“Human Safety Assessment”

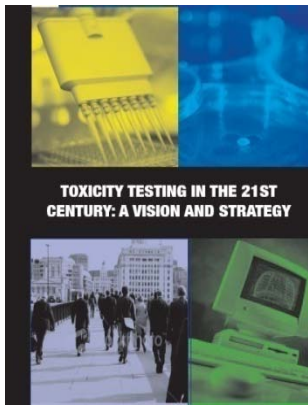
Key Tools to assist the overhaul

- Cell-based assays with appropriate level of biological detail and organization (***human tissue-derived stem cells, organ-like tissue cultures***)
- Mathematical descriptions of pathways to determine dose response (***computational systems biology***)
- Predictive computational models to go from cells to the human exposure conditions (***pharmacokinetic modeling***)

Some changes in perspective required

- Shift away from outcomes in experimental animals to perturbations of toxicity pathways in human cells
- Assess regions of safety rather than estimating risks





Strategy – Option I (NAS)

- Concerted program resident within some section of the NIH
- “Big science project”: \$1-2 billion and 10 to 20 year timeline
- Downside: need to get all pieces in place and do a wholesale transition from present approaches to new ones in one fell swoop

Strategy – Option II

- More incremental - select 5 to 10 prototype compounds/pathways and take through the steps proposed by the NAS
 - Examine progress after 3-5 year period; make mid-course corrections; expand suite of pathways
 - Set out plans for the larger scale changes after developing a sense that these approaches will be health protective
 - Still needs an integrated program, i.e., a plan, to be successful
- So-called
“Human Toxicology Project”*