

National Toxicology Program Roadmap Retreat

Christopher J. Portier, Ph.D.

Associate Director, NTP

Director, Environmental Toxicology Program

National Institute of Environmental Health Sciences



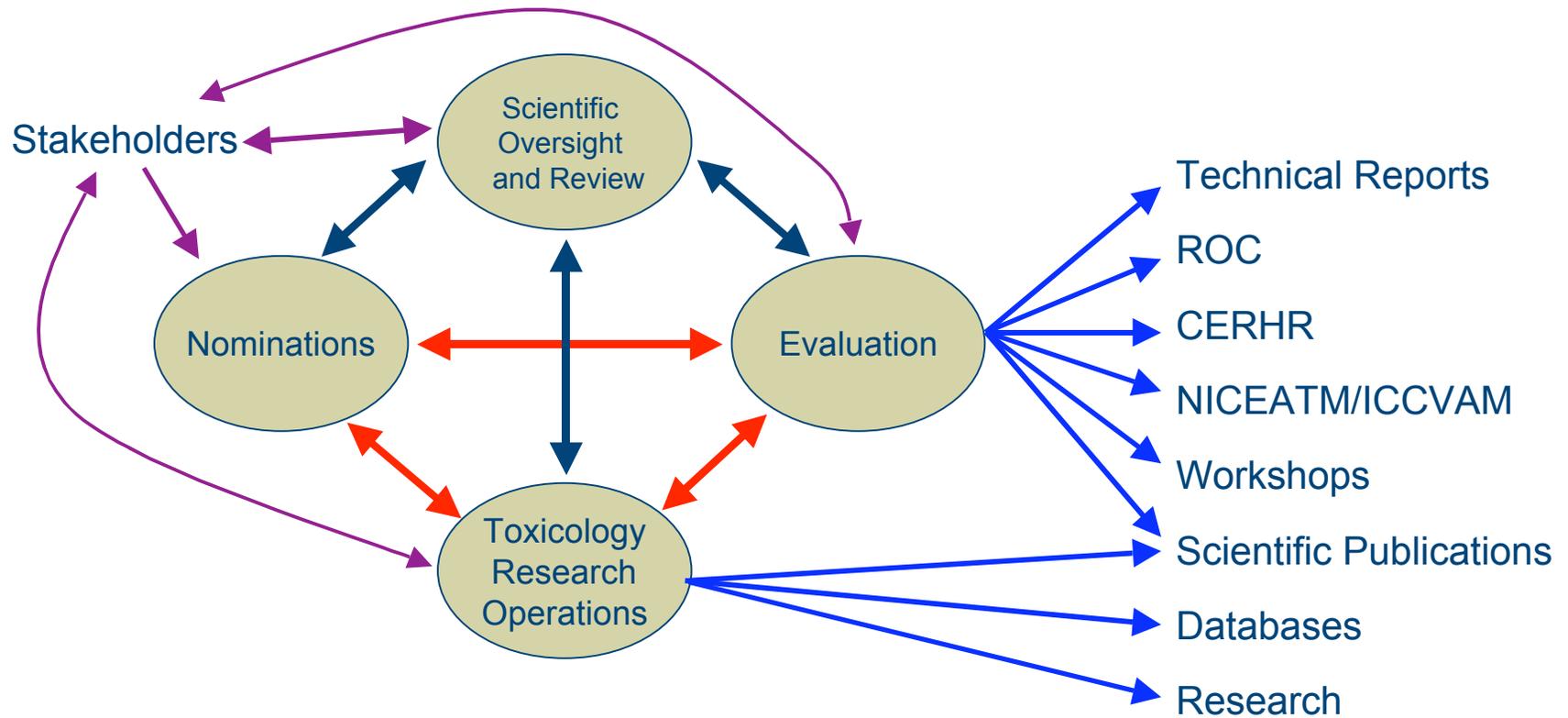
”We don’t receive wisdom; we must discover it for ourselves after a journey that no one can take for us or spare us.”

Marcel Proust (1871-1922)

NTP Vision for the 21st Century

To move toxicology from a predominantly observational science at the level of disease-specific models to a predominantly predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations.

Major Activities and Products of the NTP



Roadmap Target #1: High-Throughput Screening (HTS)

Target Date: Begin exploratory testing mid 2005

Example Activities:

- ◆ Target selection
- ◆ Compound Selection
- ◆ Experimental Design
- ◆ Funding Mechanism/Type of Activity
- ◆ Database Development
- ◆ Analysis Methods
- ◆ Effectiveness of Program
- ◆ Communication

Roadmap Target #2: Bioassay Review and Redesign

Target Dates: Begin review of bioassays immediately
Complete review of bioassays by mid-2006

Example Activities:

- ◆ Digital pathology
- ◆ Targets in the two-year chronic exposure bioassay
- ◆ Dose-selection
- ◆ Life stages and dosing patterns
- ◆ Choice of model
- ◆ Toxicokinetics
- ◆ Toxicogenomics
- ◆ Developmental toxicology screens

Roadmap Target #3: Medium-Throughput Screening (MTS)

Target Date: Analyze and report initial *C. elegans* results by mid-2005

Example Activities:

- ◆ Evaluate *C. elegans* study
- ◆ Other species and targets for MTS
- ◆ MTS design
- ◆ Select compounds
- ◆ MTS toxicogenomics target genes
- ◆ Cell line or species
- ◆ Analysis of results

Roadmap Target #4: Data Analysis and Interpretation

Example Activities:

- ◆ Existing analysis tools
- ◆ Web access
- ◆ Existing predictive toxicology tools
- ◆ Interpretation of HTS and MTS for NTP priority setting
- ◆ Assay usage in hazard identification
- ◆ Validation by ICCVAM of predictive models

A National Toxicology Program for the 21st Century - *Roadmap to Achieve the NTP Vision*

Introduction

Since its inception in 1978, the National Toxicology Program (NTP) has stood as a leader in toxicological testing and research within the United States and has contributed significantly to the scientific knowledge upon which public health decisions are based. Over the last two decades, the toxicology community has placed increasing emphasis on mechanism-based investigations. In the last few years, increasing knowledge of the human and rodent genomes have expanded the possibilities for fruitful mechanistic studies. This evolution has and will continue to lead to improvements in the interpretation of toxicology data and has already begun to influence the scientific basis for public health decisions. This change has not, however, reduced the need for the classical tests developed in the 1970s and 80s that are the basis for most decisions related to evaluation of environmental and occupational hazards and prioritization of chemicals for further testing. The ...

Roadmap Target #1: HTS Activity Matrix

SEQUENCE	TIMELINE		
	Short-term	Mid-term	Long-term

Roadmap Target #1: HTS Screening **Activity Timeline**

	Target/Compound Selection	Experimental Design/HTS Facility/Database	Analysis/Effectiveness/Communication
2005			
2006			
2007			
2008			
2009			
2010			



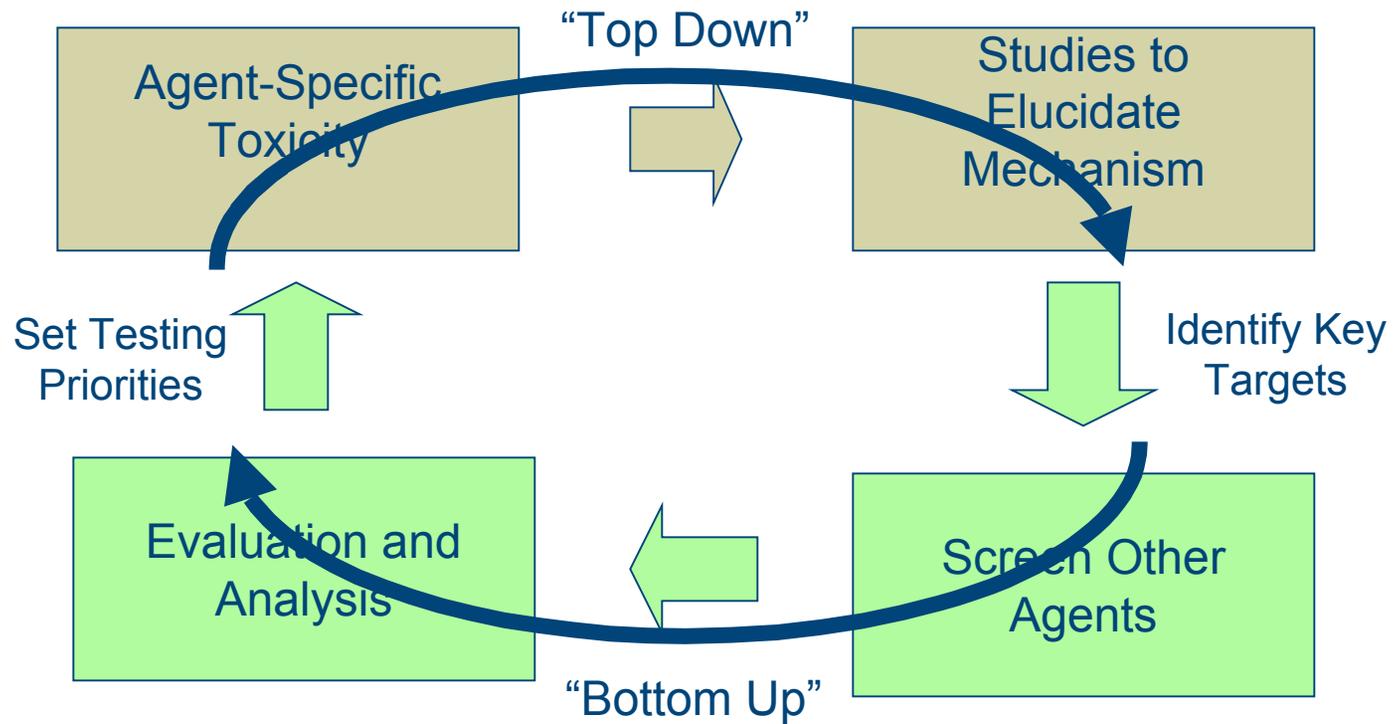
Roadmap Target #1: HTS Screening

Activity Descriptions

BSC Review Compounds^A: The initial set of compounds to be used in the HTS program can probably be selected without much formal review. The NTP has studied several hundred compounds in the last few years and stored samples of these compounds for other uses. It should be possible to choose a number of compounds from this repository to be used in the initial HTS. The NTP is encouraged to choose compounds that have known toxicity (if any) and encouraged to use at least 500 compounds in the original screening.

BSC Review Mechanisms^B: One of the most critical aspects of the HTS program will be the choice of assay to use; the list is endless. The NTP should initially choose assays that relate to mechanisms that are known to be related to toxicity such as genotoxicity, micronuclei, cellular replication and apoptosis. The choices should be reviewed by the BSC and discussed openly to develop a consensus of their future utility.

Mechanism-Based Toxicology



Advantages

- ◆ Strengthen prediction of hazards for humans
- ◆ Link to existing databases for “validation”
- ◆ Expand number of agents studied
- ◆ Turn sporadic mechanistic insights into broader knowledge base
- ◆ Improve extrapolations
- ◆ Test smarter

Challenges

- ◆ **Avoid resource drains**
- ◆ **Avoid over-interpretation**
- ◆ **Include validation at the planning stage**
 - **How?**
- ◆ **Which mechanistic assays?**
- ◆ **Who will do this?**

“The future is not some place we are going to, but one we are creating.... The paths are not to be found, but made, and the activity of making them changes both maker and the destination.”

John Schaar