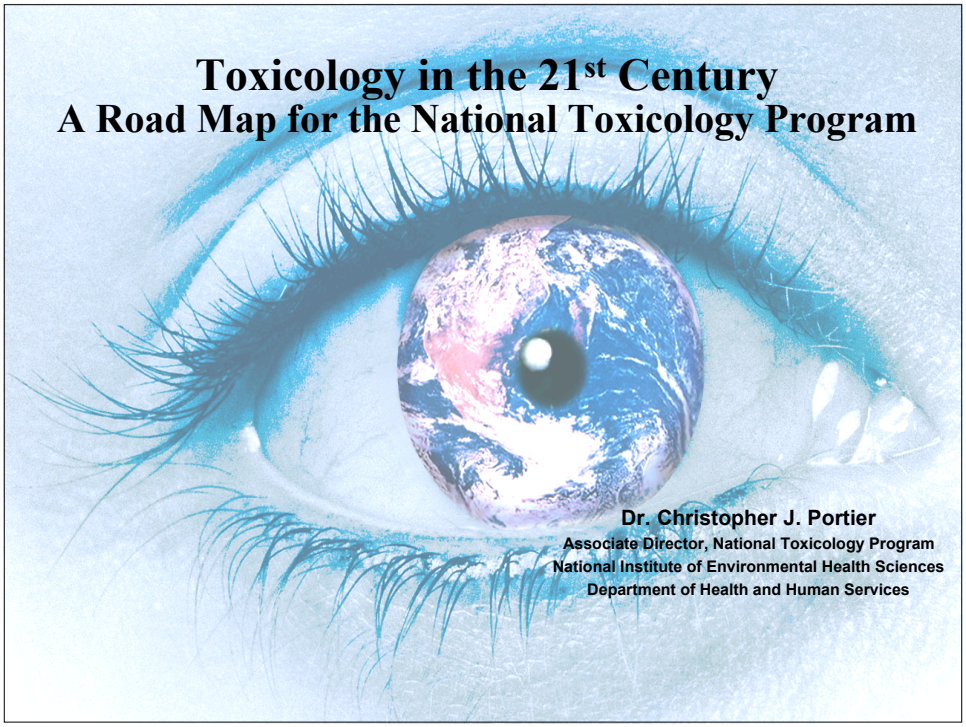
Toxicology in the 21st Century
A Road Map for the National Toxicology Program



Dr. Christopher J. Portier
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Federal Agencies that Routinely Participate in NTP Activities

- National Institute of Environmental Health Sciences (NIEHS)[1]
- National Cancer Institute (NCI)[1]
- Food and Drug Administration/
  National Center for Toxicological Research (NCTR)[1]
- Centers for Disease Control and Prevention/
  National Center for Environmental Health (NCEH)/
  Agency for Toxic Substances and Disease Registry (ATSDR)[1]
- Centers for Disease Control and Prevention/
  National Institute for Occupational Safety and Health (NIOSH)[1]
- Environmental Protection Agency (EPA)[1]
- Consumer Product Safety Commission (CPSC)[1]
- Occupational Safety and Health Administration (OSHA)[1]
- National Institutes of Health (NIH)[1]
- Department of Agriculture
- Department of Defense
- Department of Energy
- Department of the Interior
- Department of Transportation
- National Library of Medicine

[1]Member of NTP Executive Committee

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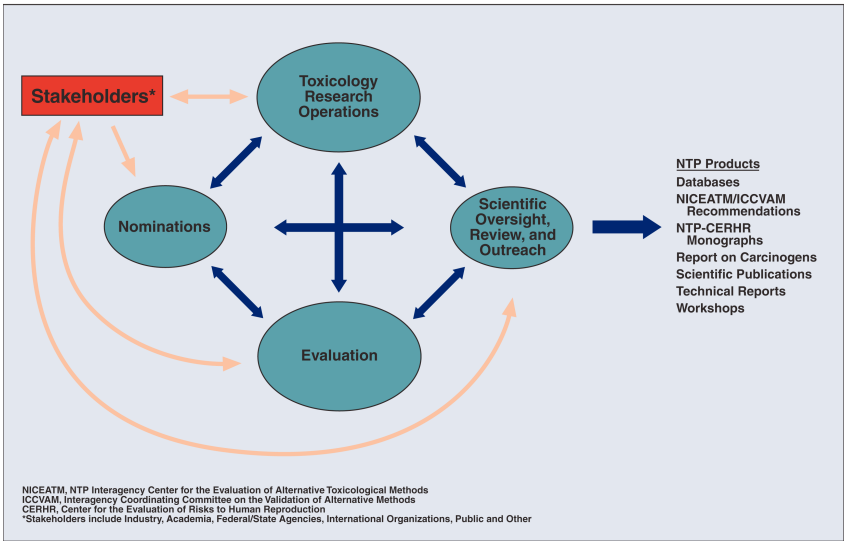
Functional Groupings of the Major Activities and Products of the NTP



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Primary Functions of Laboratories, Centers and Offices Contributing to the NTP

Nominations	NIEHS Office of Chemical Nomination and Selections (OCNS) Interagency Committee for Chemical Evaluation and Coordination (ICCEC)
Toxicology Research Operations	Toxicology Operations Branch (TOB) NIEHS Laboratory of Experimental Pathology (LEP) NCTR Research Laboratories NIEHS Division of Intramural Research Laboratories NIOSH Research Laboratories NTP Phototoxicology Center
Evaluation	Report on Carcinogens (ROC) NTP Center for the Evaluation of Risks to Human Reproduction (CERHR) NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)
Scientific Oversight, Review, and Outreach	Office of NTP Liaison and Scientific Review (ONLSR) NTP Executive Committee NTP Board of Scientific Counselors (BSC) Scientific Advisory Committee on Alternative Toxicological Methods (SACATM)

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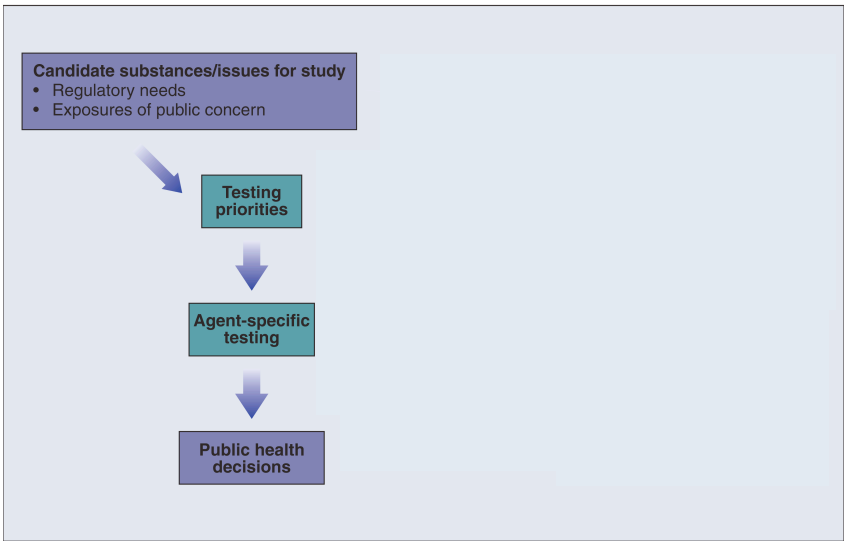
Use of Mechanistic Toxicology Studies in Public Health Decision Making



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Retreat Participants

SACATM
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Sidney Green
Stephen Safe
Martin Stephens
Katherine Stitzel

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Lynn Goldman
Carol Henry
Philip Iannaconne
Sylvia Johnson
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NTP Retreat – August 2004

- **Four Breakout Groups**
  - High-Throughput Screening
  - Bioassay Review and Redesign
  - Medium-Throughput Screening and "Omics"
  - Data Analysis and Interpretation
- **Group Tasks**
  - Clarify wording in "A National Toxicology Program for the 21st Century: Roadmap to Achieve the NTP Vision"
  - Develop "Activity Matrix" of key activities and priorities for the NTP in the next 5-10 years

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High-Throughput Screening
Activity Matrix

SEQUENCE	TIMELINE		
	Short-term	Mid-term	Long-term
	('04) Catalogue assays	('06) Analyze Metabolites from Non-Conforming	('09) Develop Universal Metabolizing System
	('05) Workshop to Select Tests	('07) Validation of Assays to Predict Mechanistic Endpoints	('10) Availability of Agents & Tissues for HTS to Extramural Scientists
	('05) Understand Metabolism	('07) Develop Systems Biology Methods for Analysis	('10) Validation of Battery of Tests for Prediction
	('05) Test ± 600 NTP Agents	('07) Develop Database as Part of TDMS/CEBS/NTP Databases	
		('07) Review After 36 Months and Periodically	('10) Review after 5 Years and Periodically

Bioassay Review and Redesign
Activity Matrix

SEQUENCE	TIMELINE		
	Short-term	Mid-term	Long-term
	('05-'07) Principle-Based Testing	('06) Evaluate Mechanistic/Dosimetry Studies	('05-'09) Evaluate Study Design Teams
	('05-'06) Digital Pathology	('06) Evaluate Timing and Duration of Exposure	('05-'10) Use of Pre-Chronic/Other to Design Chronic
	('05) Evaluate Strains and Species	('06-'08) Include Mechanistic Endpoints in Chronic	('07-'10) Nurture New Assay Development
	('06) Evaluate Subchronic/Clinical Pathology	('05-'07) Expand Non-Invasive Methods	('05-'10) Permanent Archiving of Pathology Samples
	('05-'06) Toxicokinetics	('05-'08) Reevaluate Older Bioassays	('10) Review after 5 years and Periodically

Medium-Throughput Screening[1] and 'Omics'
Activity Matrix

SEQUENCE	TIMELINE		
	Short-term	Mid-term	Long-term
	('04) Define Goals and Objectives	('06) Update Catalogue	('10) Use MTS Assays for Primary Goals
	('05) Catalogue Available Assays	('06-'08) Develop Assays to Address Gaps	('10) Use MTS for Priority Setting
	('05) Workshop on Goals, Objectives, Utility	('06-'09) Proof of Concept/Principle Studies	('10) Evaluate for Human Relevance
	('05) Criteria for Selection	('08) Determine Needs for Validation	('10) Evaluate Regulatory Acceptance
	('06) Database Issues	('05-'08) Communication	('10) Review after 5 years and Periodically

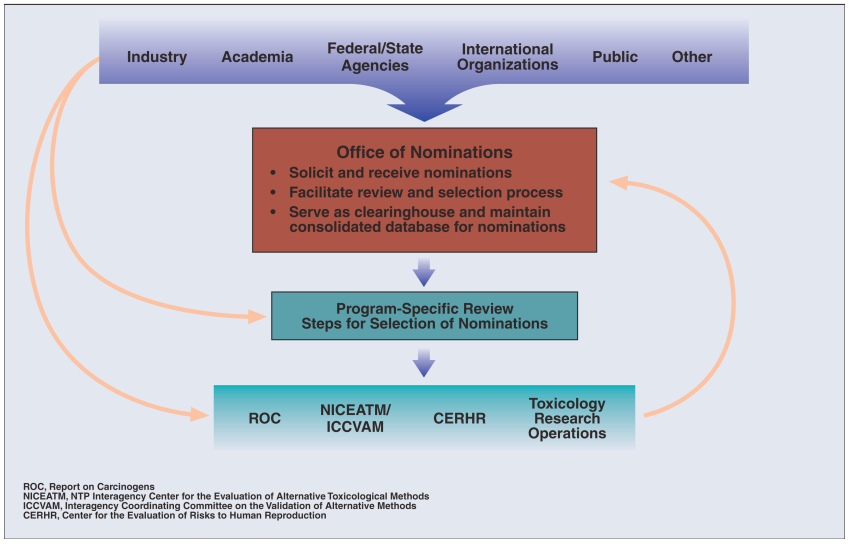
[1] Definition, goal, mammalian and non-mammalian models, sequential vs. parallel use, relationship to HTS, adjunct to traditional

Data Analysis and Interpretation[1]
Activity Matrix

SEQUENCE	TIMELINE		
	Short-term	Mid-term	Long-term
	('05) Evaluate Information Technology Needs	('08) Analyze initial NTP HTS/MTS Data (Workshop)	('10) Validate for Regulatory Needs (ICCVAM)
	('07) Workshop on HTS/MTS Analyses with Current Users	('08-'09) Validation Studies (qual. and quan.) for Test Endpoint	('10) Interaction with Decision Makers
	('06-'07) Develop Process for Identifying HTS/MTS +/- Results		
	('05-'07) Interaction with Decision Makers		('10) Review after 5 years and Periodically

[1] Enhancement, not replacement

NTP Nomination and Selection Process



ROC, Report on Carcinogens
NICEATM, NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
ICCVAM, Interagency Coordinating Committee on the Validation of Alternative Methods
CERHR, Center for the Evaluation of Risks to Human Reproduction

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21st Century Toxicology
NTP Leading the Way

- MULTI-AGENCY Participation at All Levels
- MULTI-TIERED Testing Program
- MECHANISTIC Linkage in All Tiers
- SCIENCE-BASED Priority Setting and Interpretation
- EFFICIENT Utilization of Resources

Developing the Best Science
to Achieve the Best Decisions

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