

NTP Research Concepts: Introduction

Scott Masten, PhD, DABT

Division of the National Toxicology Program
National Institute of Environmental Health Sciences

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NTP Research Concept

- A brief document outlining the NTP's current thinking regarding:
 - Rationale, approach, significance and expected outcome of a proposed research project
 - Data gaps, key issues, specific aims to address
- Proposed approach to address toxicological data needs for specific substance or issue
 - Does not contain specific details i.e. not a study design or protocol
 - Does not commit that the NTP will carry out the plan in its entirety
- Sufficient detail to understand scope, strategy and direction

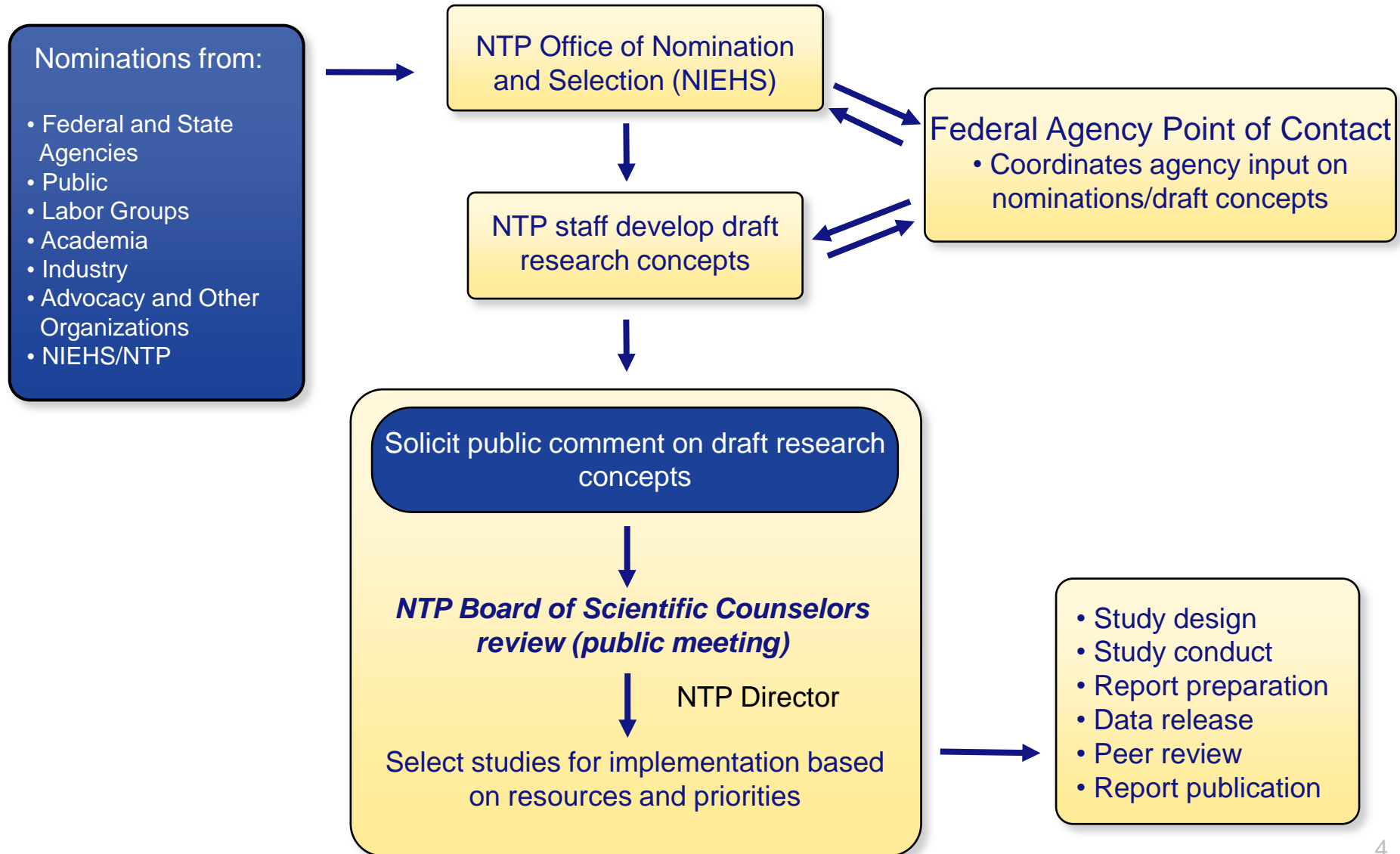


What Does the NTP Study?

- Individual or classes of chemical, biological, or physical substances with:
 - High public health concern based on the extent of human exposure and/or suspicion of toxicity
 - Substantial toxicological knowledge gaps
- Issue-based projects that:
 - Enhance the predictive ability of NTP toxicology studies
 - Address mechanisms of toxicity
 - Inform risk assessment approaches

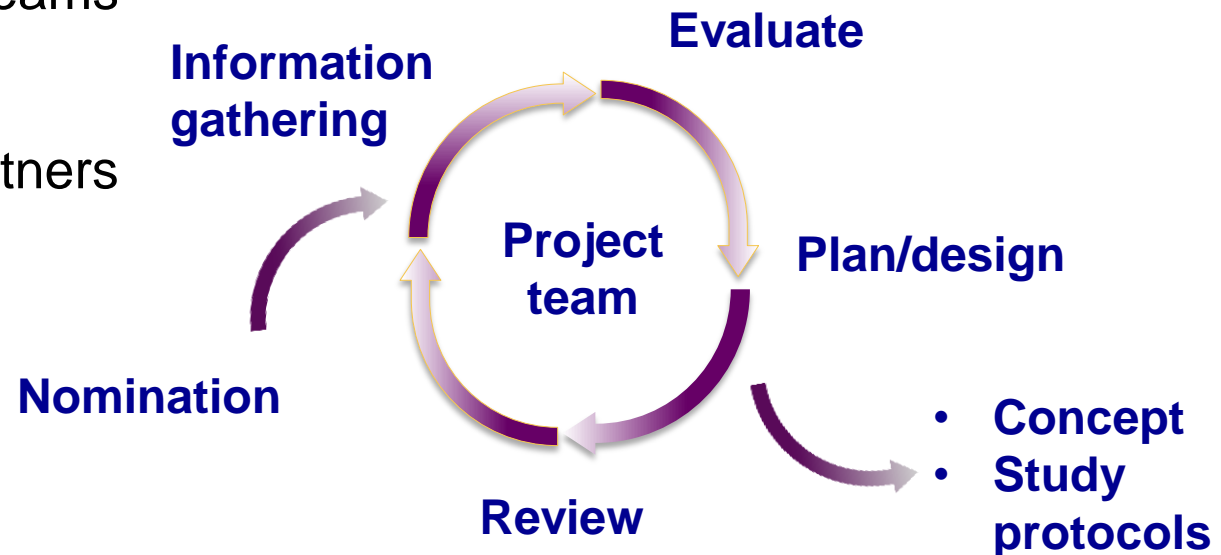


NTP Study Nomination Review Process



Development of NTP Research Projects

- Iterative approach to project development, study design, performance and interpretation
 - Phased programs with multiple review and decision points
- Scoping and problem formulation
 - Senior leadership review
 - Cross-disciplinary teams
 - Internal review
 - Engage agency partners



Approach and Strategy

- Each project is different
 - Complex questions
 - Fit within NTP research portfolio
 - Leverage other ongoing efforts
- Cannot cover all hazard endpoints of interest for a class by conducting conventional toxicology studies
 - Current limitations in Tox21 and other alternative approaches
 - *A priori* selections of individual high priority compounds for in-depth evaluation
 - Short-term studies to prioritize (many to few) for further study
- Use best tools available to address outstanding questions
 - Assemble a workable testing framework
 - Maintain flexibility for periodic adjustments



Improving confidence in toxicological profiling

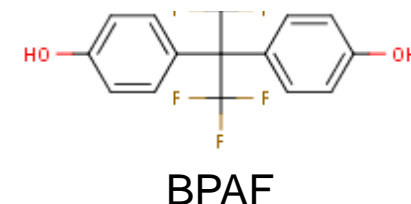
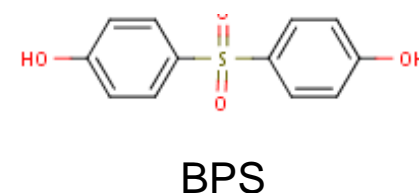
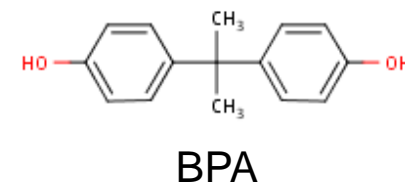
- *Read-across* endpoint information for one chemical to predict the same endpoint for another chemical, which is considered to be *similar* in some way
- Strategy for hazard assessment and data gap filling
- Can also be used to drive testing priorities
- Chemical structural vs biological similarity

	Chemical 1	Chemical 2	Chemical 3	Chemical 4	
Structure	xxxxxxxxx	xxxxxxxxx	xxxxxxxxx	xxxxxxxxx	
Property 1	●	→	○	○	
Property 2	●	→	○	←	●
Property 3	○	←	●	→	○
Activity 1	●	→	○	○	
Activity 2	●	→	○	←	●
Activity 3	○	←	●	→	○

● Existing data point ○ Missing data point

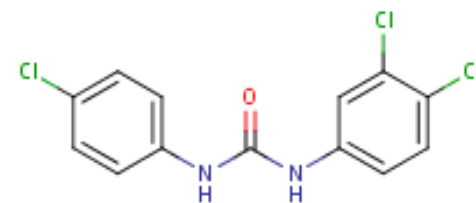
Bisphenol S and Derivatives

- Shift from BPA to BPS in certain applications
 - EPA Design for the Environment assessment of BPA alternatives in thermal paper
- Available hazard data insufficient to evaluate safety
- Multi-year NIEHS/NTP effort on bisphenols
 - CLARITY-BPA program
 - Bisphenol AF research concept 2009
 - Toxicological profiling of 30+ analogs and derivatives
 - Literature + computational analysis
- EPA Office of Children's Health Protection nomination 2014

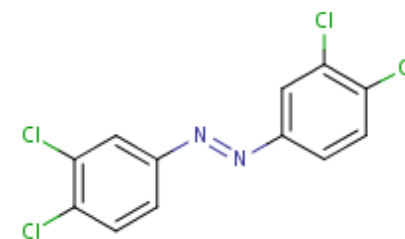
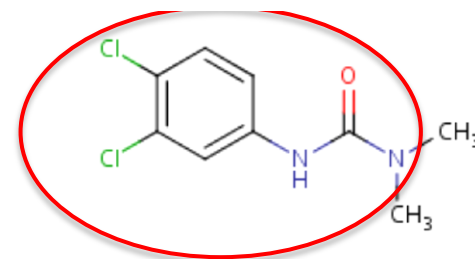
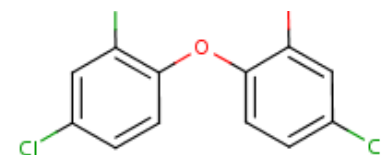


Triclocarban

- Widespread use and exposure through consumer products
- Structurally related to phenylurea herbicides
- Similar function as triclosan
 - Concept review 2008
 - Triclosan NCTR research program
- Hazard signals from traditional toxicology data
 - Not publicly available or complete
- Endocrine activity reported in literature and Tox21 needs further investigation
- FDA Proposed Rule Dec 2013 (78FR76444)
 - Additional data needed to demonstrate safety and effectiveness



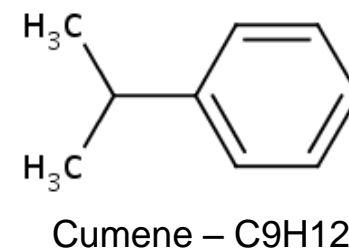
Triclocarban



TCAB

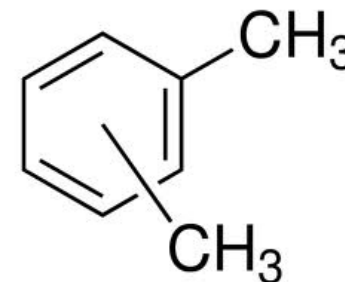
C9 Alkylbenzenes

- Presumed ubiquitous occurrence in ambient environment
 - Occur together with other similar compounds e.g. BTEX
 - Most C9s not routinely measured
- Interest in C9s triggered by cumene findings
 - TR-542 (2009) - clear evidence of carcinogenicity
- Insufficient data to support cancer and non-cancer health assessments across the class
- For certain occupational or consumer exposure scenarios, data on the mixture may be the most relevant
- To understand hazard in relation to all scenarios, need data on individual compounds or perhaps isomeric mixtures
 - When can isomers be grouped together for testing and/or assessment



Xylenes

- C8 alkylbenzenes with very high production volume and use
- Monitored and regulated as a group
- Multiple nominations to NTP over the years
- NTP TR-327 (gavage) - no evidence of carcinogenicity
- Numerous data gaps and needs
 - ATSDR Priority Data Needs
 - EPA Voluntary Children's Chemical Evaluation Program (VCCEP)
 - Inadequate data to evaluate cancer hazard
- Value of reducing uncertainty due to gaps in hazard space



NTP Research and Testing Framework

Candidate substances and issues for study

- Regulatory data needs
- Exposures of public concern

Testing priorities

Agent-specific testing

- Traditional toxicology studies
- Mechanistic studies
- Alternative model systems

Integration for public health decision-making

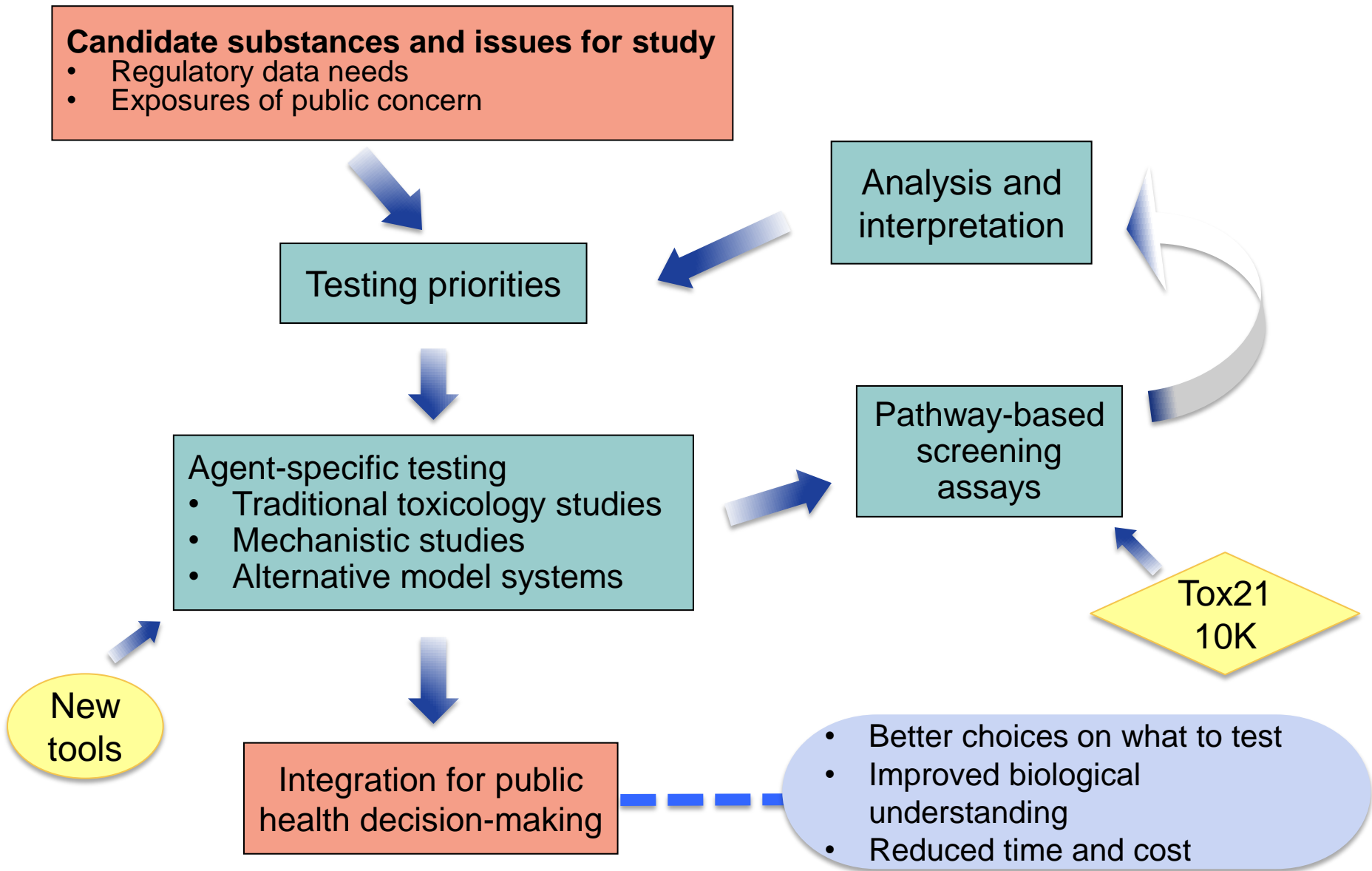
Analysis and interpretation

Pathway-based screening assays

Tox21
10K

New tools

- Better choices on what to test
- Improved biological understanding
- Reduced time and cost



Today's Session

- Review and comment on research concept and determine whether the proposed research project is an appropriate use of NTP testing program resources
- Public comments
- Presentations by project leaders
 - Bisphenol S - Dr. Vicki Sutherland
 - Triclocarban - Dr. Vicki Sutherland
 - Alkybenzenes - Dr. Brian Sayers
 - Xylenes - Dr. Matt Stout
- Clarifying questions
- Comments from assigned Board reviewers
- Board discussion

Specific Review Questions

- Comment on the merit of the proposed project relative to the mission and goals of the NTP. *The NTP's stated goals are to: Provide information on potentially hazardous substances to all stakeholders; Develop and validate improved testing methods; Strengthen the science base in toxicology; Coordinate toxicology testing programs across DHHS (<http://ntp.niehs.nih.gov/go/about>).*
- Comment on the clarity and validity of the rationale for the proposed project. Has the scope of the topic been adequately defined? Are the relevant knowledge gaps identified and clearly articulated?
- Comment on the strategy and approach proposed to meet the stated objectives of the project. Are specific aims reasonable and clearly articulated? Is the scope of work proposed appropriate relative to the public health importance of the issue(s) under consideration? If not, what modifications do you recommend? Where steps to further refine the strategy and/or approach are proposed, are they appropriate?

Specific Review Questions (2)

- There are challenges inherent to achieving the aims of any proposed project. Are the relevant challenges and/or key scientific issues identified and clearly articulated? Where approaches to overcome challenges are proposed, are they appropriate? Are you aware of other scientific issues that need to be considered?
- Rate the overall significance and public health impact of this project as low, moderate, or high. Identify any elements of the proposed project that you feel are more important than others, and/or that have a higher likelihood of success at meeting pre-defined specific aims.
- Provide any other comments you feel NTP staff should consider in developing this project.

Questions and Comments