

NIEHS Committee for Development of the NTP Vision

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TABLE OF CONTENTS

Introduction	4-6
Goals and specific aims for implementing the NTP vision.....	7-8
Research Goal 1: Develop a scientific rationale for the generation, analysis, and integration of data from emerging technologies into the characterization of environmental health effects.....	9-15
Summary of major recommendations.....	16
Research Goal 2: Identify and quantify indicators of exposure, disease, and susceptibility from animal toxicity studies that can be linked to clinical and epidemiological investigations	17-22
Summary of major recommendations.....	22
Process Goal 1: Increase the number and relevance of agents, issues, and concepts selected for toxicological evaluation by the NTP..	23-27
Summary of major recommendations.....	27-28
Process Goal 2: Develop procedures to further evaluate and characterize toxicological effects observed in the testing program and to address toxicological data needs identified by the NTP centers (CERHR, NICEATM) and the Report on Carcinogens (RoC) ...	29-31
Summary of major recommendations.....	31-32
Process Goal 3: Ensure that different types of data pertaining to a given agent or concept are fully integrated such that the best possible value can be gleaned from the information.....	33-35
Summary of major recommendations.....	35
Process Goal 4: Increase the breadth of scientific expertise in newly identified priority areas to facilitate the transfer of new technologies and methodologies to the NTP while maintaining sufficient depth in current programs.....	36-39
Summary of major recommendations.....	39
Process Goal 5: Promote synergy between the NTP and the Division of Extramural Research and Training (DERT) in areas of shared scientific interest.....	40-41
Summary of major recommendations.....	41
Communication and Translation Goal 1: Strengthen public health outreach and education about the scientific value of NTP products and services	42-45

Summary of major recommendations.....	45
Proposed NTP Organizational Chart.....	46-48

Introduction

The vision of the National Toxicology Program (NTP) aims 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.” However, before addressing the NIEHS Committee’s recommendations for implementing a NTP vision for the future, it is useful to reflect on the value and utility of NTP data in public health decision making. Pursuing the NTP vision must preserve the value of the Program in providing information critical for environmental and occupational disease prevention strategies.

During its 25+ years of existence, the NTP has been recognized world wide as the premier source of reliable data for the identification of occupational and environmental carcinogens and evaluations of human risk. The cancer bioassay program, which originated at NCI, was developed as a screen for chemical carcinogens. Because results from cancer bioassays have been used also to estimate risks of human cancer and chronic toxicity, the NTP extended the standard bioassay to a 3 dose plus control study, standardized the bioassay based on statistical considerations, enhanced the analytical chemistry evaluations, implemented improved animal hygiene requirements, provided more thorough assessments of chronic toxicity, and implemented Good Laboratory Practice into the toxicity/carcinogenicity testing program. In addition, other endpoints (e.g., hematology, clinical chemistry, sperm morphology/vaginal cytology, and micronuclei) and related studies (chemical disposition, toxicokinetic modeling, lung function) were implemented to provide greater insights and characterization of the toxicity and carcinogenicity of the agent under study. For some chemicals, toxicity studies were expanded to compare dose-response relationships between toxicity and putative mechanistic events (e.g., cell proliferation, enzyme induction, hormonal changes, alpha-2u globulin accumulation), and carcinogenicity studies included evaluations of mutations and altered expression of oncogenes and tumor suppressor genes in tumor tissues. The NTP has repeatedly examined the utility of alternative models to screen and prioritize agents for study and to reduce the number of animals and the time required to conduct hazard identification studies. Research and testing programs were also developed in immunotoxicity, neurotoxicity, genetic toxicity and reproductive and developmental toxicity. Although the main focus of the Program has been on generating toxicology and carcinogenicity data on agents of public health concern, the NTP also develops and evaluates alternative methods of determining environmental hazards and provides evaluative reviews of toxicity data to identify which agents in the general environment or workplace are most likely to pose cancer or reproductive health risks. To maintain this key role in the protection of public health, the NTP must ensure that data generated under the new vision will be as useful or more so than the current data used for health policy decisions.

With the rapid increase in knowledge of the cellular and molecular bases of disease processes, technological advances in methodologies for biological and chemical analyses, and expansion of computer based computational tools, studies of environmental interactions with complex biological systems can be performed at a level not imagined when NTP was created. Hence, it seems opportune to examine how these scientific

developments might affect the functions of the NTP. Although the NTP plays a vital role in providing comprehensive data and expert evaluations of environmental hazards relevant to health decisions for disease prevention, it is always worthwhile for a program of this nature to reevaluate periodically its approaches to environmental health research and its contributions to public health. Such an exercise might reveal ways the Program can do an even better job in advancing research programs for improved characterizations of environmental health risks. Because of uncertainties in the risk assessment process, arguments arise as to whether exposure standards established by regulatory agencies are adequately health protective or overly stringent. For example, many risk assessments involve low-dose extrapolations of effects induced in animals to potential effects in exposed humans. Because of limited information, low dose extrapolations from animals to humans have generally relied on default assumptions that are public health protective. Typically this involves converting an animal dose to a human equivalent dose, and either assuming that humans and animals are equally sensitive at equivalent doses or applying a trans-species extrapolation factor to the no- or lowest-observed effect level. Future environmental health research aimed at characterizing factors that contribute to disease causation may enable scientific data and mechanism-based predictive models to be used to address species extrapolations and account for interindividual differences in susceptibility. Also, it has long been recognized that NTP cannot adequately address the potential toxicity of all agents and mixtures that are present in our environment from commercial use or as unintended byproducts of other reactions (e.g., combustion, water disinfection, etc.). Thus, key features of the NIEHS Committee's recommendations focus on:

- 1) enhancing the rate at which the program generates useful data to characterize the toxicological effects of environmental agents of concern, classes of chemicals, and mixed exposures,
- 2) strengthening the scientific basis for estimating and characterizing human risks including occupational and environmental risks in diverse or susceptible subpopulations,
- 3) providing insightful toxicological information that can be linked to clinical and epidemiology studies, and
- 4) communicating NTP findings and their utility to the public health community, health policy decision-makers, and the general public.

The development and evaluation of mechanism based predictions of exposure-related adverse effects that integrate all available information about the biological behavior of an agent (i.e., biologically based dose-response models) will require extensive confirmation from empirical data sets, i.e., experimental validation of predictions of dose-related effects of families of chemicals or agents that act by similar mechanisms. In time predictive models that are based on greater understanding and characterization of tissue dosimetry, mechanistic interactions of environmental agents with biological systems, and linkages between cellular and molecular perturbations and disease outcome in animals and humans should be as reliable or more reliable than current rodent models are for assessing human disease risk from exposure to environmental agents. The NTP vision is designed to move the field of toxicology from an observational mode to a biologically based predictive mode. To accomplish this goal, several functional and structural changes

at the Program and Institutional levels are recommended. However, for the NTP Vision to be successful it is important that the roadmap be articulated clearly to the stakeholders so that all invested parties can work together to move the Vision forward.

Goals and specific aims for implementing the NTP vision

The major scientific goal of the NTP is to provide, either through original research or through the assembly and analysis of research done outside the program, the scientific underpinnings upon which decisions protective of public health are made about risks from exposure to environmental agents. The recommendations of the NIEHS Committee are organized into the separate but overlapping themes of research, process, and communication and translation.

The **Research** goals and their specific aims are as follows:

1. Develop a scientific rationale for the generation, analysis, and integration of data from emerging technologies into the characterization of environmental health effects.
 - a. Optimize current NTP efforts
 - b. Develop and apply new and better methods for screening chemical agents and prioritizing them for further study
 - c. Explore and integrate additional methods and technologies to generate mechanistic data to be used for the prediction of human health risk
2. Identify and quantify indicators of exposure, disease, and susceptibility from animal toxicity studies that can be linked to clinical and epidemiological investigations.
 - a. Characterize quantitative relationships between exposure and tissue dosimetry (PBPK modeling)
 - b. Characterize temporal relationships between molecular and morphological changes that occur in disease pathways
 - c. Identify indicators of exposure, physiological response, and disease pathogenesis
 - d. Provide increased analysis and interpretation of quantitative dose-response data generated in NTP toxicity and carcinogenicity studies
 - e. Obtain human physiological, biochemical, and genetic parameters to assist in the development of human risk assessment models

The **Process** goals and their specific aims are as follows:

1. Increase the number and relevance of agents, issues, and concepts selected for toxicological evaluation by the NTP.
 - a. Identify new and additional priority areas for toxicological evaluation by the NTP
 - b. Improve the internal (NIEHS) nomination process by strengthening the role of the Nomination Faculty and/or expanding the Office of Nominations
 - c. Improve the external nomination process by stimulating nominations from external sources, e.g., state government agencies, interest/advocacy groups, and poison control centers, to identify timely and relevant agents for study
 - d. Reassess the role of the Interagency Committee for Chemical Evaluation and Coordination (ICCEC)

2. Develop procedures to further evaluate and characterize toxicological effects observed in the testing program and to address toxicological data needs identified by the NTP centers (CERHR, NICEATM) and the Report on Carcinogens (RoC).
 - a. Identify data gaps, research needs, and areas for further research in NTP studies and articulate them in NTP documents and publications including technical reports, background documents for nominations to the Report on Carcinogens, CERHR expert panel reports and monographs, and the ICCVAM test method guidelines
 - b. Develop and implement mechanisms for prioritizing, pursuing, and tracking identified research needs
3. Ensure that different types of data pertaining to a given agent or concept are fully integrated such that the best possible value can be gleaned from the information.
4. Increase the breadth of scientific expertise in newly identified priority areas to facilitate the transfer of new technologies and methodologies to the NTP while maintaining sufficient depth in current programs.
5. Promote synergy between the NTP and the Division of Extramural Research and Training (DERT) in areas of shared scientific interest.
 - a. Establish a forum for information exchange between NTP scientists and DERT program administrators
 - b. Establish a process to promote DERT initiatives that address data needs identified in NTP studies and utilize NTP resources to advance environmental health science

The **Communication and Translation** goal is as follows:

1. Strengthen public health outreach and education about the scientific value of NTP products and services.
 - a. Identify and review existing documents on indicators of use of NTP products and ongoing outreach and education efforts
 - b. Develop a communication strategy and network for ongoing outreach and education targeting a broad audience of stakeholders

Research Goal 1:

Develop a scientific rationale for the generation, analysis, and integration of data from emerging technologies into the characterization of environmental health effects.

The research goals addressed here have been divided into three sections: 1) Optimize current NTP efforts; 2) Develop and apply new and better methods for screening chemical agents and prioritizing them for further study; and 3) Explore and integrate additional methods and technologies to generate mechanistic data to be used for the prediction of human health risk.

Part 1: Optimize current NTP efforts.

As an initial and readily achievable step in providing the highest quality data in support of regulatory decision-making, the NTP needs to optimize its current research efforts. The NTP should carefully examine the ongoing approaches within the NTP with the goal of ensuring that the assays used are the best available and that the maximum amount of relevant information is being gained to predict human risk. Questions that need to be addressed to help NTP best integrate and utilize testing strategies include:

- i. In regard to carcinogenicity evaluation:
 1. Is the current 2-year rodent bioassay approach to carcinogenicity evaluation optimized given the need to predict a range of risks, over a range of concentrations, in a rapid fashion and for a large number of compounds or mixtures?
 2. Do the 2-year rodent bioassay studies provide sufficient examination of mechanisms of toxicity and can modifications in the assay be made to provide more information on different potential mechanisms?
 3. To what extent could the use of genetically altered animal models enhance the bioassay, are these models available or do they need to be developed?
 4. Are some endpoints incompletely addressed with conventional models and should specific models be developed, e.g., breast cancer, prostate cancer?

- ii. In regard to non-cancer endpoints:
 1. Do the current models for assessing non-carcinogenic toxicity (i.e., developmental, immunological, neurological) allow strong conclusions to be drawn and are they being exploited fully?
 2. Are there additional toxicity endpoints, such as cardiovascular toxicity or other organ system evaluations, which should be added to the current assays?
 3. To what extent can and should physiological endpoints be used as surrogates for or supplements to assessments of toxicity (e.g., organ functional measures)?
 4. Do current models allow mechanistic hypotheses to be proposed? Are these hypotheses being tested and checked for predictive value?

- iii. In regard to exposure regimens:
 - 1. Are there sources of information not being used to help select the doses that are tested?
 - 2. What assumptions are being made in the selection of doses relative to human exposures? Can these assumptions be tested? Can improved mechanistic information be included or obtained to help reduce the number of assumptions in risk assessment models?
 - 3. Is the exposure regimen of the assay optimal with regards to animal age, frequency of dosing, duration of exposure, and follow-up?
 - 4. Is there a benefit to acquiring additional data throughout the exposure regimen to provide early indicators of toxic effects?

- iv. In regard to currently used mechanistic studies:
 - 1. Are high throughput ‘global’ assays such as microarray gene expression, proteomics, and metabolomics providing useful information for characterizing environmental health effects?
 - 2. Are ancillary approaches to pathological assessment such as immunohistochemistry, confocal or electron microscopy, and imaging being used appropriately and are they providing useful information?
 - 3. What is the biological/toxicological significance of the extensive tumor mutation data and molecular epidemiology data accumulated so far?

A. Strategy and approach:

Workshops should be held on the adequacy of NTP 2-year bioassay to predict cancer and non-cancer risks in humans; the usefulness of other NTP assays to predict non-cancer effects; and the usefulness of NTP mechanistic studies to better characterize environmental health effects. After these workshops, panels of scientific experts should convene from within and outside the NTP to review and evaluate the status and make recommendations on how to proceed. They should also include in their review the use of currently available data and techniques that will complement the conventional bioassays and provide enhanced mechanistic insight.

B. Measures of accomplishment:

The first measure will be to have in hand the reports of various workshops or review boards with analyses of the current state of the assay and which, if any, modifications should be made. The next milestone should be the incorporation of new protocols into the testing contracts issued by NTP. A third measure will be the report of data from the newest set of toxicological assays, with an emphasis on how any incorporated changes are providing significant additional or different data which impacts the decision making process.

C. Feasibility of achieving specific aims:

Reviews of the NTP testing strategies have been performed in the past, and appropriate modifications have been made. An expanded version of such reviews should be

achievable, though the accumulation and organization of the huge amount of relevant data will require careful forethought and possibly the development of improved data management strategies.

D. Relevance to the NTP mission and public health:

The 2-year bioassay and other NTP toxicity evaluations have been crucial tools for providing data for decisions made by the public and regulatory communities. Frequent and thorough evaluations of these assays and possible modifications, relevant to both cancer and non-cancer endpoints, based on quality science are essential. Health policy decision makers need to be able to rely on the NTP to update testing strategies as required to provide the best information possible, and a careful review of the bioassay is a necessary component of the program.

E. Timeline for implementation:

The evaluation of the current assays should proceed immediately with highest priority, as many decisions regarding the implementation of new strategies will depend on the status of the current program. Workshops should be developed in the earliest stages of the roadmap and should be held within the first 18 months of the plan. Adjustments in the study designs should immediately follow the workshops to begin to build confidence in alternate designs. Development of key databases should be accomplished during and shortly after the process of workshop-based analysis, based on recommendations of the participants. Modification of current assays and incorporation of additional methods should occur 3 - 5 years after completion of the reviews. Additional time will be necessary to evaluate the utility of these modifications.

Part 2. Develop and apply new and better methods for screening chemical agents and prioritizing them for further study.

The NTP should continue to focus its efforts on providing toxicological evaluations for as many chemical agents and combinations of agents as can be achieved with currently available and emerging technologies. To help meet this challenge, the NTP should increase the number of agents that are evaluated by implementing higher-throughput computational and experimental methods to augment and improve the predictive ability and relevancy of traditional toxicological methods. Since the entire universe of chemical agents cannot be evaluated for potential toxicological effects in any reasonable time frame, approaches must continually be refined to screen and prioritize chemicals so that limited resources are used for evaluating those agents with the highest suspicion of hazard. These methods could routinely be applied as preliminary toxicological screens for evaluating the need for further in-depth toxicological studies. For the vast majority of chemical agents, little or no hazard information is available, and the NTP should continue to play a leading role in developing this information. The NTP has the necessary expertise, resources, and demonstrated competence to undertake this endeavor. The NTP should develop clear strategies for prioritization using mechanistic information obtained on individual agents that can be applied to common classes of compounds.

A. Strategy and approach:

i. Challenges

There are potentially a number of roadblocks and challenges that the NTP will face in implementing a new approach to screening substances for further testing. One of the foremost challenges will be the amount of resources that can be allocated to this aim. This will depend on whether or not new resources will be added to the program. If the current level of resources remains static, a prioritization plan will need to be implemented to determine how resources will be distributed. The utility of the tests for screening and prioritization will have to be demonstrated to regulatory agencies and the public.

ii. Path forward:

a. Short-term activities/actions:

An inventory of potentially useful test methods should be undertaken through examination of the scientific literature, holding of public workshops and public solicitation of new methods. A broad range of available and promising *in vitro* and *in vivo* short-term toxicological test systems (e.g., *C. elegans*) designed to measure cellular responses (e.g., cytotoxicity, receptor binding, activation/disruption of signal transduction pathways, enzyme induction/inhibition, cellular transport, cell cycle disruption, changes in cellular ultrastructure, genetic damage, macromolecular adducts, and gene, protein, and metabolic expression profiling) should be considered. Potential tests should be prioritized based on their association with postulated mechanisms of toxicity and feasibility for cross-laboratory repeatability and incorporation into a high-throughput screening mode. The highest priority test systems should then be selected for formal validation.

An inventory of potentially useful available SAR/QSAR prediction modeling tools should be undertaken, considering whether any single or combination of available tools will meet the NTP's needs. Toxicological endpoints for which SAR/QSAR prediction software is currently available include skin sensitization, dermal absorption, estrogen receptor binding, mutagenicity, and carcinogenicity.

b. Long-term activities/actions:

Building on the knowledge gained from ii.a. above, a "core" set of specific toxicological responses associated with postulated mechanisms of toxicity should be identified. A panel of short-term test systems designed to evaluate this "core" set of specific toxicological responses should be developed and used in a tiered approach for screening/prioritization of chemical agents for more in-depth studies. Such a panel of test systems could assess both fundamental toxicological perturbations (e.g., cell cycle disruption) and toxicological perturbations on a functional systems level (e.g., endocrine disruptor screening panel).

SAR/QSAR predictions should take an ever increasing role in selecting substances for toxicological evaluations and in designing the most appropriate short-term and in-depth studies to be undertaken as part of the NTP's toxicological evaluations.

The NTP must establish a mechanism and suitable process for reporting results of toxicological evaluations that utilize only SAR/QSAR analysis and short-term test methods.

iii. Future approaches:

The NTP should continue to monitor and evaluate, and implement as necessary, promising novel short-term test systems. The NTP should move from the “passive” approach of identifying new test methods to actively supporting the development of such test methods through interactions with NIEHS/DERT and NIEHS/DIR. Every attempt should be made to work with the broader scientific community to identify a minimal set of toxicological test methods that would be useful for screening and prioritizing chemical agents.

B. Measures of accomplishment:

One measure of accomplishment is the development of criteria for prioritization. The NTP should add new toxicological screening methods to those presently being used so that more substances can be evaluated more rapidly. The number of substances considered for evaluation and the number of test methods/systems validated and utilized in toxicological evaluations should increase significantly within 5 years. The data, which should be widely accessible in electronic format, must be useful to the scientific and regulatory community.

C. Feasibility of achieving specific aims:

Since the risk of achieving the specific aims is low and the reward that will be gleaned from accomplishing these aims is high, it is important that the requisite resources be directed to fulfilling this aim. Screening assays can provide valuable information for preliminary hazard identification; however, further evaluations may be necessary to identify target organs and address dose-response, life-stage susceptibility, genetic factors, etc. All available and emerging technologies, particularly new methods, should be evaluated for potential utilization.

D. Relevance to the NTP mission and public health:

Accomplishment of this aim will provide meaningful data for preliminary hazard identification of chemicals to which humans are exposed and selection of high priority compounds for further toxicological evaluation.

E. Timeline for implementation:

In 5 – 10 years, the NTP should be routinely using screening panels of rapid assays to prioritize chemicals for evaluations of multiple endpoints. Within the first two years, the NTP should identify, evaluate, and rank according to their utility, new high throughput testing methods that can be used to screen agents. During the subsequent three years, these test methods must be validated and by the end of five years the most promising test methods should be incorporated into the NTP’s testing program.

Part 3. Explore and integrate additional methods and technologies to generate mechanistic data to be used for the prediction of human health risk.

Specific Aims:

- i. A major focus of NTP efforts should be to evaluate existing and newly emerging methods and technologies for their utility in the hazard assessment process. These approaches should be integrated into testing paradigms as appropriate. Examples of these are genomic analysis and proteomic techniques to examine global changes in gene and protein expression and activity.
- ii. Specific efforts should be directed toward the development of alternative models that may reduce the number of animals used in the safety assessment process. Transgenic and knockout animal models should be considered.
- iii. Emphasis should be placed on the integration of methods that provide both hazard identification and a mechanistic understanding of the biological responses in the organism, and on the development of alternative models.
- iv. Development of mechanistically based assays (*in vitro* and short term *in vivo* assays) that provide information on dose-response will be important for the creation of high-throughput screening panels. Although cancer is a major interest, efforts should specifically include the identification of testing methods with utility in non-cancer endpoints. Furthermore, the NTP should develop clear strategies for the prioritization of compounds and the analyses of data derived from high throughput techniques.
- v. Imaging techniques, and in particular those amenable to *in vivo* studies, such as PET, MRI, or CT should be evaluated and incorporated where practical.
- vi. The NTP should ensure that close partnerships with other agencies are developed and nurtured in the process of validating new methods and in defining critical pathways of toxicity that need to be evaluated. Validation must include both scientific validity of new techniques and risk assessment validation, which must involve the establishment of criteria for acceptable predictive value of new methods.

A. Strategy and approach:

It will be necessary to convene groups of individuals with experience in both target systems/tissue toxicity and specific techniques to evaluate current methodologies, evaluate potential applications of new techniques, and establish endpoints appropriate for inclusion as mechanistic based screens. In some instances the techniques may be appropriate for multiple target tissues, but it is anticipated that many will be unique. These teams may be led by NTP scientists, but should also include experts from within the NIH intramural research community and from outside of the NIH. Financial support must be provided for assessment of novel techniques with a group of known test articles and for the subsequent evaluation of the predictive value of the specific method or panel of tests. Interactions with NIEHS/DERT and NIEHS/DIR as well as the broader scientific community are needed to identify informative toxicological test methods that will yield data of value to the NTP and its stakeholders. Furthermore, the NTP should develop mechanisms for encouraging follow-up and feedback from DIR/DERT scientists, perhaps

through funding of cooperative research, postdoctoral trainees, and publicizing data needs (see Process Goals 4 and 5).

B. Measures of accomplishment:

The most significant measure of accomplishment will be an examination of how testing strategies evolve over the next 10 years. As screening panels are developed that allow for more rapid detection of hazardous agents, the number of chemicals and rate at which they can be screened and evaluated for potential toxicity should increase. Furthermore, confidence in using new strategies as rapid screens should increase. The integration of novel methods will involve validation of individual assays as well as screening panels, and the number of chemicals evaluated as part of this validation will also be an indicator of success in this area.

C. Feasibility of achieving specific aims:

As our understanding of biological processes expands, it should be possible to develop mechanistically based tests that can be used to evaluate risk in a rapid, high-throughput fashion, e.g., by incorporating these data into validated biologically based dose-response models that predict disease outcome (see Research Goal 2, specific aim 3). Although the molecular and cellular events in disease processes are complex, the number of potential mechanisms by which agents bring about adverse effects may decrease as we learn to recognize critical common toxicological pathways (e.g., alterations in cell signaling, induction or inhibition of apoptosis, altered DNA repair, disruption of the cell cycle, etc.). It is possible that a small panel of tests could be designed to address a majority of these mechanisms. Though these tests may not immediately replace the current standard assays in toxicology testing, they should shorten the process from nomination to decision. The NTP should provide guidance to the regulatory community and the public on the usefulness of the new test methods and how the generated data can be used in a risk assessment framework.

D. Relevance to the NTP mission and public health:

These efforts should enable the NTP to more successfully and efficiently meet its goals of providing sound scientific information to serve as the basis for risk assessment and regulatory activities. To maintain this key role, the NTP must ensure that data generated with these new methods and technologies will be as useful or more so than the current data that are used for health policy decisions.

E. Timeline for implementation:

Within the next two years, the NTP should identify high priority endpoints and begin to evaluate promising new and established techniques that could be used as mechanism-based screens for toxicological evaluation or to provide additional information in the hazard identification process. At the same time, databases with information on toxicological effects should be established for use in the selection of positive and negative controls to verify the predictive value of these tests. By the end of the fifth year, at least 2 screening panels should be established, one that addresses mechanisms of carcinogenesis and one that addresses non-cancer endpoints.

Summary of major recommendations:

1. Examine current NTP approaches to ensure that the best assays are used and the maximum amount of relevant information is being gained from NTP studies
2. Identify, evaluate, and implement high-throughput computational and experimental methods to screen and prioritize substances for further testing
3. Develop a panel of short-term test systems designed to evaluate a “core” set of specific toxicological responses associated with postulated mechanisms of toxicity
4. Establish a mechanism for reporting results of toxicological evaluations that utilize SAR/QSAR analysis and short-term test methods
5. Actively support the development of short-term test methods
6. Develop alternative models that may reduce the number of animals used in the safety assessment process
7. Integrate methods that provide mechanistic data for use in risk assessment
8. Evaluate and incorporate imaging techniques
9. Establish criteria for acceptable predictive value of new methods

Research Goal 2:
Identify and quantify indicators of exposure, disease, and susceptibility from animal toxicity studies that can be linked to clinical and epidemiological investigations.

This goal can be achieved through research that quantitatively links exposure metrics with intermediate events in disease pathogenesis and through research that provides a better understanding of the processes involved in the development of rodent diseases caused by environmental agents and their relationship to early human disease indicators.

To accomplish this goal, the following specific aims were identified:

1. Characterize quantitative relationships between exposure and tissue dosimetry (PBPK modeling)
2. Characterize temporal relationships between molecular and morphological changes that occur in disease pathways
3. Identify indicators of exposure, physiological response, and disease pathogenesis
4. Provide increased analysis and interpretation of quantitative dose-response data generated in NTP toxicity and carcinogenicity studies
5. Obtain human physiological, biochemical, and genetic parameters to assist in the development of human risk assessment models

Specific Aim 1: Characterize quantitative relationships between exposure and tissue dosimetry (PBPK modeling)

A. Strategy and approach:

The NTP should establish and obtain at least a minimal toxicokinetic data set, specifically absorption and elimination kinetics of the parent compound, for all agents selected by the program for study prior to the initiation of any *in vivo* toxicity studies. These data are critical for the design and interpretation of toxicity and mechanistic studies. Once minimal data requirements are established for all agents, this effort can be expanded to develop experimental and computational approaches for the estimation and validation of ADME parameters (absorption, distribution, metabolism, and elimination) for classes of compounds or the effects of other agents on these parameters. The NTP should develop and validate PBPK models for specific agents of concern (toxic agents with documented human exposure) to characterize the time-dependent target tissue concentration of putative toxicant(s). This specific goal can best be accomplished by establishing multidisciplinary teams, which at a minimum would include a toxicologist, chemist, modeler, and statistician, for each agent under consideration to identify data needs, define the appropriate model structure, and facilitate generation of data and the validation and utilization of the model. Since it is not feasible to develop PBPK models for all agents under study, it will be necessary to establish criteria to prioritize the agents for which a model will be developed. For example, high priority should be given to toxicants for which there are measurable human exposure; for such agents a validated PBPK model would be useful in characterizing human dosimetry. The development of submodel libraries (e.g., *in utero*, perinatal, lactational, GI absorption, permeation of the blood-brain barrier) would facilitate the PBPK modeling effort. A dedicated multidisciplinary

pharmacokinetic modeling core should be established within TOB to increase expertise and in-house capacity in dosimetry modeling and to coordinate the modeling efforts of the NTP. This group would be comprised of modelers, analytical chemists, and statisticians, whose role would be to assist with study design, generate and model data, and validate PBPK models that are developed on NTP agents of concern. The primary function of the TK modeling core would be to serve the needs of the NTP. Training programs and user-friendly tools should be developed to facilitate the utilization of models by NTP scientists and regulatory agencies.

B. Measures of accomplishment:

The most important measure of accomplishment is the increased utilization of PBPK models by NTP scientists and regulatory agencies. Well-developed dosimetry models should provide a greater understanding of the behavior of agents (including mixtures) of concern in animal models and provide an improved scientific basis for trans-species and route-to-route extrapolations. Increased utilization of computational modeling will be reflected in the increased frequency of incorporation of PBPK models into dose-response analyses in NTP Technical Reports and risk assessments.

C. Feasibility of achieving specific aims:

It should be feasible to obtain a minimum toxicokinetic data set for all agents selected for study. It is not feasible to develop PBPK models for all agents under study. Therefore, it will be necessary to establish criteria to prioritize those agents for which a PBPK model will be developed. Since computational modeling is an iterative process (typically involving data generation, preliminary model development, experimental testing of model predictions, model refinement, and experimental testing of new model predictions), it will also be important to establish criteria to determine when the modeling effort for a particular compound is deemed adequate.

D. Timeline for implementation:

Criteria for model development should be established immediately.

Specific Aim 2: Characterize temporal relationships between molecular and morphological changes that occur in disease pathways

A. Strategy and approach:

The temporal relationships between molecular and morphological changes that occur in disease pathways need to be characterized to understand disease pathogenesis. The NTP should utilize cellular and molecular techniques and resultant data to further demonstrate exposure-related effects and to predict disease outcome for related compounds. The morphologically based evaluation of tested chemicals needs to be extended to a combined evaluation that incorporates molecular endpoints that can be linked to putative mechanisms of action for toxicants. NTP study design teams should be encouraged to evaluate 90-day toxicity data and mechanistic information on the specific agent or related compounds to predict site-specific dose-response relationships, providing a rationale for the prediction, and specifying what additional information would have been helpful. These predictions should be based on all available information and include modeling of

quantitative relationships between early events and predicted endpoints of concern when possible. This activity will stimulate thinking in the Program on data needs to accurately predict chemically induced toxic and carcinogenic effects. Data from the subsequent 2-year study would then be used to evaluate the prediction. For the long-term, it will be essential that predictions be tested experimentally. However, with experience and the generation of mechanistic data that support predictive models, it may be possible that reliable predictions can be derived for agents that act by common pathways. To accomplish this aim, the NTP should support research investigating spontaneous and dose-dependent biological changes that occur during the pathogenesis of commonly observed rodent diseases, including neoplasia. For example, investigators could use “omic” technologies as an aid for molecular profiling (gene mutations, gene expression, and altered biological signaling) of temporal changes occurring in spontaneous and chemically induced lesions. To directly support this research, the NTP should increase the visibility and usability of the NTP tumor archive and establish a repository of tissue arrays for intramural, extramural, and external use. As data become available, the NTP should develop and validate computational models that link temporal molecular changes to disease outcome.

B. Measures of accomplishment:

One quantifiable measure of accomplishment is increased use of the NTP tumor archive and the tissue array repository to identify molecular and morphological changes in disease pathways. Increased incorporation of molecular data into NTP Technical Reports should complement morphological evaluations and provide data that can be linked to putative mechanisms of action for toxicants. Another measure would be an increase in the ability to predict toxic or carcinogenic agents (e.g., by CERHR or the RoC) with limited toxicity data based on strong predictive indicators (e.g., benzidine-based dyes, diazoaminobenzene). Predictions for the latter agents were based on their metabolism to known human carcinogens. Future predictions may be based on measurements of early events if time- and dose- dependent relationships between those events and the development of endpoints of concern are adequately characterized and validated.

C. Feasibility of achieving specific aims:

Although the NTP can provide tissue and additional tools for investigation, the feasibility of this specific aim depends on the commitment and cooperation of intramural, extramural, and external researchers. These interactions should be encouraged to the fullest extent possible. One approach would be to develop a NTP postdoctoral program that would place young scientists in DIR labs to characterize dose-dependent changes in early events involved in environmental disease processes (e.g., mutagenesis, DNA repair, altered signal transduction, oxidative stress, and altered gene expression). The generation of data to create models that link temporal molecular changes to disease outcomes will require input from multiple sources, including NTP, NIEHS-DIR, NIEHS-DERT, and other federal agencies that support biomedical research.

D. Timeline for implementation:

Some aspects of this aim can be implemented immediately (e.g., creating a tissue array repository, creating a laboratory-based NTP postdoctoral program); however, the linking of molecular changes to disease outcomes will require significant associations with research groups that investigate the impact of environmental stressors on disease processes.

Specific Aim 3: Identify indicators of exposure, physiological response, and disease pathogenesis

A. Strategy and approach:

Non-invasive indicators of exposure, physiological response, and disease pathogenesis need to be identified in rodent models to facilitate the linkage to human studies. The NTP should support pilot longitudinal studies to investigate if new serum and urinary indicators can be predictive of dose-related disease onset, outcome, pathogenesis, and/or susceptibility. When promising indicators are identified (see Specific Aim 4), the NTP should establish criteria for prospective utilization of these indicators in NTP studies and establish a repository of longitudinally collected samples from long-term studies, e.g., serum and urine. These samples should be provided to the intramural and extramural investigators for follow up studies.

The nature of NTP nominations is changing and expanding (e.g., drugs positive for QT interval prolongation, agents that cause thyroid hormone disruption). There is an increasing need to incorporate non-invasive technologies (e.g., imaging) and in-life endpoints (e.g., body temperature, auditory function, pulmonary function, cardiac function) into NTP studies for evaluating potential chemically induced adverse physiological effects. Non-invasive technologies (e.g., imaging) should be explored for their utility to identify early/preneoplastic lesions, to follow their progression to cancer with continued exposure, and to follow their possible progression or regression if exposure is stopped. The NTP needs to incorporate existing methods into the testing paradigms and establish these methods in the NTP contract laboratories. New methods should be developed and validated.

B. Measures of accomplishment:

Imaging technology should improve the ability of pathologists to detect small or multiple lesions in an intact animal and would allow better temporal characterization of disease events. The utilization of non-invasive indicators for characterization of disease processes should be apparent as a new addition in NTP Technical Reports. If any serum or urinary parameters were true indicators of exposure or response, they would be extremely valuable for the development and validation of biologically based pharmacokinetic and pharmacodynamic models that link exposure to disease outcome. The use of these data in model development should be evaluated.

C. Feasibility of achieving specific aims:

Several new methods and technologies that would be adequate to address these specific aims have been developed. Only through investment in this type of research will it be

possible to determine the feasibility of routinely incorporating these endpoints into toxicology studies.

D. Timeline for implementation:

The predictive value of selected indicators needs to be determined within a 5-10 year time frame.

Specific Aim 4: Provide increased analysis and interpretation of quantitative dose-response data generated in NTP toxicity and carcinogenicity studies

A. Strategy and approach:

The NTP should provide increased analysis and interpretation of data generated in NTP studies to help users of the data including the public better understand the relevance and utility of NTP findings. The NTP should conduct formal cancer dose response assessments and benchmark dose estimations on noncancer endpoints from subchronic and chronic studies. These analyses should include characterization of relationships between tissue dosimetry and time- and dose-dependent effects on early indicators, intermediate events, and disease endpoints to provide a quantitative context for evaluation of early markers. As described under Specific Aim 1, toxicokinetic data will be collected and dosimetry models will be created for all agents that undergo *in vivo* toxicity studies. Thus, the dose-response analyses should include alternative measures of dose (e.g., exposure, internalized dose, target tissue dosimetry). Specific Aims 2 and 3 address the need to collect additional information on tissue specific molecular alterations and non-invasive indicators of exposure and response. Dose-response analyses of these early and intermediate events in comparison to dose-response analyses of disease endpoints would be useful for testing the hypothesis that early markers can serve as statistical surrogates of low dose effects.

B. Measures of accomplishment:

Increased analysis and interpretation of NTP data should be incorporated into all NTP technical reports and publications.

C. Feasibility of achieving specific aims:

This aim is very feasible as the NTP already has the tools and resources to provide increased analysis and interpretation of data generated in NTP studies.

D. Timeline for implementation:

Dose-response analyses and interpretations should be provided for all studies immediately.

Specific Aim 5: Obtain human physiological, biochemical, and genetic parameters to assist in the development of human risk assessment models

A. Strategy and approach:

While the NTP does not conduct human risk assessments, the NTP should play a vital role in providing sound scientific data to regulatory agencies for this purpose. The NTP

should support research to obtain human physiological, biochemical, and genetic parameters to assist in the development of human risk assessment models. This research program should determine the range of human variability in metabolic activation or detoxication of agents selected by the NTP for study. The NTP should establish and utilize *in vitro* and short term *in vivo* models to evaluate the effects of human polymorphisms, differences in levels of enzyme expression, and the impact of overlapping substrate specificities among isozymes on the ADME of agents under study. Once pertinent data have been obtained, the NTP should develop human PBPK models for high priority agents. In addition, the NTP should support research to investigate human variability in genetic susceptibility. The NTP should explore the utility of obtaining time- and dose-dependent data on intermediate events from tissues with specific susceptibility genes knocked out or gene products partially inhibited or overexpressed (e.g., DNA repair genes, p53, receptors, regulators of the cell cycle) for evaluating differences in human susceptibility to disease response.

B. Measure of accomplishment:

NTP technical reports should begin to provide characterizations of animal dosimetry and response in comparison to predicted dosimetry and response in humans, including susceptible subpopulations.

C. Feasibility of achieving specific aims:

The success of this specific aim will depend on strengthening interactions and collaboration with epidemiologists, clinical researchers, and agencies involved in human exposure assessment. Establishing formal interactions with DIR investigators and other agencies involved in human studies can help to achieve this goal.

D. Timeline for implementation:

Implementation depends on the availability of human data. The generation of chemical-specific human data will require input from multiple sources, including NTP, NIEHS-DIR, NIEHS-DERT, and other federal agencies that support biomedical research.

Summary of major recommendations:

1. Establish a minimal TK data set for all agents
2. Develop and validate PBPK models for agents of concern
3. Establish a multidisciplinary pharmacokinetic modeling core within TOB to coordinate the modeling efforts of the NTP
4. Develop training programs and user-friendly tools to facilitate use of models
5. Characterize cellular and molecular events in disease pathogenesis
6. Provide opportunity for NTP postdoctoral trainees to work in DIR laboratories
7. Encourage study design teams to predict site-specific dose-response relationships and identify data needs
8. Increase visibility and usability of the NTP tumor archive, and establish a repository for tissue arrays and longitudinal samples
9. Incorporate non-invasive technologies and in-life endpoints into NTP studies
10. Provide increased analysis and interpretation of NTP data
11. Humanize animal dosimetry and response models

Process Goal 1:
Increase the number and relevance of agents, issues, and concepts selected for toxicological evaluation by the NTP.

This is both a research goal (*which* agents, issues, and concepts to select for toxicological evaluation) and a process goal (*how* to improve the nomination process of soliciting, reviewing, and selecting agents and issues/concepts for study).

The current nomination process is primarily oriented to identify and prioritize compounds that would be suitable for hazard identification and characterization using the current toxicology models. The nomination process needs to respond efficiently to the changing priorities of NTP stakeholders (health regulatory and research agencies, the scientific and medical communities, and the public), emerging environmental health threats, and the increased capabilities of the NTP testing program.

The following specific aims were identified to accomplish this goal:

1. Identify new and additional priority areas for toxicological evaluation by the NTP
2. Improve the internal (NIEHS) nomination process by strengthening the role of the Nomination Faculty and/or expanding the Office of Nominations
3. Improve the external nomination process by stimulating nominations from external sources, e.g., state government agencies, interest/advocacy groups, and poison control centers, to identify timely and relevant agents for study
4. Reassess the role of the Interagency Committee for Chemical Evaluation and Coordination (ICCEC)

Specific Aim 1: Identify new and additional priority areas for toxicological evaluation by the NTP

A. Strategy and approach:

While a chemical-by-chemical approach is still necessary to accomplish the mission and goals of the NTP, it is likely that the nature of NTP nominations will evolve to include more emphasis on biological mechanisms in addition to hazard identification of specific compounds. Hypothesis-driven concepts are being nominated for evaluation by the program (e.g., TEF methodology) and will provide new challenges for study design. The testing paradigm should also evolve from the characterization of single compounds to characterization of mixtures of compounds that act through similar and dissimilar modes of action or affect the behavior of any of the components. Humans are rarely exposed to single compounds; rather they are exposed daily to complex mixtures of compounds. Although mixtures have proven difficult to study, the NTP should develop models that address chemical/chemical interactions and drug/chemical interactions. Potential additional priority areas are numerous and may include ambient air pollutants, lifestyle factors (e.g., diet, exercise, alcohol consumption, and smoking), agents that cause cardiac toxicity.

The NTP should consider developing formal programs to assist in identifying emerging, and unidentified hazardous exposures. The NTP should foster interdisciplinary

collaborations with scientists that have not traditionally participated in the nomination process including environmental chemists, earth and atmospheric scientists and geologists with the capability to utilize new analytical methods (such as TOF-MS) for identifying non-target analytes in environmental and biological media. The NTP should strengthen collaborations with other government agencies that are involved in assessing environmental and occupational exposure to chemicals. This may be accomplished by creating interagency working groups that are charged with identifying agents with potential human exposure. However, the criteria for selection should not be based on exposure data alone. Lack of evidence of human exposure should not eliminate evaluation of an agent if useful mechanistic information can be obtained.

B. Measures of accomplishment:

An increase in the number of nominations and study starts may not be the most significant measure of accomplishment since new priority areas are likely to pose new challenges. One measure of accomplishment is the development and incorporation of novel study designs and research approaches to address more complex issues.

C. Feasibility of achieving specific aims:

Workshops and use of public communication vehicles will be necessary to identify high priority agents and issues for study. It will also require innovative methodology, technology, and study design to adequately address challenging and complex issues.

D. Relevance to the NTP mission and public health:

The NTP seeks nominations of studies that fill significant gaps in the knowledge of the toxicity of chemicals or classes of chemicals, address mechanisms of toxicity or enhance the predictive ability of future NTP studies.

E. Timeline for implementation:

The NTP needs to begin to identify new priority areas in the next year and develop these areas over the next 3-5 years.

Specific Aim 2: Improve the internal (NIEHS) nomination process by strengthening the role of the Nomination Faculty and/or expanding the Office of Nominations

A. Strategy and approach:

Presently, the role of the Nomination Faculty is to provide an initial review of the chemical nomination, its supporting documentation, and additional literature to provide a recommendation for consideration of the nomination by the Interagency Committee for Chemical Evaluation and Coordination (ICCEC). While individual NTP staff may initiate chemical nominations on behalf of NIEHS, this has not been a significant source of chemical nominations. Members of the Nomination Faculty or study scientists could prepare nominations for consideration by the faculty similar to the process utilized by the Toxicogenomics faculty. NTP postdoctoral trainees have reviewed ATSDR documents for potential nominations and should be encouraged to participate actively in the nomination process. However, it is not anticipated that this will result in a significant increase in the number of nominations to the program. The nomination process could be

facilitated by the identification of data gaps and research needs in NTP documents and publications including technical reports and background documents for nominations to the Report on Carcinogens. These identified research needs may serve as additional sources of internal NTP nominations (see Process Goal 2).

Rather than simply reviewing chemical nominations, it is recommended that the Nomination Faculty be restructured such that smaller focused groups are formed to develop hypothesis driven nominations similar to the TEF project. To diversify and broaden the faculty, DERT and DIR representatives could serve as ad hoc members of the faculty to provide expertise related to a particular class of agents, issue/concept, or methodology.

Currently, the Nomination Faculty does not provide a significant role in the generation of chemical nominations. In the short-term, the role of the faculty could be strengthened as described above. However, if strategies to increase the number and relevance of nominations were successful, then the Nomination Faculty would be quickly overwhelmed. The current Office of Nominations is understaffed and needs to have increased capacity to review and process an increased number of nominations, and/or more complex nominations to the program. Additional staff members are needed to initiate and develop NIEHS sponsored nominations, to contact and collaborate with external nominators, and to respond to the anticipated increase in external nominations.

B. Measures of accomplishment:

The most important measure of accomplishment would be an increased number of nominations moving forward to the ICCEC and being selected for study by the NTP.

C. Feasibility of achieving specific aims: This aim is highly feasible.

D. Timeline for implementation:

The Nomination faculty should be restructured and its role and activities redefined immediately. In its present form, it is not fulfilling a significant role in the nomination process. It is recommended that additional staff members be hired into the Office of Nominations as soon as possible.

Specific Aim 3: Improve the external nomination process by stimulating nominations from external sources, e.g., state government agencies, interest/advocacy groups, and poison control centers, to identify timely and relevant agents for study

A. Strategy and approach:

The NTP Executive Committee members provide a number of nominations selected for study by the NTP. However, some agencies are more active in the nomination process and are structured to provide a continual source of nominations. One way to encourage representation and diversity in the nomination process is for the Office of Nominations/NTP to sponsor and facilitate an annual public meeting of federal and state agencies and labor, occupational, environmental, and advocacy groups to discuss and prioritize chemical compounds or concepts of public health concern. The NTP would

provide guidance on the nomination principles for NTP studies, and the participants would be asked to provide a rationale for the nomination. The output from the meeting would be a list of prioritized compounds to be developed further by the Office of Nominations staff.

In order to increase our public service commitment, the NTP needs to expand the areas from which it solicits nominations. Additional sources of nominations need to be identified and tapped to ensure that the nominations accurately reflect the needs of the public and regulatory agencies. The Office of Nominations should communicate and collaborate with state government agencies (EPA, USGS, etc) and poison control centers to identify timely and relevant agents for study. The solicitation and communication of nominations needs to be customized to target different stakeholders. Rather than initiating a broad call for nominations, the correspondence needs to address specific areas and identify questions/hypotheses that can be specifically addressed by a particular group. For example, what are the common concerns/complaints from the public on indoor air quality? Which chemicals frequently exceed guidance values in drinking water?

Creating a web-based form similar to that utilized by the CEHR would facilitate the ease of external nominations, particularly public nominations; initial responses to nominees should be automated. In addition, a database of compounds that have been nominated or studied previously should be developed and linked to the web-based nomination form. The form should be available as hard copies or electronically at professional and public meetings such as SOT to encourage on-site nominations.

B. Measures of accomplishment:

While increased numbers of nominations is certainly the most quantifiable measure of accomplishment, the more important measure is the selection of nominations that address data needs of the regulatory agencies and public health concerns.

C. Feasibility of achieving specific aims:

The success of this aim relies on effective and targeted communication between the Office of Nominations and the external nominator. It is important that federal and state agencies and municipal organizations understand the mission and goals of the NTP, participate in the nomination process, and seek the NTP as a resource to address scientific questions and respond to public health concerns. The Office of Nominations will need additional staff to increase its capacity to respond to the potential increase in the number and complexity of nominations. Without additional staff, the present nomination process could be easily overwhelmed.

D. Timeline for implementation:

Potential external nominators should be identified and correspondence describing the mission and goals of the NTP and the nomination process should be initiated immediately.

Specific Aim 4: Reassess the role of the Interagency Committee for Chemical Evaluation and Coordination (ICCEC)

A. Strategy and approach:

It is recommended that the role of the ICCEC be restructured to provide earlier guidance on priority setting on a broader range of nominations in addition to providing review and approval of more developed nominations. This would require the preparation of shorter 2-5 page executive summaries by the contractor, with electronic links to relevant citations, in addition to more extensive toxicity literature reviews for high priority nominations. These executive summaries should be more readily evaluated by the ICCEC and may be more appropriate for dissemination to other DIR personnel and the Nomination faculty. Based on the initial review of shorter executive summaries by ICCEC, extensive background documents would only be developed on those agents or concepts that have a high likelihood of undergoing further study and testing. In addition, shorter briefs would be more appropriate for agents that will not be tested extensively using the standard toxicity tests but will be evaluated in *in vitro* high throughput assays.

B. Measure of accomplishment:

An increased number of nominations moving forward to the ICCEC and subsequent study starts would be one measure of accomplishment but equally important would be a reduction in the time needed to complete the Nomination and Selection Process.

C. Feasibility of achieving specific aims:

Members of the ICCEC should be consulted before implementing significant changes in the Nomination and Selection Process. The Statement of Work for the contract may need to be revised accordingly.

D. Timeline for implementation:

Significant changes to the ICCEC review process could be implemented within 1 year.

Summary of major recommendations:

1. Develop models that address chemical mixtures
2. Develop programs to identify emerging and unidentified hazardous exposures
3. Strengthen collaborations with other government agencies that are involved in assessing environmental and occupational exposure to chemicals
4. Identify data gaps and additional research needs in NTP documents to feed the nomination process
5. Restructure the Nomination Faculty such that smaller focused groups, including DIR and DERT representatives, are formed to develop hypothesis driven nominations
6. Expand the Office of Nominations to initiate internal nominations and respond to external nominations
7. Reassess the role of ICCEC
8. Sponsor and facilitate an annual public meeting to discuss and prioritize chemical compounds or concepts of public health concern

9. Identify additional sources of nominations that have not been traditionally tapped (state government agencies, interest/advocacy groups, poison control centers)
10. Create a web-based form to facilitate the ease of nominations

Process Goal 2:

Develop procedures to further evaluate and characterize toxicological effects observed in the testing program and to address toxicological data needs identified by the NTP Centers (CERHR, NICEATM) and the Report on Carcinogens (RoC).

CERHR: NTP Center for the Evaluation of Risks to Human Reproduction

NICEATM: NTP Interagency Center for the Evaluation of Alternative Toxicological Methods

ICCVAM: Interagency Coordinating Committee on the Validation of Alternative Methods

The following specific aims were identified to accomplish this goal:

1. Identify data gaps, research needs, and areas for further research in NTP studies and articulate them in NTP documents and publications including technical reports, background documents for nominations to the Report on Carcinogens, CERHR expert panel reports and monographs, and the ICCVAM test method guidelines (*CERHR already does this*)
2. Develop and implement mechanisms for prioritizing, pursuing, and tracking identified research needs

Specific Aim 1: Identify data gaps, research needs, and areas for further research in NTP studies and articulate them in NTP documents and publications including technical reports, background documents for nominations to the Report on Carcinogens, CERHR expert panel reports and monographs, and the ICCVAM test method guidelines

A. Strategy and approach:

Most data evaluations and research reports include an articulation of the scientific data gaps that need to be filled to permit a more complete understanding of the potential risk of the agent. With the exception of the NTP CERHR, the NTP has not traditionally included this assessment in its publications. NTP staff involved in the preparation of technical reports and other documents should draft distinct sections on data gaps and research needs that would aid in better understanding of the mechanism or mode of action, cross-species extrapolation, dose-response relationships for sensitive endpoints of interest or the characterization of other toxicities not included in the published report. Standard procedures for peer review and public comment would also be used to reach consensus on the relative importance of the NTP identified data needs. Simple reliance on passive dissemination of these data needs through publication would not be sufficient and additional strategies are recommended. These could include compilation of the identified data needs on a semi-annual basis and publication in *Environmental Health Perspectives*, Federal Register notices, the NTP website, and transmittal to DIR and DERT for consideration for inclusion in new or ongoing research programs, Program Announcements, Areas of Special Interest, Small Business Innovation Research Grants (SBIR), and Requests for Applications (RFAs).

B. Measures of accomplishment:

Accomplishment of this aim will be demonstrated by successful inclusion of consensus research data needs in all NTP publications and regular dissemination of these needs to the broader scientific community. Success in disseminating research needs will be shown by web page hits, internal staff interactions, and public inquiries.

C. Feasibility of achieving specific aims:

This is highly feasible. Identifying areas for further research is a routine part of the scientific process and no additional resources or expertise beyond those currently utilized in the NTP's research and review activities is anticipated.

D. Relevance to NTP mission and public health:

The NTP's mission to generate and evaluate toxicological data to aid in characterization of human health hazards must extend beyond our present knowledge to include identification of data gaps and uncertainties in the underlying science base, which if addressed would lead to an overall better understanding of human health hazards associated with exposure to environmental agents.

E. Timeline for implementation:

The activities described here can and should be implemented immediately.

Specific Aim 2: Develop and implement mechanisms for prioritizing, pursuing, and tracking identified research needs

A. Strategy and approach:

It is not sufficient to identify and disseminate research data needs. NTP (TOB/Office of Nominations) should take initial responsibility for prioritizing the data needs internally and seeking review and comment on the prioritized data needs. NTP should not bear responsibility for pursuing all data needs but should consider those that fit into their overall mission and stimulate adoption of additional data needs by other researchers and research agencies.

In order for the NTP to respond to the need for mechanistic data by regulatory agencies and to provide a linkage between mechanism and disease, the NTP must promote investigations of hypotheses that arise as a result of NTP initiated studies or that are identified as data gaps. It is recommended that an investigative toxicology group, similar to those in pharmaceutical companies, be established within DIR to assist the NTP with addressing mechanistic questions that are generated in the testing program. Other mechanisms to address the need for a focused research laboratory should be explored to the fullest extent possible.

NTP staff working in concert with other DIR and DERT staff will need to frame the identified research needs in terms that the intramural and extramural community can relate to; i.e., recommending additional "guideline type" toxicology studies is unlikely to be pursued by researchers outside government and private industry. Most data needs will fall into categories such as mechanisms, human variability and susceptibility, and low dose response; if properly articulated, these needs have a reasonable chance of being

successfully addressed by the broader scientific research community. Additionally, the NTP could promote investigative collaborative research within DIR or through DERT as described in other goals.

A web servable software system for tracking research needs, ideally integrated with NTP reports and publications, should be created. It would be useful to track all published NTP reports by citation or NIH publication number. CRISP (Computer Retrieval of Information on Scientific Projects), SPIRES (Scientific Publication Information Retrieval and Evaluation System), and ISI's (Institute for Scientific Information) citation databases serve as good models; newer search cluster engines (Vivisimo) and text-mining tools may prove especially useful in this regard. Each identified data need could be given a unique code and entered into a tracking database along with the relevant NTP citation. This would allow for efficient semi-automated tracking of NTP data needs and sponsored research addressing those needs.

B. Measures of accomplishment:

As with any new process, creation and implementation is not a measure of success in of itself. Prioritizing by consensus, adoption of identified high priority data needs by the NTP or other researchers into their research program and demonstration that research to address high priority data needs facilitated health hazard or risk assessments will indicate success of this effort.

C. Feasibility of achieving specific aims:

This is highly feasible. Only an *efficient* process that would feed new study ideas into the NTP research and testing program should be created. Communication and dissemination of priority research needs and managing a tracking system, while feasible, will require modest additional resources.

D. Relevance to NTP mission and public health:

The NTP's mission to generate and evaluate toxicological data to aid in characterization of human health hazards will be better served by an iterative process that identifies uncertainties and initiates further research to lead to an overall better understanding of human health hazards associated with exposure to environmental agents.

E. Timeline for implementation:

Initial efforts to develop mechanisms for prioritizing, pursuing, and tracking research needs can and should be implemented immediately. Within one year, a sufficient number of NTP reports containing identified research needs should be available to begin assessing the feasibility of different options for prioritizing, pursuing, and tracking research needs. Within two years, formal mechanisms for prioritizing, pursuing, and tracking research needs should be implemented.

Summary of major recommendations:

1. Identify data gaps, research needs, and areas for further research in NTP studies and articulate them in NTP documents and publications

2. Compile the identified data needs on a semi-annual basis and disseminate them to the broader scientific community
3. Develop and implement mechanisms for prioritizing, pursuing, and tracking identified research needs
4. Establish an investigative toxicology group within DIR to assist the NTP with addressing mechanistic questions that are generated in the testing program
5. Create a web servable software system for tracking research needs
6. Promote collaborative research within DIR and through DERT

Process Goal 3:

Ensure that different types of data that pertain to a given agent or concept are fully integrated such that the best possible value can be gleaned from the information.

As new approaches are applied to toxicology it is important to ensure that different types of data that pertain to a given agent or concept are fully integrated such that the best possible value can be gleaned from the information.

There are three different levels of integration:

- (A) The integration of different types of data within a single NTP study; these may include *in vitro* data on an agent of concern, tissue dosimetry, toxicokinetic data, biochemical/physiological endpoints, pathology, imaging data, PBPK-PD models based on the results of TK and tissue dosimetry studies, “omics” data, and extramural research on samples from a NTP study
- (B) Integration of data across multiple NTP studies
- (C) Integration with different data types derived from other NTP/NIEHS/DIR organizations; e.g., NCT (National Center for Toxicogenomics), DIR, extramural community

A. Strategy and approach:

1. Data acquisition

The first step to effective integration is to ensure that the most relevant questions are being asked about a given agent, groups of agents, or concepts and that the most appropriate data are obtained.

The composition of the study design team should be reevaluated and include additional expertise to ensure that the right questions are being asked to acquire the most relevant data. Efforts should be made to ensure that the study design teams have the skills that will allow for both an effective study design as well as interpretation of the different types of data.

For broader concepts/issues, consideration of the use of workshops and seminars as a pre-design phase should be explored. Inclusion of DERT in the early phase of the study will aid in the inclusion of the extramural community.

Publication of a NTP quarterly update page in *Environmental Health Perspectives* or *Toxicological Sciences* is proposed as well as the NTP website that would specifically advertise NTP studies that are being planned or designed. These vehicles would be used to call for input, ideas, comments, and requests for samples and may stimulate broader input into the design of the studies. This information should be included in the NTP “Update” before studies are initiated to stimulate input from the readers.

Continue to explore the use of R03 grants as vehicles for special studies. Revise the program to increase interactions between extramural investigators and NTP study

scientists. Include a grantee workshop to obtain and evaluate recommendations on how to integrate the additional data they have generated.

2. Informatics

Currently TDMS captures data from core studies. As different types of datasets are obtained, databases/informatics should be engineered to capture all the data types from different sources for a given study such that all data is linked on an animal-by-animal basis where possible.

3. Interpretation

As new types of data are collected on NTP studies, there will be a need for increased coordination of the study design and evaluation teams for the analysis and integration of data since the study scientist may not have the expertise in specific analyses (e.g., genomic and proteomic bioinformatics). In addition, the study scientist may change during a study due to retirement, reassignment, or other reasons.

Expertise in analysis of new data types needs to be brought into the program (See Process Goal 4) to ensure that the best possible evaluation and integration of data is accomplished. The NTP postdoctoral trainees may offer expertise for analysis and integration of specific datasets into NTP studies.

As part of the study, documentation of specific data analysis, integration plans, and rationale need to be fully described during the conduct of the study.

4. Data reporting and integration

The current formats for official reporting of NTP data should be evaluated to ensure that the most appropriate vehicles are used for reporting, interpretation, and integration of varied datasets. For example, conclusions in NTP technical reports are based primarily on evidence of carcinogenicity from histopathological evaluations.

The question is whether the technical report series is the most appropriate publication vehicle for integration of all data in a 2-year NTP study. Consideration should be given to the establishment of a new publication series that will allow integrative analyses on potentially diverse datasets and cross-study analyses. This could be prepared, reviewed, and published as an official NTP document. Due to space limitations, peer reviewed journal publications may not always be the best vehicle for a full evaluation of such integrative analyses. In addition, incorporation in the toxicology and technical report series may not be appropriate.

Enhanced web publishing of NTP data and interpretations should be explored.

5. Integration with extramural datasets

As extramural toxicology/informatics databases are developed, efforts should be made to ensure that the NTP databases are integrated or that the data can be easily exchanged between databases [e.g., NTP and CEBS (Chemical Effects in Biological Systems) database and EPA DSSTox (Distributed Structure-Searchable Toxicity) database].

6. Evaluation of the utility of new datasets

There should be an ongoing review of data that are “routinely” obtained in NTP studies to evaluate their utility in priority setting, decision-making, and interpretation.

As new datasets are obtained, there should be defined project goals and specific timelines to evaluate the utility of new data types so that decisions can be made as to whether to continue to routinely collect such data.

7. Identification of knowledge gaps

The integration process should formally identify data gaps and new research questions for follow-up in future studies. These may serve to stimulate new nominations to be studied by NTP and extramural investigators.

DELT should be involved in the process to identify areas where new DELT initiatives may help to better characterize the biological responses observed in NTP studies or to fill identified knowledge gaps.

B. Measures of accomplishment:

Measuring the degree of “integration” of data can only be made through a peer-review process. This assessment could be part of the formal BSC review process of technical and toxicity reports, or done by an ad hoc panel review on specific areas of research.

C. Feasibility of achieving specific aims:

These aims are highly feasible because in most cases they refer to the enhancement or modification of processes that are already in place in NTP.

D. Timeline for implementation:

Most changes in this process could be implemented immediately.

Summary of major recommendations:

1. Restructure study design teams to include additional expertise to generate and interpret different types of data
2. Include DELT staff in the early phase of study design to stimulate collaboration with extramural scientists
3. Use communication vehicles to solicit external input into the design of studies
4. Explore the use of RO3 grants as vehicles for special studies
5. Capture diverse data sets on a single data management system
6. Explore the development of a publication series on integrated analyses
7. Ensure that NTP databases are compatible with other databases
8. Continually evaluate the utility of various datasets

Process Goal 4:

Increase the breadth of scientific expertise in newly identified priority areas to facilitate the transfer of new technologies and methodologies to the NTP while maintaining sufficient depth in current programs.

It is anticipated that over the next 5-10 years there will be significant turnover in NTP personnel due to attrition, primarily retirements. Maintenance of talented and competent staff will be imperative for ensuring that the NTP remains a leader in toxicology testing and research and consistently provides scientific data of the highest quality for public health decisions. The NTP needs to develop a proactive strategy to fill positions that will be vacant due to impending retirements.

The nature of NTP nominations is changing and expanding; thus, there is an increasing need to incorporate new technologies and methodologies into the testing programs. The need for external expertise is also likely to increase as the nomination process moves from consideration of specific individual chemicals to development and testing of groups of chemicals as well as hypotheses and concepts.

A. Strategy and approach:

The following sources and approaches for increasing scientific expertise were identified to accomplish this goal:

1. Training of current NTP staff
2. NTP postdoctoral trainees
3. New hires
4. Increased collaborations with DIR scientists
5. Promote synergy between NTP and DERT in areas of shared scientific interest
6. Increased collaborations with federal and state agencies, private industry and academic institutions
7. Establishment of new contracts

Before seeking out these sources of expertise, it is important to consider all of the NTP goals so that expertise can be expanded in targeted areas. Although classical toxicology training is crucial for maintaining expertise in the program, it will be necessary to hire and collaborate with individuals that have expertise that is more diverse and experience with the technologies and methodologies that are required to achieve the NTP Vision. Benefits to those providing expertise to the NTP are numerous and may include shared resources, scientific publications and recognition, and easy access to NTP archived tissue and biological samples.

1. Training of current NTP staff

There should be continued training of current NTP staff to expand the in-house expertise base. Specific training programs (molecular biology techniques, “omics”, PBPK modeling, etc.) may be needed to enhance the skills of staff scientists. This may be accomplished by NTP workshops, continuing education courses offered by professional societies or universities, and through direct interactions with NTP contract laboratories. The management staff should assess the needs of the program and the staff and should

provide time and resources for additional training. It is likely that the current NTP staff will need to assume additional roles and responsibilities as positions are vacated.

2. NTP postdoctoral trainees

Postdoctoral trainees are a valuable resource and can provide the skills necessary for transferring new technology, methods and assays to the program. Presently, the NTP postdoctoral trainees are functioning as NTP study scientists. While this assignment fulfills an important role, the function of the training program needs to be more clearly articulated within the framework of the entire program. More specifically, the trainees should be encouraged to receive training in additional offices and centers of the program including the Nominations Office, NICEATM, CERHR, and the RoC, as well as in other capacities including contract laboratory management or the conduct of mechanistic research within DIR laboratories. This could be accomplished by short focused rotations with the appropriate group leaders and center directors and/or by developing programs specific to the career goals of the trainee. More importantly, the NTP needs to utilize the expertise of the postdoctoral trainees. The NTP has not fully tapped into individual knowledge and talents of the trainees to increase the breadth or depth of expertise in the program. The trainees should be encouraged to maintain and share their skills by serving as experts in their respective disciplines.

3. New hires

When considering new hires, the NTP needs to target recruits in new areas (cardiotoxicity, molecular/cellular biology, etc.) and expand depth in areas where there is current expertise. This is very difficult to accomplish simultaneously. While not appropriate or feasible in all cases, there needs to be a mechanism to retain talented postdoctoral trainees as permanent personnel. With the likelihood that additional FTEs will not be available in the future and may actually decrease in number, it will become critical for the NTP to maintain a critical mass of government employed personnel to serve as unbiased representatives of the program. Retention of trainees is one of the most thorough and efficient mechanisms for the transfer of institutional knowledge. This transfer of knowledge will become increasingly more important as senior scientists retire from the program. Mechanisms to ensure efficient transfer of knowledge from current NTP staff to new personnel include job shadowing and assignment of primary and secondary study scientists to study design teams. Documentation of study design meetings, dose selection rationale, and design team recommendations were considered to be some of the most crucial and effective mechanisms to transfer information. To ensure that a chemical file is maintained adequately and uniformly, a checklist of required documents (background documents, study design minutes, dose selection memos, pertinent email correspondence) should be monitored by the Central Data Management staff. The CDM staff can then prompt study scientists to provide the necessary documentation.

4. Increased collaborations with DIR scientists

The current level of interaction and collaboration of NTP scientists with DIR scientists is not optimal. There is little incentive for DIR investigators to be involved in NTP studies and, in fact, many impediments to collaborations have been identified. The DIR Board of

Scientific Counselors (BSC) and NIEHS Committees on Promotion (COP) often do not review NTP collaborations positively. Either the impediments need to be removed or additional incentives for DIR scientists need to be established. The NIEHS/NTP director, the SD of DIR, and the Associate Director of NTP should view DIR and NTP collaborations as mutually beneficial and consistent with the mission and environmental health goals of the Institute as well as the broad NIH goal to stimulate interdisciplinary research teams. The BSC and COP should be encouraged to recognize and reward the merits of a close interaction between DIR and NTP. At the same time, additional incentives, including shared postdoctoral trainees, supply money or travel funds could be offered to foster productive collaborations.

DIR scientists could play a significant role in providing the NTP with additional expertise in at least two key areas. First, DIR investigators could serve as expert “consultants” on an as-needed basis as ad hoc members of study design and evaluation teams and the various faculties (Nominations, Toxicokinetics, Toxicogenomics). Second, laboratory collaborations between DIR and NTP should be established and supported to conduct hypothesis-driven research that may provide mechanistic information for a particular compound or class of compounds and may facilitate the transfer of new methodologies to the NTP testing program. These collaborations would require a commitment from the DIR investigator for a limited amount of time to provide expertise on a defined question or project.

5. Promote synergy between NTP and DERT in areas of shared scientific interest

See Process Goal 5

6. Increased collaborations with federal and state agencies, private industry, and academic institutions:

The NTP should consider all potential sources of scientific expertise and should develop interactive relationships and collaborations with as many as possible. The NTP is uniquely situated to tap into the expertise of scientists employed in federal and state agencies, private industry, and academic institutions located in Research Triangle Park and surrounding cities. Due to proximity, it should be feasible to collaborate and consult with local expert scientists on a regular basis.

7. Establishment of new contracts

Perhaps the most efficient way to incorporate new technologies and methodologies into the testing program and simultaneously provide a mechanism for the conduct of NTP hypothesis-driven research is the establishment of a new contract at a laboratory with technical expertise in these methodologies.

B. Measures of accomplishment:

The most important measure of accomplishment is ensuring that competent personnel fill key positions and fulfill primary responsibilities within the program so that a lapse in function or scientific quality does not occur. Input from diverse sources of expertise leads to the acquisition and use of additional data in the characterization and prediction of human health risks.

C. Feasibility of achieving specific aims:

Most of these mechanisms for increasing scientific expertise are feasible. While the establishment of a new contract may be the most formal and expensive mechanism for increasing NTP expertise, it may be necessary to provide adequate quality control, assay validation, and reproducibility for utilization of technologies and methodologies in the program.

D. Relevance to the NTP mission and public health:

Maintenance of talented and competent staff and collaborations with other scientists will be imperative for ensuring that the NTP remains a leader in toxicology testing and research and consistently provides scientific data of the highest quality for public health decisions.

E. Timeline for implementation:

Due to the significant attrition of NTP personnel that is likely to occur in the next 5-10 years, the NTP needs to develop a proactive strategy to replace vacant positions and ensure scientific expertise in the program. Additional efforts to establish collaborations with NTP should begin immediately.

Summary of major recommendations:

1. Develop a proactive strategy to fill positions within NTP
2. Hire and collaborate with individuals that have diverse expertise and experience with new technologies and methodologies
3. Provide continued training of current NTP staff
4. Utilize the individual expertise of postdoctoral trainees
5. Encourage DIR investigators to serve as expert “consultants”
6. Develop interactive relationships and collaborations with all potential sources of scientific expertise

Process Goal 5:
Promote synergy between the NTP and the Division of Extramural Research and Training (DERT) in areas of shared scientific interest.

This goal focuses on promoting communication and synergy between the NTP and DERT scientists to identify shared scientific interests and promote collaboration in areas such as chemical nomination, toxicology assessment, and the application of toxicology data to environmental health science.

The following specific aims were identified to accomplish this goal:

1. Establish a forum for information exchange between NTP scientists and DERT program administrators
2. Establish a process to promote DERT initiatives that address data needs identified in NTP studies and utilize NTP resources to advance environmental health science

Specific Aim 1: Establish a forum for information exchange between NTP scientists and DERT program administrators

A. Strategy and approach:

This specific aim addresses the need for enhanced communication between NTP scientists and DERT program staff on activities related to NTP chemical nominations, toxicology reviews and studies, and the basic research funded by DERT. Two specific strategies are proposed to accomplish this aim. First, is the establishment of a regularly scheduled series of meetings or “brown bag” sessions involving both NTP and DERT staff. DERT scientists should also be encouraged to participate in the meetings. The meetings would focus on discussion of the process of NTP nominations, the results of studies that could be further enhanced by extramural research, and ongoing research and activities supported by DERT that could dovetail with NTP goals and activities. Information exchange is the initial step towards developing collaborative research initiatives between the two programs. Databases that track DERT’s grants [SPIRES (Scientific Publication Information Retrieval and Evaluation System)] and federally funded biomedical research projects [CRISP (Computer Retrieval of Information on Scientific Projects)] currently exist and can be accessed via the DERT website.

Second, is to formalize, expand, and articulate the role and responsibilities of the DERT liaison to the NTP and to identify a NTP point of contact for DERT-NTP activities. The NTP point of contact would work directly with the DERT liaison to plan “brown bag” sessions and other forums for information exchange, e.g., joint workshops.

B. Measures of accomplishment:

An important measure of accomplishment would be the establishment of a quarterly seminar series or meetings with active participation that promote information sharing between NTP scientists and DERT program administrators. Implementing the strategies outlined, would fuel the chemical nomination process, improve toxicology study designs,

and foster relationships between the NTP scientists and the extramural research community.

C. Feasibility of achieving specific aims:

Greater information exchange between NTP and DERT program administrators is highly feasible and would accomplish mutual program goals.

D. Timeline for implementation:

Enhanced communication between NTP and DERT can be implemented immediately.

Specific Aim 2: Establish a process to promote DERT initiatives that address data needs identified in NTP studies and utilize NTP resources to advance environmental health science

A. Strategy and approach:

NTP studies generate both biological information and samples that may be of great utility to the extramural research community. The DERT liaison to the NTP should work closely with the NTP point of contact to coordinate efforts aimed at developing research initiatives that address needs identified in NTP studies or to utilize NTP samples to advance areas of environmental science of interest to DERT program administrators. This would enable extramural scientists to capitalize on available resources to facilitate basic or translational research aimed at identifying biomarkers of exposure or mechanisms of disease processes. Studies involving biological samples will inherently require sample repositories. The NTP currently has archived samples of blood, urine, and tumors from a selected number of toxicology studies.

B. Measures of accomplishment:

The most important measure of accomplishment would be the development and release of program announcements tailored to both NTP and DERT research needs. Success of these programs could be monitored through receipt of meritorious applications that lead to the publication of high impact reports and the development of commercial products to improve public health.

C. Feasibility of achieving specific aims:

This aim is highly feasible although the release of program announcements will require approval by the NIEHS National Advisory Environmental Health Sciences Council.

D. Timeline for implementation:

This aim can be implemented immediately.

Summary of major recommendations:

1. Establish regularly scheduled meetings between NTP and DERT staff
2. Formalize, expand, and articulate the role and responsibilities of the DERT liaison to the NTP and identify a NTP point of contact for DERT-NTP activities
3. Develop DERT research initiatives that address needs identified in NTP studies or utilize NTP samples to advance environmental health science

**Communication and Translation Goal 1:
Strengthen public health outreach and education about the scientific value of NTP products and services.**

To accomplish this goal, outreach and communication must be targeted to the broad community of scientists, regulatory and research agencies, and the general public. The following specific aims were identified:

1. Identify and review existing documents on indicators of use of NTP products and ongoing outreach and education efforts
2. Develop a communication strategy and network for ongoing outreach and education targeting a broad audience of stakeholders

Specific Aim 1: Identify and review existing documents on indicators of use of NTP products and ongoing outreach and education efforts

A. Strategy and approach:

The NTP should identify and review past and ongoing efforts by the NTP in outreach and education. This includes written reviews (about usage of NTP products and services), government reports, pamphlets, and published literature. It also includes less tangible aspects of communication such as feedback about information disseminated at scientific meetings, inquiries made directly to the NTP, and administrative infrastructure to support activities in outreach and education. A summary report would be developed that highlights ongoing efforts, impacts, and additional needs. Review of these efforts by an outside contractor specializing in science communication should be considered.

B. Measures of accomplishment:

One important measure of accomplishment is the development of a summary report highlighting the existing efforts and impact in outreach and education by the NTP. This will serve as a basis for identifying where communication efforts are currently targeted and where they are needed. Targeted efforts may result in expanding an existing initiative or developing new initiatives to address specific needs.

C. Feasibility of achieving specific aims:

It is highly feasible to conduct a review of existing efforts in community outreach and education.

D. Relevance to the NTP mission and public health:

Communication and outreach is critical so that the public is able to make full use of NTP products and services and will recognize the NTP as a primary resource for public health information. With sufficient knowledge and awareness of NTP functions and operations, the public may be able to provide meaningful comment and input on program priorities and directions.

E. Timeline for implementation:

All aspects of this aim can and should be implemented immediately.

Specific Aim 2: Develop a communication strategy and network for ongoing outreach and education targeting a broad audience including stakeholders

A. Strategy and approach:

The NTP has ongoing outreach and education efforts aimed primarily at the regulatory community. This is logical given the importance of NTP research findings in regulatory decision-making. However, there is a need to expand the scope of these efforts to reach a broader audience of basic (non-regulatory) scientists and the general public. The NTP should develop a strategy for communication that addresses the need for public health information targeted to a range of audiences and delivered using appropriate communication tools and outlets.

Communication messages should focus on the high quality science conducted by the NTP to support regulatory decision-making and public health research. Specific programs and accomplishments of the NTP could be featured in targeted messages or “success stories” such as EMF, cell phones, endocrine disruptors, and the use of alternative models. Messages could also be developed to inform the public and scientific communities about NTP services such as the chemical nomination process and the availability of archived samples (blood, urine, tissue, and tumors) and computational models to support basic mechanistic and predictive toxicology research. The latter of these services could be coordinated with DERT program scientists to specifically reach the extramural research community (See Process Goal 5). Messages could be delivered using a variety of formats, depending on the target audience, such as editorial pages in open access journals such as *Environmental Health Perspectives* (EHP) or pamphlets that could be distributed at scientific and town hall meetings. The NTP could have a dedicated section in EHP for “NTP news” similar to that for DERT.

An important aspect of message development is identifying and reaching the target audience. This includes a broad range of audiences both internal and external to the NIEHS. A NTP liaison to the NIEHS communications office is recommended to provide timely and accurate information about the significance of NTP findings. Internal communication between programs of the NTP and within the NIEHS should be fostered through workshops and meetings involving representatives from a variety of programs including DERT, DIR, and ICCVAM. The desired outcome is to foster communication and scientific collaboration on topics of shared interest. Management support is critical to ensure that these efforts are successful.

There is an existing framework within the NTP to support communication efforts aimed at regulatory agencies. However, there are several additional avenues for communication with Federal agencies that should be considered. These include existing interagency workgroups such as the NTP Executive Committee, the NIEHS-sponsored NAS/NRC Committee on Emerging Issues on Environmental Contamination and Data, and the newly formed EPA-sponsored NAS/NRC Committee on Future Approaches to Toxicology Testing. Other forums include the NIEHS National Advisory Environmental Health Sciences Council and workgroups sponsored by federal agencies. The NTP will

have to engage and educate the regulatory community and the public on the usefulness of the new test methods and how the generated data can be used in a risk assessment framework.

The framework to support communication efforts could be expanded to encompass a larger range of activities and audiences including nonregulatory scientists and the general public. The NTP, DIR, and DERT should promote the usage of NTP resources (data, samples, and mathematical models) in basic research conducted by intramural and extramural scientists. This will foster communication with the scientific community through acknowledgements and citations in the published literature while advancing basic mechanistic and predictive toxicology research. For example, the data needs identified in a NTP toxicology study could trigger a solicitation to the extramural community to stimulate research in this area (see Process Goal 2). NTP data and biological samples would be made available to the extramural researchers to support their research. These targeted solicitations would encourage the incorporation of new technologies (genomics, proteomics, imaging) and model systems (*C. elegans*, *in vitro* systems), as appropriate, to address the basic research questions. The NTP and DERT would collaborate to establish priorities for compound selection and specific data needs that could be addressed by an external solicitation.

The NTP should enhance the visibility of its programs within and outside of the NIEHS. The public should be as familiar with the mission of the NTP as they are with that of the EPA and should recognize the NTP as a primary resource for public health information. The NTP should develop a “message logo” and advertising campaign that promotes the “essence” of the NTP mission and its contribution to environmental health. To improve public awareness of the program, the NTP should hold more town hall meetings to discuss the NTP and its activities. Fact sheets should be prepared in lay terms for some of the technical reports or highly visible compounds. Detailed abstracts from the technical reports and other NTP documents should be in plain English.

The NTP should develop an easy access website highlighting both general information and detailed scientific information from toxicology studies and reviews. A public-friendly site would provide general information about NTP structure and resources and include scientific information, such as the “success stories”, that are developed for other active outreach efforts. In addition, websites for other agencies and organizations should be encouraged to provide links to the NTP website.

Developing and implementing a communication strategy of this scope will require that personnel within the NTP specifically plan, coordinate, and implement improved outreach and education activities. Individuals designated as NTP point of contacts would streamline the process of communication across all levels. Management support is essential for the success of any communication strategy.

B. Measures of accomplishment:

The most important measure of accomplishment is the development of a general communication strategy targeting a variety of scientific and lay audiences. As part of this

plan, the NTP should develop specific short term and long-term goals for communication and criteria for evaluating the effectiveness of these efforts. Plans for parsing administrative responsibilities would be included to streamline internal and external communication efforts.

C. Feasibility of achieving specific aims:

Developing and implementing a communication strategy is feasible but will require a phased effort. Initially, a general plan should be developed that highlights existing strengths and identifies specific needs. Specific short-term and long-term goals and objectives would be developed to address these strengths and needs.

D. Relevance to the NTP mission and public health:

Communication and outreach is critical so that the public is both able to make full use of NTP products and services and able to maintain sufficient knowledge and awareness of the NTP's function and operations to allow for meaningful comment and input on program priorities and directions.

E. Timeline for implementation:

Communication is an ongoing and multi-faceted process that will be implemented over the course of several years. Implementation will require management support for personnel and resources needed to implement the communication strategy.

Summary of major recommendations:

1. Identify and review the impact of past and ongoing efforts by the NTP in outreach and education
2. Develop a strategy for communication targeted to a range of audiences and delivered using appropriate communication tools and outlets
3. Promote the usage of NTP resources in basic research conducted by intramural and extramural scientists
4. Develop a "message logo" and advertising campaign that promotes the "essence" of the NTP mission and its contribution to environmental health
5. Hold regular town meetings to improve public awareness of the NTP
6. Ensure that NTP communication to the public is in lay terms/plain English
7. Reorganize and restructure the NTP website to make it more public-friendly

Proposed NTP Organizational Chart

The NIEHS committee and other groups were asked to provide recommendations for how to best structure the NTP to provide valued scientific information and to ensure its optimal utilization in the protection of public health. An appropriate NTP organizational structure needs to be created to achieve the goals outlined in the NTP roadmap. Specific recommendations for restructuring the NTP are presented below and salient features are depicted in the accompanying proposed NTP organizational chart.

1. It is recommended that all non-laboratory functions of the NTP be organized into one or two branches within the Environmental Toxicology Program (ETP). In the organizational chart, these are designated as the Toxicology Operations Branch and the Toxicology Studies Branch.
2. The NTP/NIEHS Director reports to the Secretary of DHHS regarding NTP activities and to the Director of NIH regarding NIEHS activities. Therefore, it is recommended that the Associate Director of NTP (Director, ETP) report directly to the NTP/NIEHS Director (independent of Scientific Director of DIR) on activities and functions that are required to operate and manage the NTP testing program.
3. Establish a dedicated multidisciplinary pharmacokinetic modeling core within the "Toxicology Studies Branch" to increase expertise and in-house capacity in dosimetry modeling and to coordinate the modeling efforts of the NTP. Incorporate all NTP ADME/TK/PBPK activities in one organizational unit with a clearly defined reporting structure.
4. Identify liaisons from DERT and DIR, specifically, epidemiology, clinical research and biostatistics, to interface and collaborate with the NTP study design and evaluation teams.
5. Establish an investigative toxicology group within DIR to assist the NTP with addressing mechanistic questions that are generated in the testing program.
6. The scientific review process should be clearly defined and transparent so all participants know what to expect. It is recommended that staff scientists that conduct NTP-related laboratory research report directly to the Associate Director of NTP and be reviewed by the NTP Board of Scientific Counselors (the DIR Board of Scientific Counselors reviews Principle Investigators).
7. Principle Investigators and staff scientists in DIR laboratories should be encouraged to participate as consultants to NTP study design and evaluation teams. This would provide opportunities for intellectual input from DIR scientists into the design and interpretation of mechanistic studies conducted on NTP

agents. In some cases, the NTP will provide DIR laboratories with research fellows and resources to help NTP generate needed environmental health data at the cellular and molecular levels.

8. Establish internal and external committees to review the current and desired NTP organizational structure.

Proposed NTP Organizational Chart

