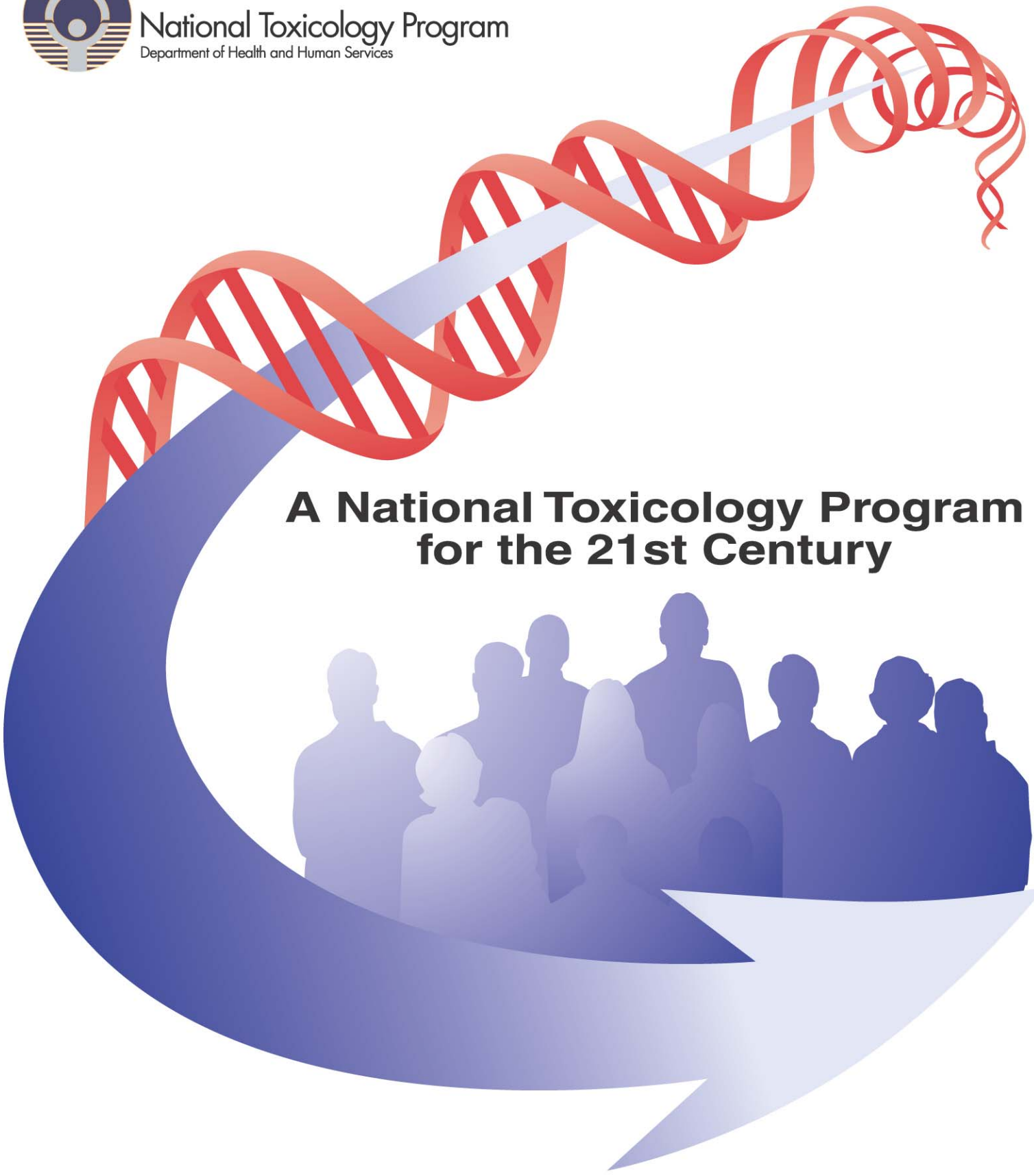
National Toxicology Program
Department of Health and Human Services



A National Toxicology Program for the 21st Century

A Roadmap for the Future

A National Toxicology Program for the 21st Century

Roadmap to Achieve the NTP Vision

The National Toxicology Program (NTP) is a world leader in providing scientific information that improves our ability to evaluate potential human health effects from chemical and physical exposures. The NTP maintains a number of complex, interrelated research and testing programs that provide unique and critical information needed by health regulatory and research agencies to protect public health. Its four goals are to:

- Coordinate toxicological testing programs within the Department of Health and Human Services.
- Develop and validate improved testing methods and, where feasible, ensure that they reduce, refine, or replace the use of animals.
- Develop approaches and generate data that strengthen scientific knowledge about potentially hazardous substances.
- Communicate information about potentially hazardous substances to health regulatory and research agencies, scientific and medical communities, and the public.

Appendix A provides a brief overview of the main functional components of the NTP.

Purpose

Since its inception in 1978, the NTP has periodically reviewed its research portfolio in order to ensure the NTP is utilizing the best possible science to address its public health mission. In August of 2003, after 25 years of existence, the NTP decided it was again time to review its activities and steer a course for the program into the 21st century. With this in mind, the NTP and the National Institute of Environmental Health Sciences (NIEHS) began a yearlong process to create a "roadmap" for the NTP ("NTP Roadmap"). The goal was to develop a strategy by which the NTP would take advantage of current and emerging research opportunities to maximize its positive impact on public health. The NTP Roadmap, developed with input from leading researchers in academia, industry, government, and advocacy groups, addresses the goals of the NTP Vision (see below) and provides a framework for setting NTP research priorities to achieve the most efficient and effective research portfolio possible. The NTP Roadmap, which has grown in complexity and scope during its development, identifies the challenges and opportunities confronting the NTP today and discusses the directions envisioned for the NTP in the 21st century in three main areas: refining traditional toxicology assays, developing rapid, mechanism-based predictive screens for environmentally induced diseases, and improving the overall utility of NTP products for public health decisions.

> *The NTP Vision for the 21st Century*:
> *To support the evolution of 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.*

The Challenge for the NTP

Over the last two decades, scientists have increasingly studied critical cellular and molecular events (mechanisms) that lead to adverse responses to toxicants. Mechanistic information enhances interpretation of, but does not currently replace, traditional approaches to toxicological evaluation that are the basis for most decisions related to product safety, environmental and occupational hazard assessments, and priority setting for detailed chemical toxicity testing. Mechanistic information may also be useful in the identification of biomarkers of exposure and effect that facilitate the linkage between laboratory research and human risk. Improving the quality, quantity, and utility of mechanistic knowledge is a major impetus behind the NTP Vision. Therefore, as we move forward, the NTP seeks to identify and incorporate more mechanistic approaches into its toxicology assessments and to undertake a systematic and continuing evaluation of the data derived from these new approaches to determine their value in providing improved information for making public health decisions.

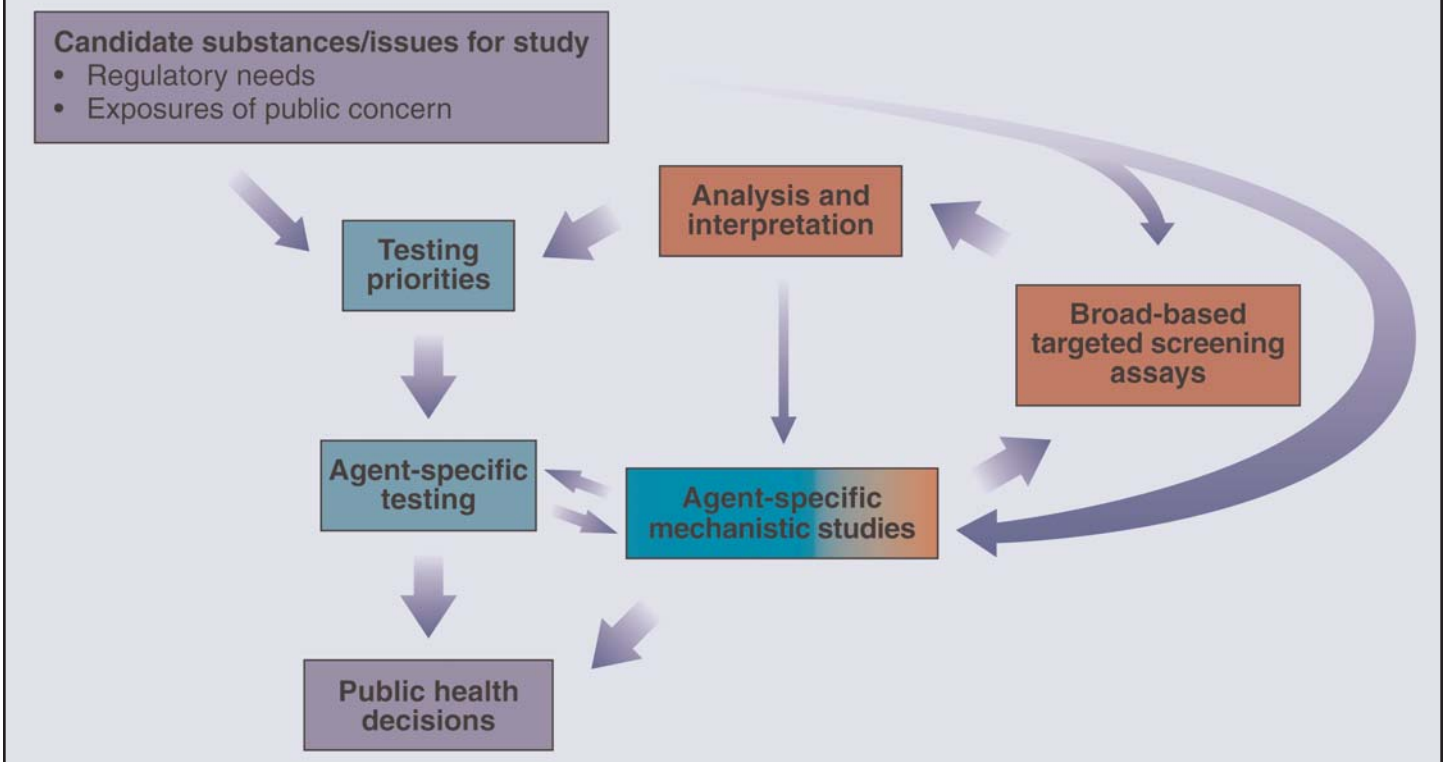
The NTP envisions that over the next decade utilization of our rapidly expanding knowledge of the physiological, biochemical, and molecular bases of disease will lead to the development of, and a gradual transition to, vastly improved and higher-throughput methods for predicting the toxicological impacts of environmental agents. The

NTP recognizes that this transition in methods from predominantly mammalian screens toward more in vitro systems and non-mammalian models must be carefully planned and systematically evaluated to assure scientific and regulatory utility. The NTP is confident that through sustained leadership in creating and applying these mechanistic toxicology tools, we will generate the scientific information and understanding necessary for public health decision-makers to use these new tools to reduce the burden of environmental disease.

The challenge for the NTP and health regulatory and research agencies is to examine the impacts of the growing list of anthropogenic exposures as well as those of natural origin encountered in our daily lives, while also providing the best scientific data possible on the toxic potential of each exposure. Unfortunately, several factors complicate this challenge: the large number of chemical substances in commerce, the complexity of environmental exposures, and the uncertainties about how genetic variability and/or lifestage might interact with environmental exposures to affect risk. The NTP can only address a small fraction of these exposures if it is to provide sufficient information to meet the extensive data needs under the current regulatory risk assessment paradigm; therefore, the NTP must strive to use evolving scientific technologies and expertise to test more efficiently.

Figure 1 illustrates the general flow of the current (teal) NTP research and testing program and highlights additions to the NTP research portfolio (rust) that support the NTP Vision. Currently, nominated substances are selected for study based largely on regulatory needs and deficiencies in the scientific data on safety for substances with significant human exposures. The NTP designs and carries out resource-intensive programs of study to identify observations of toxicity in animals. Mechanistic studies often follow to strengthen these observations and improve our understanding of why or how a specific toxicity occurs. This information ultimately contributes to decisions that affect public health including risk assessment and risk management activities.

Figure 1. Use of Mechanistic Toxicology Studies in Public Health Decision-Making



Mechanistic studies have helped to identify some of the key processes associated with disease initiation and promotion; key processes that should now become targets for a broader evaluation of exposures. At the same time, molecular biology, robotics, and informatics have developed sufficiently to provide the research community with tools to obtain mechanistic data on a greater number of chemicals using a variety of different test systems in a relatively short period of time. Together, this knowledge and these tools will permit the NTP to place greater emphasis on evaluating a broad range and large number of environmental exposures for key mechanistic endpoints and to use this information to guide further research and testing.

The NTP Roadmap places an increased emphasis on the use of alternative assays for targeting the key pathways, molecular events, or processes linked to disease or injury and attempts to incorporate them into a research and testing framework. These less expensive, higher throughput assays will be used to evaluate, or "screen," a greater number of substances and establish priorities for their placement in the existing research and testing program. The results of these screening studies could also potentially stimulate the conduct of more extensive, agent-specific mechanistic studies. The consequence of adding these elements to the NTP's research and testing program is that specific substances or mechanistic hypotheses can feed into the traditional testing program in new ways, leading to an enhanced public health impact. In addition, the NTP envisions collection of these screening data into publicly accessible databases available to the scientific community for addressing questions about the molecular basis of environmentally induced disease.

The remainder of this document identifies new NTP initiatives and changes to NTP programs that are a necessary part of addressing the vision. In developing this roadmap, the NTP sought input from numerous groups including its federal partners, its advisory committees, and the public. If implemented successfully, this framework should allow the NTP to broaden its testing activities to include more exposure scenarios, address susceptibility issues related to the variability in human genetics, and provide better and more targeted scientific guidance for making public health decisions aimed at preventing or reducing adverse health effects.

Roadmap for the NTP Vision: Toxicology Research and Testing

For more than a quarter century, the current battery of toxicology and cancer assays used by the NTP has provided extensive and useful data for predicting human health hazards and protecting public health. These assays will continue to be performed for that purpose. *Any changes in the research portfolio of the NTP will be consistent with the principle that the research conducted, data collected, and analyses performed should have direct relevance to current and future public health decisions.* As such, it is important to ensure that changes in the NTP testing program are acceptable to and developed in concert with NTP-member agencies and the broader scientific community.

Current Research Activities: Over the past two decades, the NTP has expanded the breadth of its evaluations of individual agents and the number of endpoints critically assessed in its bioassays, especially the chronic exposure, 2-year rodent carcinogenicity studies. The initial phase of implementation of the NTP Roadmap will involve a formal review of the designs of all NTP assays to critically analyze their predictive power and determine whether the protocols for these studies should be altered. This review will cover the selection of species and strains of wild type and genetically modified models, the life stages for exposure, the adequacy of current endpoints, and what additional endpoints to target to achieve the goal of optimal utility for scientific/regulatory decisions.

Timeline: Within 18 months, the NTP will examine the design of the current 2-year rodent cancer bioassay. Within 3 years, similar reviews will be conducted on the designs of noncancer studies (*e.g.*, developmental toxicity, immunotoxicity, neurotoxicity) to assure that the data generated are adequate to identify agents of highest concern for effects on human health.

The NTP envisions that studies of gene and protein expression and of metabolic profiling in tissues of exposed animals will play an important role in helping to characterize the response to toxicants and, therefore, lead to a better understanding of the mechanisms through which agents alter disease incidence and progression. These findings will also help to identify appropriate mechanistic targets for further investigation. To improve upon our classical toxicological studies, the NTP plans to incorporate certain functional genomics tools (toxicogenomics, proteomics, and metabolomics) currently available for studying cellular responses into some of its bioassays.

Timeline: Within 12 months, the NTP will devise a strategy for the design of targeted, genomic analyses that focus on endpoints of toxicity being addressed in current studies and that can be performed routinely. The goal of these analyses is to provide mechanistic information useful both for an improved understanding of the toxicity of a given chemical and for the optimal selection of mechanistic targets for high-throughput screening (HTS, see page 5). It will also permit the application of toxicity findings for the chemical under study to other chemicals that target the same mechanism(s). Some of the critical elements for development of these analyses include the identification of targeted genes or gene products, the choice of platform (*e.g.,* slide arrays, bead arrays), and the linkage of the analyses' findings to databases of the NIEHS' National Center for Toxicogenomics (NCT) and NTP-member agencies. The NTP hopes to coordinate these activities, to the extent possible, with ongoing efforts in the public and private sectors. Data collection using some of these genomic analyses is already underway, and once sufficient data are collected, they will be evaluated for their utility and predictability for toxicity. The NTP will seek input from its advisory committees and the broader scientific community in the evaluation of these data.

Roadmap Activities: Toxicology Research Operations

- Review existing protocols and designs and change as needed
- Expand endpoints targeted in *in vivo* studies to include functional genomics
- Develop a high-throughput capability for mechanistic targets
- Further evaluate and refine the use of non-mammalian animal models
- Improve the use of toxicokinetic information
- Expand the use of imaging technologies

The NTP will continue to explore the use of non-mammalian, *in vivo* assays as potential alternative models in toxicology testing. The current NTP project on *Caenorhabditis elegans* (*C. elegans*) should be completed in the next 3 years. This project's objective is to determine the utility of *C. elegans* as a screen for developmental, neurological, and behavioral toxicities. If *C. elegans* is sufficiently sensitive to specific agents with known neurological and behavioral toxicities, the NTP will expand this project to address a broader array of agents. Following its completion, the NTP will evaluate other non-mammalian species as potential medium-throughput screens for additional toxicity endpoints.

Timeline: The NTP plans to hold a workshop within the next 3 years to gain input and recommendations about which promising non-mammalian models to explore.

A critical aspect to understanding or predicting the potential toxicity of a given agent is knowledge about its absorption, distribution, metabolism, and elimination (ADME). Physiologically based pharmacokinetic (PBPK) models have been used successfully for prediction of ADME in humans based on computational models and minimal experimental data. The NTP will continue to develop PBPK models for priority compounds including, where appropriate, more data derived from *in vitro* techniques (partition coefficients, transport parameters, etc.). The NTP plans in the future to address the estimation of key parameters in these models by taking advantage of information on quantitative structural activity relationships (QSAR) and from other predictive tools. Potentially, information on chemicals from HTS will provide data for determining QSARs for use in PBPK modeling. The goal of this expanded activity is to enable the NTP to link exposure to biological effect in a more quantitative way.

The NTP currently emphasizes in the design of its studies full incorporation of the three principle concepts of alternatives-replacement, reduction, and refinement. Further, to be consistent with the Animal Welfare Act and the Public Health Service rules on animal use, the NTP requires that all animal studies be designed to eliminate or, at least, minimize any potential pain or distress. The NTP also requires that investigators and/or contractors have training in humane experimental techniques and, as possible, promotes the use of non-invasive approaches in animal studies. The NTP will hold to these principles and practices as it implements the NTP Roadmap.

Finally, the tools available for acquiring images from tissue sections, carcasses, and live animals have dramatically improved in the last 5 years. The NTP plans as soon as possible to apply these technologies routinely to NTP bioassays as a means for improving the speed and precision of pathology reviews and to

make procedural changes in these reviews to include two- and three-dimensional measures of lesions on slides and in tissues. These imaging tools could dramatically alter the statistical power of many of the studies conducted by the NTP and reduce the number of animals needed for any given assay.

Timeline: An immediate goal is to institute the routine capture of digital images from all pathology slides generated in the NTP 2-year rodent cancer studies and to develop and employ techniques in image analysis to guide the review and systematic evaluation of lesions and tumors. A longer-term goal will be to provide a digital imaging archive of present and past studies on the NTP web site.

New Research Activities: Traditional toxicity testing methods, while of great value in predicting biological responses, are time consuming and resource-intensive. Of the approximately 80,000 chemicals in commerce, relatively few have been fully evaluated for their potential to cause toxicity. Furthermore, new chemical entities are constantly being synthesized. The Environmental Protection Agency (EPA) receives over 2,300 pre-manufacturing notifications each year. Of these, 10-15% have information that suggests the need for more extensive toxicological evaluations. While it is clearly not the responsibility of the NTP to address all of these data needs, it is our responsibility to promote improvements in the science of toxicology that would allow the NTP to efficiently address the large number of agents for which it is responsible. Current testing protocols limit the NTP to providing toxicology and/or carcinogenicity data for only several dozen agents annually. To expand beyond these limits, the NTP needs rapid screening systems that provide information on the toxicity of chemicals, if only for the purpose of helping prioritize agents for more extensive testing. HTS holds the promise of fulfilling this need. HTS is a process for evaluating hundreds to thousands of agents rapidly using robotics to implement tests for activity within *in vitro* biological systems under a variety of conditions. For the purposes of the NTP Roadmap, HTS would entail rapid screening for alterations to mechanistic targets. It also holds the potential to test complex mixtures or evaluate combinations of experimental conditions that would be impossible to conduct in classical *in vivo* assays.

The NTP must overcome some significant challenges before HTS becomes useful as a predictive toxicology tool. These challenges include the development and selection of methods to be used and the development of interpretative models for using HTS data to predict human or animal responses with acceptable accuracy. Because HTS assays are mechanism-based, their predictive capability is limited by our understanding of the biological processes that are key targets of toxicity. This knowledge is evolving, but will be imperfect for the foreseeable future. Still, the potential advantages of HTS are sufficiently great, and the information that may be gained is of such importance to the overall NTP vision for the 21st century, that HTS should be a high priority research area.

The NTP will seek advice from external scientists on the agents to test by HTS, but at a minimum, the list initially will include all applicable agents previously studied by the NTP plus additional agents agreed upon by NTP-member agencies. On a yearly basis, the NTP will review the list of agents targeted for HTS and through the NTP Executive Committee keep NTP-member agencies informed about the HTS proj-

Roadmap Activities: High-Throughput Screening (HTS)

Short-term Activities

- Catalogue available assays
- Convene working groups to provide advice on selection of assays
- Develop assays
- Identify initial set of chemicals for testing

Mid-term Activities

- Continue assay development
- Validate individual assays
- Develop methods for analysis of data
- Develop HTS database
- Review effectiveness

Long-term Activities

- Develop mechanisms to make chemical sets and tissue banks available for external researchers
- Evaluate HTS data for predictability of toxicity
- Develop a communication plan
- Review effectiveness

ect. The NTP in collaboration with its member agencies and with advice from extramural basic science researchers will develop the assays for HTS. Their focus will be on cellular targets and responses that are highly suspected or known to influence disease etiology and/or influence our interpretation of the relevance of findings in laboratory studies to the potential for risk of disease in humans. The NTP anticipates that these assays will use a wide range of exposure concentrations (several orders of magnitude) and both human and animal sources for materials (cells, tissues, genes, receptors, etc.) to ensure that major uncertainties in extrapolating the results from animals to humans and from high to low exposures can be addressed. The database created by this activity will be peer-reviewed by the NTP Board of Scientific Counselors (BSC) and publicly available. Mechanistic endpoints initially targeted by the HTS program may include genotoxicity, cytotoxicity, cell proliferation, apoptosis, and critical receptor-mediated activities for which commercially available assays already exist.

The NTP will convene working groups of scientists selected for their expertise in targeted areas and drawn from government, academia, and industry to provide advice on the selection of HTS assays. Because a rich database on the potential mechanisms of carcinogenicity and reproductive and developmental toxicity already exists, the initial focus will be on assays that evaluate mechanisms of toxicity for these endpoints. The NTP anticipates initially convening one working group per year to examine available HTS assays for critical mechanistic endpoints (*e.g.*, DNA damage/repair, disruption of the cell cycle, mitochondrial toxicity, etc). The NTP will pursue the development of HTS assays by NIEHS intramural scientists and through partnerships with the extramural scientific community. The accepted assays will be adapted for HTS in NTP contract laboratories. The NTP will pursue ways to make the HTS assays, chemicals, tissues, cell lines, and other associated materials available to the extramural scientific community for collaborative research.

Timeline: The NTP plans to convene the first HTS working group within the first 8 months of 2005 and have an HTS facility active within 20 months. Prior to the first meeting of the HTS working group, NTP staff will identify the initial set of chemicals for HTS that will include, at a minimum, appropriate chemicals from the 500 plus agents evaluated in NTP carcinogenicity and reproductive and developmental toxicity studies.

Results from the HTS project will help guide refinements to the choice of model(s) and designs for further testing. The NTP anticipates that acquisition of knowledge regarding the mechanistic targets of groups of chemicals will allow the program, in the long run, to more effectively identify the most appropriate chemicals for in depth toxicological characterization and the optimal species and strains of wild type and genetically modified rodent models to use in evaluations of chemical safety.

The NTP will develop an active communication plan for the HTS program that focuses on education about its goals, the assays, and the proper interpretation and use of the data in hazard evaluations of chemicals.

Roadmap to a Vision: NTP Nominations

Currently, the individual programs within the NTP [*e.g,* Report on Carcinogens (ROC), Toxicology Research Operations, the Center for the Evaluation of Risks to Human Reproduction (CERHR), the NTP Center for Phototoxicology (NCP), and the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)] separately receive nominations. In addition, although there are common elements, each group has its own process for the review and selection of nominations. Nominations are generally received from a variety of stakeholder groups including environmental groups, the public, industry, academia, and federal, state, and local governments. In addition, nominations may arise within NTP programs, for example, when findings from NTP studies result in a recommendation for additional testing or when they support a nomination to the ROC.

While this process has worked well in the past, predominantly for prioritization of chemicals for toxicity testing, the greater emphasis on knowledge gained from mechanistic evaluations will affect the nature of the nominations. Additional emphasis on mechanistic toxicity will likely result in nominations for evaluations of targeted endpoints for specific set of chemicals, nominations of test methods for use as screening approaches, and nominations of concepts. Thus, the ability to handle this broader scope of nominations will necessitate increased coordination within NTP programs (*e.g.*, data analysis, informatics, etc.) and with the NTP's interagency partners.

The NTP will establish an Office of Nominations to serve as a clearinghouse for nominations. This office will receive nominations, triage them to the appropriate NTP programs, and maintain a database of all nominations and the actions on them. *Figure 2* illustrates this concept.

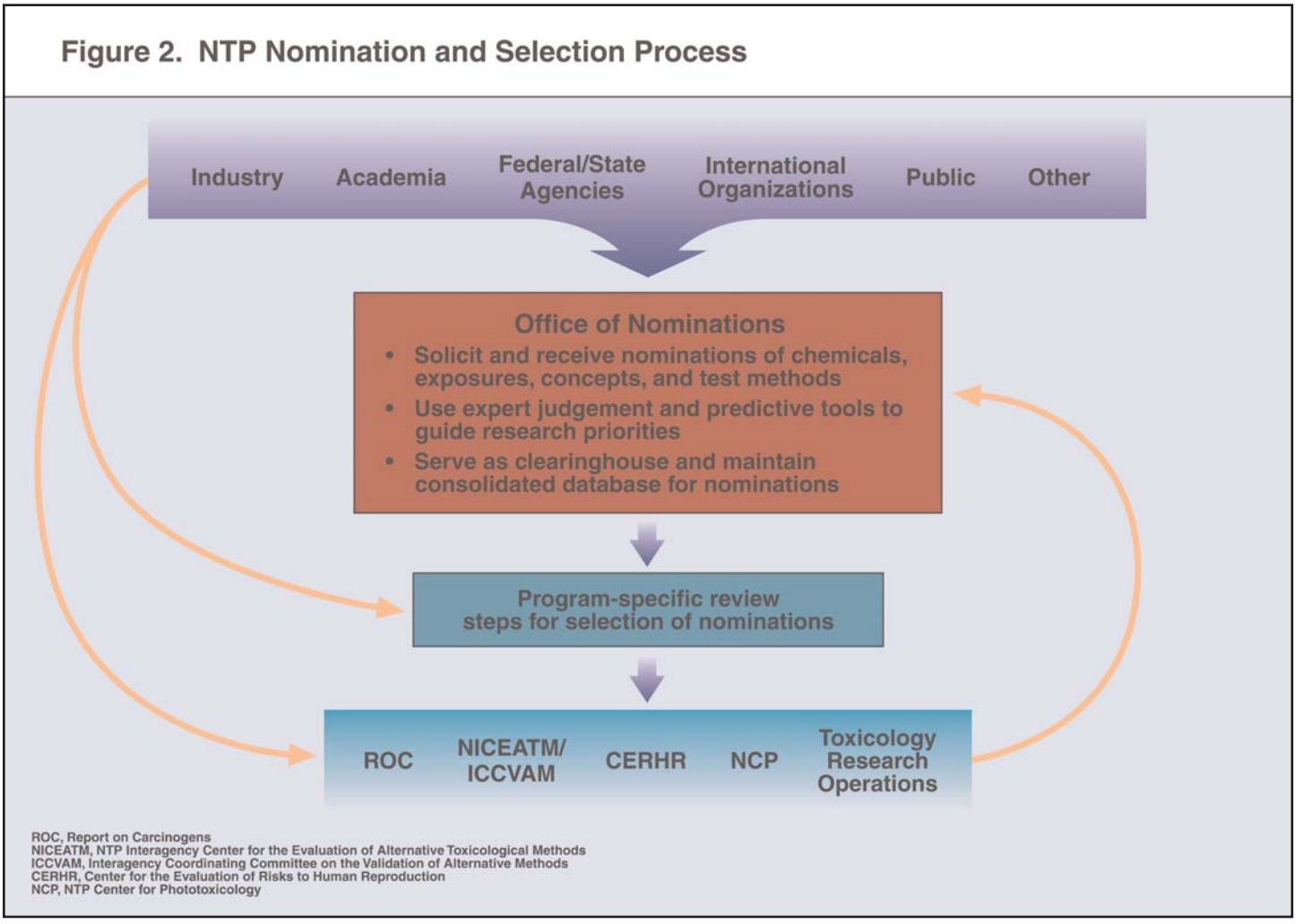
Timeline: The NTP plans to establish the Office of Nominations by early 2005 and have the database functional by 2006.

Roadmap to a Vision: Evaluation

Data alone do not constitute knowledge; knowledge comes from the interpretation of data through the scientific method. Although the NTP can develop and implement new testing procedures and generate data that may enable toxicology to evolve toward a more predictive science, interpretation and analysis of these data are critical and cannot rest wholly with the NTP. The ultimate responsibility for making decisions that impact public health rests predominantly with international, national, and state regulatory authorities. But, the private sector must also understand the basis for regulatory decisions that affect each and every person. The NTP must work with all its stakeholders to ensure that the context and nature of data generated by the NTP are clearly articulated and support risk assessment decisions based on scientific information of the highest quality.

The key to the future of predictive toxicology is through an improved understanding of how data on mechanism are relevant to human health hazards and risk. Developing this understanding will not be an easy task. One must identify the mechanisms to be studied, determine which assays are best for characterizing these mechanisms, determine which agents are known to work through these mechanisms, and then compare these results with findings from agents of known relevance to human health. This process will be iterative and require constant feedback between obtaining data, evaluating these data, and determining what needs to be done next. As this process moves forward, the NTP will communicate its understanding of the validity and predictability of these data to allow appropriate use in public health decision-making. The NTP recognizes that it has an obligation to prevent the misuse or misunderstanding of the significance of data from unvalidated assays by regulatory agencies and the public. *Activities and assays developed under the NTP Roadmap will be done in cooperation and consultation with the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) to maximize their value to regulatory agencies.*

Figure 2. NTP Nomination and Selection Process



The scientific expertise and skill needed to generate, evaluate, and interpret mechanism-based data do not reside at the NTP alone. In order to ensure the most effective development and use of mechanistic information as predictive tools in toxicology, the NTP will engage the external scientific community by holding workshops and developing appropriate research contracts, grants, and cooperative agreements. In addition, the NTP will establish or sponsor training programs in needed areas.

Roadmap to a Vision: Partnerships

The NTP has always used an open and inclusive process to develop the science necessary to address key issues of public health concern. In order to remain a leading source of objective, scientific data for public health decisions, the NTP must continue to adhere to this basic premise.

Improving Information Dissemination: Some improvements could be made to strengthen the NTP's ties to the scientific community, public health agencies, and stakeholders and to a public concerned about environmental hazards and health risks. The NTP will review its outreach activities and seek ways to broaden communication about its programs and priorities through electronic and printed materials, its web site, and exhibits at national/international meetings.

Key to the success of the NTP is its ability to deliver a research product with well-understood limitations and strengths. The majority of this research is in the form of technical data from NTP studies accumulated in NTP databases and scientific reports (ROC and NTP-CERHR Monographs) derived from these and other data. However, the databases maintained by the NTP are technically complicated and not easily accessible by individuals with limited experience in the types of data the NTP produces. It is critical that the NTP develop better tools to enable public access to both NTP data and NTP reviews. *Using the concept of a single portal, the NTP will partner with other agencies, especially the National Library of Medicine, to provide user-intuitive, web-based tools to access NTP databases: tools that can intelligently search these databases, identify appropriate resources, and report them in a manner useful to scientists, regulators, and NTP stakeholders.*

Broadening Scientific Input: The NTP also needs to strengthen stakeholder participation through expanded communication and outreach and provide improved means to keep abreast of current and future NTP activities. The NTP will provide guidance to aid NTP staff in determining the appropriate points in any research activity where NTP stakeholders can play important roles. The NTP will hold conferences and workshops to bring stakeholders together to provide input and direction on targeted issues associated with implementation of the NTP Roadmap's activities. Such efforts will enhance opportunities for interested groups to contribute substantively to these activities and play an appropriate role in guiding the NTP's priorities. *Both the BSC and the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) will serve as important advisors to help guide the NTP forward with implementation of the NTP Roadmap.*

The modifications to NTP research and testing programs described previously will require an expansion of the expertise traditionally included on NTP study design teams. The NTP believes that an untapped, current source for that expertise resides in the basic research scientists at NTP-member agencies and their grantees. Working through the agencies represented on the NTP Executive Committee, the NTP will link basic researchers with NTP design teams to expand the expertise needed to address changes in its study designs.

Expanding Ties with Federal Partners: Many other research groups within the federal government have ongoing activities intended to improve and advance their programs as they progress in the 21st century. The NTP will make every effort to collaborate with these groups to ensure an optimal use of resources. Of note is the NIH Roadmap that will contribute substantively to our understanding of the biological basis of disease. The activities of the NIH Roadmap will allow the NTP to strengthen its activities in mechanism-based toxicology through the identification of critical pathways affecting disease incidence and progression. *The NTP will partner with the NIH in common research areas.*

Both the NIEHS and the EPA are currently sponsoring committees of the National Academy of Sciences to address critical needs in certain aspects of toxicology. *The NTP will remain a partner with the NIEHS and the EPA on these activities and use the recommendations from these consultations to improve its research efforts.*

The EPA is also establishing a new Computational Toxicology Initiative that will provide better tools for more rapid risk assessment and more efficient strategies for prioritizing chemicals for screening and testing. *The NTP will work closely with the EPA to ensure that the NTP Roadmap and the EPA Computational Toxicology Initiative are complementary.*

The Food and Drug Administration (FDA) has issued a "Challenge and Opportunity on The Critical Path to New Medical Products" to address the growing crisis in moving basic discoveries to the market where they can be made available to patients. *The NTP will work with the FDA to determine how predictive toxicology might contribute to this process.*

The National Institute for Occupational Safety and Health (NIOSH) has recently focused its research programs to address its National Occupational Research Agenda (NORA). *The NTP will work with NIOSH to determine how predictive toxicology might contribute to this process.*

Summary

The NTP Roadmap outlines a framework by which the NTP will modify, adapt, and improve its programs to better address its mandate in providing scientific information for protection of public health. While preserving its core research and testing functions and in concert with NTP-participating agencies, this plan outlines an orderly process for the selection, performance, analysis, and utilization of data from additional assays designed to examine general mechanisms of response of biological systems to chemical and physical stressors.

Data derived from selected mechanistic assays have informed interpretation of the findings from traditional NTP bioassays for many years, but they have not been extensively used in the selection of individual agents for study or to help define scientific hypotheses that might be approached in a coordinated bioassay testing program. The generation of mechanistic information in short duration or medium/high-throughput assays for priority setting will create databases of biological observations that can be examined for their predictive value. This offers hope that at some point, predictive models and approaches will become validated and utilized in reaching public health decisions for the many new chemicals, products, and mixtures to which humans are exposed in modern society.

The transition of toxicology from a low-throughput, observational science to a high-throughput, predictive science focused on target-specific, mechanistic observations is a challenging but necessary goal. However, successful achievement of this goal must be an iterative process to evaluate and assess technologies/activities/programs and optimize their effectiveness. Recognizing that existing programs can also be improved, the NTP Roadmap calls for a reevaluation of many aspects of the standard toxicology and cancer bioassay protocols. Specific new activities begin with an expanded strategy for NTP nominations charged with the selection of both agents and assays to create meaningful predictive mechanistic databases. The new approaches outlined in this roadmap will also require an expansion of the NTP's current approach for study design to include a wider set of disciplines and the development and utilization of a broader array of data. New methods of data analysis will be created to provide better integration of toxicokinetic information into existing program outputs, mechanistic and toxicokinetic information into predictive models of injury and disease, and predictive models into the evaluation components of the NTP (ROC, CERHR, NCP, and NICEATM/ICCVAM) and government regulatory agencies.

A central theme in all these activities is to be mindful of the animal resources needed and strive to address the 3Rs effectively-**reduce** the number of animals used in these research programs, **refine** the endpoints to derive the maximum amount of information possible with the minimum amount of pain and suffering, and **replace** species currently used with lower species or *in vitro* systems.

Finally, the NTP Roadmap calls for the creation of even stronger ties between NTP-participating agencies and the larger scientific/regulatory community. Expanding existing partnerships with public health agencies and basic research programs will be necessary to address the elements of this roadmap and facilitate its implementation and will make effective communication an increasingly important component of the program's activities. The ultimate success of the NTP Roadmap will be measured in tangible improvements in public health as a result of changes in the way we identify toxicants and understand and minimize the potential impacts of their exposures on human health. The NTP, the larger toxicology community, and the public must be receptive to change if we are to take full advantage of the promise of predictive toxicology for improving public health decisions.

As noted by philosopher John Schaar,

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

Appendix A

Overview of Current NTP Functional Activities

The major research activities of the NTP[1] are summarized in Figure A1. These include the organization of functional groupings of several laboratories, centers, and offices within the NTP structure as shown in Appendix B; generally, individual scientists within the NTP perform duties that cross the functional groupings depicted in Figure 2 (see page 7). In all, 15 federal agencies participate in these activities on a routine basis (Appendix C).

In general, the NTP receives **nominations**, such as substances, agents, or issues of concern, for evaluation mostly from federal agencies. After review and acceptance of a nomination, the chemical or agent is assigned to the relevant research laboratory or center. If the nomination requires the acquisition of new scientific data, it is assigned to a group from **Toxicology Research Operations** where teams of NTP scientists design and conduct the appropriate research program. The toxicology databases produced by the NTP all arise from the studies developed and conducted by the Toxicology Research Operations. Their activities are multifaceted covering a wide range of possible toxicological assays and are conducted through contracts or in the laboratories of NTP-member agencies including the NIEHS, NCTR, NIOSH, EPA, the NCEH/ATSDR, and others.

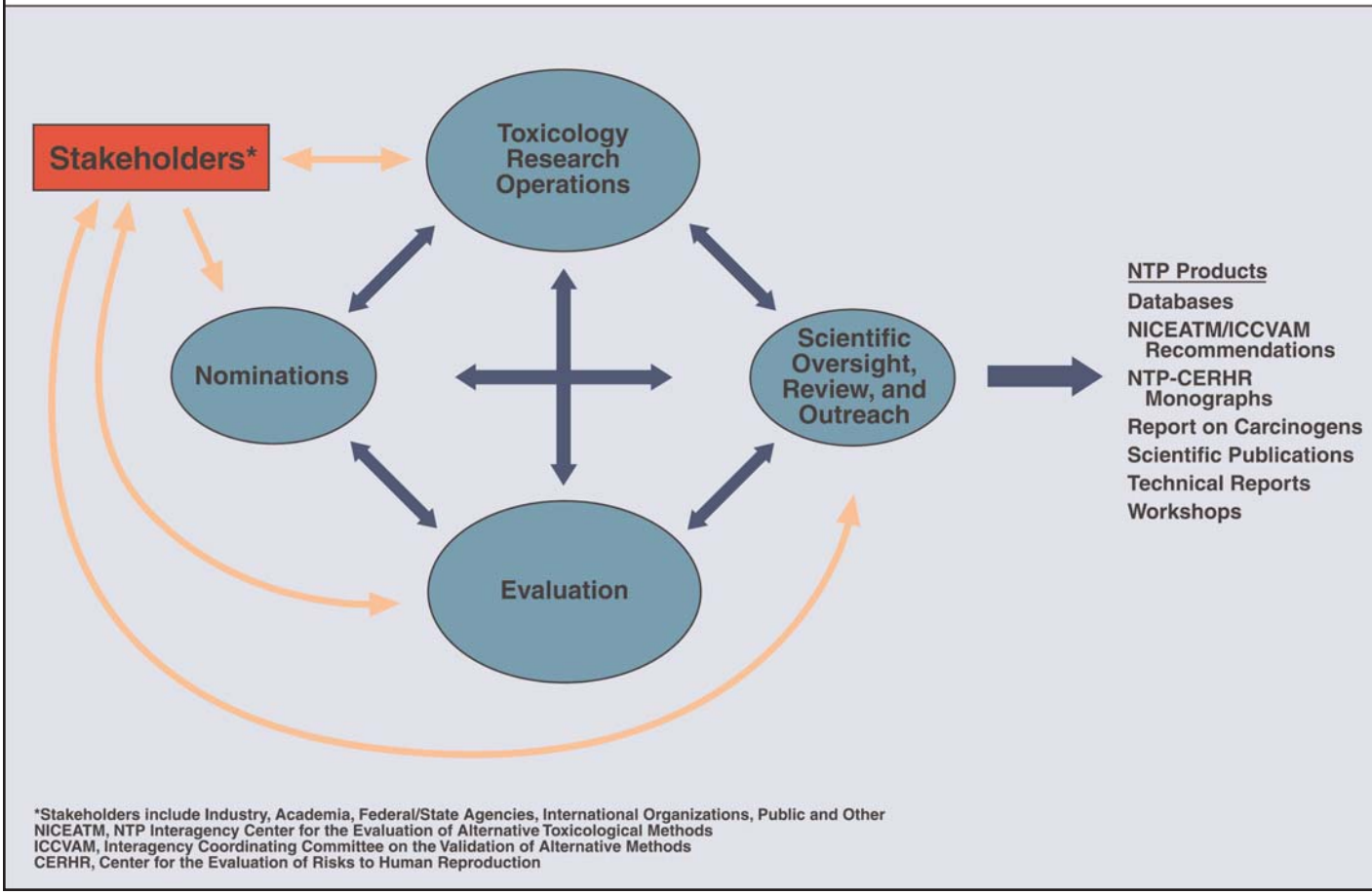
Evaluation of research is central to most of the products produced by the NTP. Studies conducted through the Toxicology Research Operations result in reports in the NTP Toxicology Report series and NTP Technical Report series and/or publications in the scientific literature. All of these documents undergo some form of both internal and external peer review. Formal reviews of published data are also conducted to develop reports that identify and communicate specific hazards such as the ROC and NTP-CERHR Monographs. The NTP also coordinates the evaluation of alternative toxicological models through NICEATM and ICCVAM to promote the development, validation, and harmonization of alternative toxicological test methods to reduce animal use, refine testing procedures to reduce pain or suffering, and/or replace animals with lower organisms or *in vitro* systems. Finally, the NTP supports a large number of workshops to address specific areas of concern, identify data gaps, and develop guidance on the design, conduct, and interpretation of toxicological findings.

Scientific oversight and review of the NTP is multifaceted. All NTP activities are under the Director of the NIEHS who is also the NTP Director. Agency oversight of the activities of the NTP is coordinated through the NTP Executive Committee (see Appendix C). In addition, the BSC, a federally chartered advisory committee whose members are appointed by the Secretary of Health and Human Services, advises the NTP on all aspects of its research and testing activities. Similarly, the SACATM provides advice to the NTP, the NIEHS, NICEATM, and ICCVAM in areas related to the development, implementation, and validation of alternative methods for safety assessment. The NIEHS Director appoints members to this federally chartered advisory committee.

No changes are envisioned for scientific review and oversight, although the groups involved in this activity will play an integral part in the implementation and evaluation of all NTP initiatives.

[1]See Appendices B and C for the definition of acronyms used in this Appendix.

Figure A1. Functional Groupings of the Major Activities and Products of the NTP



*Stakeholders include Industry, Academia, Federal/State Agencies, International Organizations, Public and Other
NICEATM, NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
ICCVAM, Interagency Coordinating Committee on the Validation of Alternative Methods
CERHR, Center for the Evaluation of Risks to Human Reproduction

Appendix B

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

Appendix C

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

[1]Member of NTP Executive Committee

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