

## **Toxicology in the 21<sup>st</sup> Century: The Role of the National Toxicology Program**

### **A Draft Vision for the National Toxicology Program**

In 1995, the National Toxicology Program (NTP) initiated a program to use mechanism-based toxicology to develop, evaluate, and validate better toxicological test methods. The effort has led to major changes in toxicology at the national and international level. In recent years, mechanism-based toxicology has led to a significant improvement in the scientific basis for public-health decisions, but has not dramatically reduced the need for the empirical tests developed in the 1970's and 80's that were the basis for many decisions that relate to product safety, evaluation of environmental and occupational hazards, and prioritization of chemicals for further testing. It is time to focus on changing the scientific basis for decision making and work toward replacing older empirical tests with faster, mechanism-based assays. Two activities must occur simultaneously if this change is to occur. First, we need to aggressively incorporate new laboratory methods into the NTP testing program and insure that data produced can meet the high quality standards of the NTP. Second, we need to develop strategies for the integration of new types of scientific data into the decision-making process. The replacement of the empirical disease-specific testing models of the 1970's and 80's with mechanism-driven models for the new millennium is a daunting challenge. The NTP can and should provide the context whereby new models, new methods and new approaches to the evaluation of data can be used confidently to make appropriate decisions that protect the public and the environment. Only through the acceptance of these new approaches in setting public health priorities will we be able to show that better science truly leads to better decisions.

### **Background**

The last decade of the 20<sup>th</sup> Century and the first 2 years of the 21<sup>st</sup> Century have seen dramatic changes in the biological sciences. From the sequencing of the genome in numerous species to the ability to scan single cells for broad spectrum changes in gene expression, the tools available to toxicology and the skills needed to appropriately use these tools have changed dramatically. With this in mind, it is time for the NTP to carefully evaluate its function and role in providing leadership in both toxicological research and toxicological testing for the United States. Over the next year, the NTP intends to outline a philosophy and vision as we move into the 21<sup>st</sup> Century. This vision is intended to provide a framework for moving 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. As a vision for the NTP is developed, a roadmap towards achieving that vision will also be developed. Some of the changes and directions in the roadmap will be specific to the NTP, its operations and its personnel while others apply to the broader field of toxicology as it is currently practiced.

The mission of the NTP is to provide toxicological evaluations on substances of public health concern, develop and validate improved (sensitive, specific, rapid) testing

methods, develop approaches and generate data to strengthen the science base for risk assessment and to communicate with stakeholders (government, public, industry, academia, environmental community) involved in the application and use of scientific data in making decisions about the safety of agents routinely encountered by humans. The overall goal of the NTP, encompassed by these mission elements, is to provide the best science possible for preventing disease due to human exposures. The changing nature of biological science is such that this goal can never really be attained; it is a goal that requires constant diligence to insure that the tools of modern biological science are used appropriately and efficiently. In its current manifestation, the NTP accomplishes its mission and chases this goal through toxicological testing in contract laboratories, collaboration and cooperation with multiple federal agencies, toxicological research and testing at the National Center for Toxicological Research (NCTR) of the Food and Drug Administration (FDA), human exposure and toxicity research at the National Institute of Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention (CDC), biological, toxicological, clinical and epidemiological research in the intramural laboratories of the Division of Intramural Research (DIR) at the National Institute of Environmental Health Sciences (NIEHS), support of research grants through the Division of Extramural Research and Training (DERT) of the NIEHS, NTP Centers including the Report on Carcinogens (ROC), the Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), Center for the Evaluation of Risks to Human Reproduction (CERHR), the Phototoxicology Center (NTPPTC) at the NCTR, and the National Center for Toxicogenomics (NCT), collaboration and support of research with other national and international toxicology and public health agencies, review and evaluation of data gaps in our understanding of environmentally induced diseases through the Office of Nominations (NTPON) and focused conferences and symposia, and communications to a broad spectrum of stakeholders using public meetings, electronic media and print media managed by the NTP Liaison and Scientific Review Office (NLSRO). In developing a vision and road map to guide the efforts of the NTP for the next decade, the function and activities of each of these components of the Program will be studied and specific directions to improve their functionality towards addressing the goal of the NTP will be developed.

In reviewing the overall activities of the NTP, it is clear that some activities are more effective than others in providing national and international leadership in their respective areas of focus. However, there are some key areas of activity in all aspects of the NTP that could be improved and these areas will form the basis for most of the changes needed to guide the Program into the next decade. Two of the primary responsibilities of the NTP are the translation of basic research methods into tools for improving the scientific evaluation of health risks and the development of guidance on interpreting scientific data when making public health decisions. Currently, all of the various entities that make up the NTP are struggling with the rapid changes in biology brought on by the surge of new tools in molecular biology and computer science. It is imperative that the Program develops a focused and coordinated effort to rapidly incorporate these changes into our activities. During the same period of rapid change experienced by the biological sciences, information technology was exploding with faster computers, international linkage of desktops and software tools that are able to accomplish tasks that only a few

years ago seemed impossible. Science is rapidly approaching a point where hypotheses will be developed and evaluated using information gathered from diverse locations across the globe. As with new molecular tools, the Program needs to develop a focused and coordinated effort to support and implement these new computational tools into our overall activities.

A core element of the NTP is the design, conduct, evaluation and communication of toxicological tests in a broad number of areas of toxicological concern ranging from genetic toxicity to carcinogenesis. Through the testing program, the NTP has been a leader in developing and implementing experimental designs that not only address data gaps for the agent being tested, but contribute to our fundamental understanding of toxicity in the broader context. This strength of the testing program needs to be further developed to insure that every evaluation done by the testing program contributes to knowledge-based safety evaluations that use the broadest possible range of scientific evidence in reaching a decision. As new methods are developed and gain greater acceptance in developing public health decisions, our dependence on the traditional testing paradigms should diminish. During this time of transition, scientific quality and clarity must be preserved to insure that decisions based solely upon new methods do not endanger the health of the public or introduce greater scientific uncertainty than the approaches used in the last century.

Only through a concerted effort focused on the linkage between mechanism and disease will toxicology achieve sufficient predictiveness to replace disease specific testing models with mechanism-focused assays that are cheaper, faster and closely linked to disease incidence and progression. The NTP's current focus on developing a vision and roadmap for the future should enable the Program to lead the field of toxicology into the 21<sup>st</sup> Century and to continue to provide the scientific data and knowledge necessary to improve public health.