NATIONAL TOXICOLOGY PROGRAM

ANNUAL REPORT FOR FISCAL YEAR 2004

National Institute of Environmental Health Sciences, National Institutes of Health
National Center for Toxicological Research, Food and Drug Administration
National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention

June 2006

Department of Health and Human Services

National Toxicology Program

NIH Publication No. 06-5990

FREQUENTLY USED ABBREVIATIONS

ATSDR	Agency for Toxic Substances and Disease Registry
CDC	Centers for Disease Control and Prevention
CERHR	Center for the Evaluation of Risks to Human Reproduction
CPSC	Consumer Product Safety Commission
DOD	Department of Defense
DOE	Department of Energy
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
ICCEC	Interagency Committee for Chemical Evaluation and Coordination
ICCVAM	Interagency Coordinating Committee for the Validation of Alternative Methods
NCI/NIH	National Cancer Institute of the National Institutes of Health
NCP	NTP Center for Phototoxicology
NCTR/FDA	National Center for Toxicological Research of the Food and Drug Administration
NCEH/CDC	National Center for Environmental Health of the Centers for Disease Control and Prevention
NICEATM	NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
NHANES	National Health and Nutrition Examination Survey
NIEHS/NIH	National Institute of Environmental Health Sciences of the National Institutes of Health
NIH	National Institutes of Health
NIOSH/CDC	National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention
NIST	National Instititute of Standards and Technology
NLM	National Library of Medicine of the National Institutes of Health
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PBPK	Physiologically Based Pharmacokinetic
RoC	Report on Carcinogens

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OVERVIEW OF THE NATIONAL TOXICOLOGY PROGRAM

MISSION AND GOALS

Currently, the Toxic Substances Control Act Chemical Substance Inventory, first published in 1979, lists over 80,000 chemicals as being available for sale and use in the United States. Approximately 850 active pesticide ingredients are formulated into approximately 17,000 pesticide products. An estimated 500-600 new industrial chemicals are introduced annually into US commerce. The effects of many of these substances on human health are unknown, yet people and our environment may be exposed to them during their manufacture, distribution, use, and disposal or as pollutants in our air, water, or soil. While relatively few substances are thought to pose a significant risk to human health, safeguarding the public depends upon identifying the effects of these agents as well as certain naturally occurring chemicals, and determining the levels of exposure at which they may become potentially hazardous to humans.

The Department of Health Education and Welfare (now the Department of Health and Human Services, HHS) established the National Toxicology Program (NTP) in 1978. The NTP is an interagency program whose mission is to evaluate agents of public health concern by developing and applying the tools of modern toxicology and molecular biology. In carrying out its mission, the NTP has several goals to:

- provide evaluations of 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.
- communicate with all stakeholders including government, industry, academia, the environmental community, and the public.

ORGANIZATIONAL STRUCTURE AND OVERSIGHT

Three agencies, the National Institute of Environmental Health Sciences of the National Institutes of Health (NIEHS/NIH), the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention (NIOSH/CDC), and the National Center for Toxicological Research of the Food and Drug Administration (NCTR/FDA), form the core for this program (Figure 1). The NTP is located administratively at the NIEHS/NIH and the Director of the NIEHS/NIH serves as the NTP Director. The National Cancer Institute of the National Institutes of Health (NCI/NIH) was a charter agency of the NTP and continues to participate on the NTP Executive Committee. The NCI/NIH carcinogenesis bioassay program was transferred to the NIEHS in July 1981. Questions and inquiries about the NTP can be directed to the NTP Office of Liaison and Scientific Review (919-541-0530 or *liaison@starbase.niehs.nih.gov*, see Communication and Public Outreach, page 6).

NTP Management

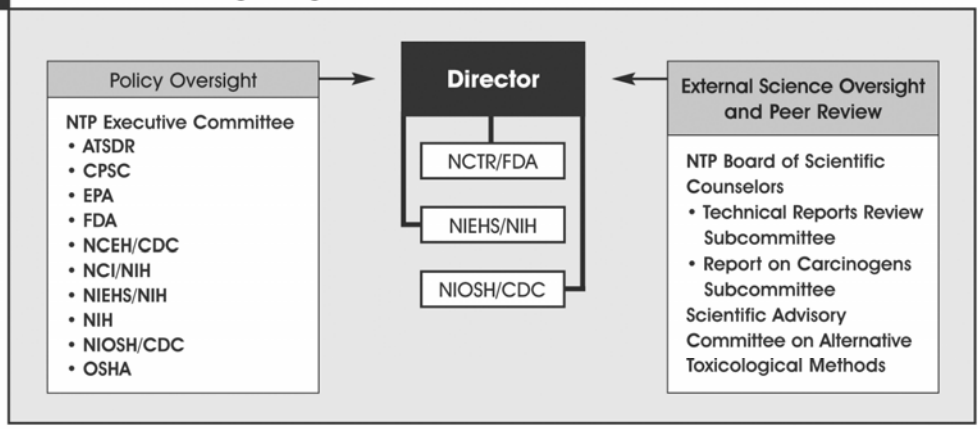
Dr. Kenneth Olden, Director of NIEHS/NIH and NTP
Dr. Christopher J. Portier, NTP Associate Director

Agency Program Management

NCTR/FDA: Dr. William T. Allaben, Associate Director for Scientific Coordination
NIEHS/NIH: Dr. Christopher J. Portier, Director, Environmental Toxicology Program
NIOSH/CDC: Dr. Albert E. Munson, Director, Health Effects Laboratory Division

Staff of the agencies involved with the program and their contact information are provided in Appendix 1.

Figure 1 **National Toxicology Program**



ATSDR, Agency for Toxic Substances and Disease Registry; CPSC, U.S. Consumer Product Safety Commission; EPA, U.S. Environmental Protection Agency; FDA, Food and Drug Administration; NCEH/CDC, National Center for Environmental Health of the Centers for Disease Control and Prevention; NCI/NIH, National Cancer Institute of the National Institutes of Health; NCTR/FDA, National Center for Toxicological Research of the Food and Drug Administration; NIEHS/NIH, National Institute of Environmental Health Sciences of the National Institutes of Health; NIH, National Institutes of Health; NIOSH/CDC, National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention; OSHA, Occupational Safety and Health Administration.

Advisory Board and Committees

NTP Board of Scientific Counselors

The NTP Board of Scientific Counselors ("the NTP Board") provides scientific oversight to the program including its centers. The NTP Board can be composed of up to 35 scientists, primarily from the public and private sectors. A list of the current membership (as of October 2004) is provided in Table 1. The NTP Board's members serve terms of up to four years. Members of the NTP Board are distributed among the parent committee and two standing subcommittees in order to provide the necessary scientific expertise to the program. The NTP Board's Technical Reports Review Subcommittee meets approximately once a year and provides peer review of NTP long-term toxicology and carcinogenesis technical reports. This subcommittee also provides peer review by mail of NTP toxicity studies. The Report on Carcinogens Subcommittee of the NTP Board provides external scientific evaluation and peer review of substances nominated for listing in or delisting (removal) from the Report on Carcinogens (see page 13). Additional information about the NTP Board, including minutes from its meetings, are accessible on the NTP website (*http://ntp.niehs.nih.gov/* select "Advisory Board & Committees") or from Dr. Barbara S. Shane (NIEHS/NIH).

Contact Information: NTP Liaison and Scientific Review Office, Dr. Barbara S. Shane, Executive Secretary, NIEHS/NIH, P.O. Box 12233, MD A3-01, 111 T.W. Alexander Dr., Research Triangle Park, NC 27709; T: (919) 541-4253; *shane@niehs.nih.gov*.

Table 1. NTP Board of Scientific Counselors Membership Roster

Name and Title	Affiliation	Term Ends	Board Service[1]
Larry S. Andrews, Ph.D. Director, Toxicology Department	Rohm and Haas Company Spring House, PA	12/31/04	NTP BSC TRRS
Diane F. Birt, Ph.D. Distinguished Professor & Director, Center for Research on Botanical Dietary Supplements Department of Food Science & Human Nutrition	Iowa State University Ames, IA	6/30/06	NTP BSC TRRS
Aaron E. Blair, Ph.D., M.P.H. Occupational & Environemental Epidemiology Branch	National Cancer Institute, NIH Bethesda, MD	6/30/05	NTP BSC RoC
Gail Charnley, Ph.D. Principal	Health Risk Strategies Washington, DC	6/30/05	NTP BSC RoC
Harvey Checkoway, Ph.D., M.P.H. Professor, Department of Environmental Health & Epidemiology School of Public Health & Community Medicine	University of Washington Seattle, WA	6/30/05	NTP BSC RoC
George P. Daston, Ph.D. Research Fellow Miami Valley Laboratories	The Proctor and Gamble Company Cincinnati, OH	6/30/06	NTP BSC
Elizabeth Delzell, M.S.P.H., S.D. Professor, Department of Epidemiology School of Public Health	University of Alabama Birmingham, AL	6/30/06	NTP BSC RoC
Michael R. Elwell, D.V.M., Ph.D. Research Advisor Pathology, Drug Safety Evaluation	Pfizer Global Research and Development Groton, CT	6/30/05	NTP BSC TRRS
Howard Frumkin, M.D., Dr.P.H. Professor, Department of Environmental & Occupational Health The Rollins School of Public Health	Emory University Atlanta, GA	6/30/05	RoC
Thomas A. Gasiewicz, Ph.D. Professor, Department of Environmental Medicine Environmental Health Sciences Center	University of Rochester School of Medicine Rochester, NY	6/30/05	NTP BSC TRRS
John P. Giesy, Jr., Ph.D. Distinguished Professor, Department of Zoology	Michigan State University East Lansing, MI	6/30/06	NTP BSC TRRS
Shuk-Mei Ho, Ph.D. Professor , Department of Surgery Division of Urology	University of Massachusetts Medical School Worcester, MA	6/30/05	NTP BSC TRRS
Charlene A. McQueen, Ph.D. Professor, Department of Pharmacology & Toxicology College of Pharmacy	University of Arizona Tucson, AZ	6/30/06	NTP BSC TRRS
Maria T. Morandi, Ph.D., C.I.H. Assistant Professor, Department of Environmental Sciences School of Public Health	University of Texas Houston, TX	6/30/06	NTP BSC RoC
Barbara C. Pence, Ph.D. Associate Vice President for Research Associate Dean for Research in the Graduate School Professor, Department of Pathology	Texas Tech University Health Sciences Center Lubbock, TX	6/30/05	NTP BSC RoC
James A. Popp, D.V.M., Ph.D. CEO	Stratoxon LLC Lancaster, PA	6/30/05	NTP BSC RoC
Stephen M. Roberts, Ph.D. Professor, Center for Environmental & Human Toxicology	University of Florida Gainesville, FL	6/30/05	NTP BSC TRRS
Mary Vore, Ph.D. Professor & Director, Graduate Center for Toxicology	University of Kentucky Lexington, KY	6/30/05	NTP BSC TRRS
Cheryl Lyn Walker, Ph.D. Professor, Department of Carcinogenesis M.D. Anderson Cancer Center	The University of Texas Smithville, TX	6/30/05	NTP BSC TRRS

Name and Title	Affiliation	Term Ends	Board Service[1]
Bruce S. Weir, Ph.D. William Neal Reynolds Professor, Department of Statistics	North Carolina State University Raleigh, NC	6/30/05	NTP BSC

Scientific Advisory Committee on Alternative Toxicological Methods

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) is a federally chartered advisory committee established on January 9, 2002, in response to the ICCVAM Authorization Act of 2000 (Public Law 106-545). SACATM advises the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), and the Director of the NIEHS regarding statutorily mandated duties of ICCVAM and activities of NICEATM (see page 22). SACATM provides advice on priorities and activities related to the development, validation, scientific review, regulatory acceptance, implementation, and national and international harmonization of new, revised, and alternative toxicological test methods. Alternative methods are those that reduce, refine (lessen or avoid pain and/or distress), or replace the use of animals in testing. SACATM also provides input on ways to foster partnerships and communication with interested parties. The NIEHS Director appoints 15 voting members to the SACATM and membership as defined in the ICCVAM Authorization Act of 2000, includes representatives from academia, state government, industry, and animal protection organizations (Table 2). Members serve rotating terms of up to four years. The SACATM typically meets once a year. Additional information about SACATM, including minutes from its meetings, is available on the NTP website (*http://ntp.niehs.nih.gov/* select "Advisory Board & Committees") or from Dr. Kristina Thayer (NIEHS/NIH).

Contact Information: NTP Liaison and Scientific Review Office, Dr. Kristina Thayer, Executive Secretary, NIEHS/NIH, P.O. Box 12233, MD A3-01, 111 T.W. Alexander Dr., Research Triangle Park, NC 27709; T: (919) 541-5021; *thayer@niehs.nih.gov*.

Table 2. Scientific Advisory Committee on Alternative Toxicological Methods Membership

Name and Title	Affiliation	Term Ends
Daniel Acosta, Jr., Ph.D. Dean, College of Pharmacy	University of Cincinnati Cincinnati, OH	6/30/06
Rodger D. Curren, Ph.D. President	Institute for In Vitro Sciences, Inc. Gaithersburg, MD	6/30/05
Jack H. Dean, Ph.D. President & Scientific Director Sanofi-Synthelabo Research Division	Sanofi-Synthelabo, Inc. Malvern, PA	12/30/04
Nancy Flournoy, Ph.D. Professor, Department of Statistics	University of Missouri-Columbia Columbia, MO	6/30/06
Alan M. Goldberg, Ph.D. Director, Center for Alternatives to Animal Testing Bloomberg School of Public Health	Johns Hopkins University Baltimore, MD	6/30/06
Sidney Green Jr., Ph.D. Professor, Department of Pharmacology	Howard University College of Medicine Washington, DC	6/30/05
A. Wallace Hayes, Ph.D. Visiting Scientist	Harvard School of Public Health Boston, MA	6/30/05
Nancy A. Monteiro-Riviere, Ph.D. Professor, Department of Clinical Sciences College of Veterinary Medicine Center for Cutaneous Toxicology	North Carolina State University Raleigh, NC	6/30/06

Name and Title	Affiliation	Term Ends
Stephen H. Safe, Ph.D. Distinguished Professor, Department of Veterinary Physiology and Pharmacology College of Veterinary Medicine	Texas A&M University College Station, TX	6/30/06
Jacqueline H. Smith, Ph.D.	Chesapeake Consulting Team Royal Oak, MD	6/30/06
Carlos Sonnenschein, M.D. Professor, Department of Anatomy and Cellular Biology	Tufts University School of Medicine Boston, MA	6/30/05
Martin L. Stephens, Ph.D. Vice President for Animal Research	The Humane Society of the United States Washington, DC	6/30/06
Katherine A. Stitzel, D.V.M	West Chester, OH	6/30/05
Peter Theran, V.M.D. Consultant	Massachusetts Society for the Prevention of Cruelty to Animals (MSPCA) Boston, MA	6/30/05
Calvin C. Willhite, Ph.D. Toxicologist, Department of Toxic Substances Control	California Environmental Protection Agency Berkeley, CA	6/30/06

NTP EXECUTIVE COMMITTEE

The NTP Executive Committee provides programmatic and policy oversight to the NTP Director. The Executive Committee meets once or twice a year in closed forum. Members of this committee include the heads (or their designees) from the following federal agencies:

- Agency for Toxic Substances and Disease Registry (ATSDR)
- Consumer Product Safety Commission (CPSC)
- Environmental Protection Agency (EPA)
- Food and Drug Administration (FDA)
- National Center for Environmental Health (NCEH) of the CDC
- National Cancer Institute (NCI) of the NIH
- National Institute of Environmental Health Sciences (NIEHS) of the NIH
- National Institute for Occupational Safety and Health (NIOSH) of the CDC
- Occupational Safety and Health Administration (OSHA)

ADDRESSING SCIENTIFIC AND REGULATORY NEEDS

The NTP is committed to the concept of "good science for good decisions." This allows the program to be flexible and innovative in its approach toward addressing public health concerns related to exposures to chemical and physical agents at home, in the workplace, and in the environment. The NTP has expanded its scope beyond cancer to include examining the impact of substances on non-cancer outcomes such as those affecting reproduction and development and the immune, respiratory, and nervous systems. As part of this effort, the NTP Center for Evaluation of Risks to Human Reproduction (CERHR) was created in 1998.

The NTP recognizes that initiatives addressing critical knowledge gaps in toxicological evaluations offer the best opportunities for preventing environmentally mediated diseases. Therefore, the program's testing of substances is evolving to include more mechanism-based toxicology studies that focus on understanding the modes of action of chemical agents (see "Program for the 21st Century", page 10). In recent years, the NTP has placed a greater emphasis on providing human relevance to the interpretation and understanding of toxicological information generated using animal or *in vitro* cell models. This is imperative in

order to be at the forefront in research efforts to improve risk assessment methodologies for quantifying the sequence of events that starts with chemical exposure and ends with toxicity. Examples of activities it covers include:

- the increased application of mechanistic information and scientific judgment in the deliberations for listings in the Report on Carcinogens.
- an enhanced effort to examine the merits of alternative testing methods that may provide better information than current models using fewer animals, causing less pain or distress, and potentially provide improved data to reduce uncertainties in risk assessments.
- an increased effort to collect information on a broad variety of exposures (either environmental or occupational), mixtures of concern, and life stage susceptibility.

Nationally, the NTP rodent bioassay is recognized as the standard for identification of carcinogenic agents; however, the NTP continues to work to reduce the use of experimental animals and develop and validate alternative testing methods. This effort led to the creation of the NICEATM in 1998. The NTP will continue to work with the ICCVAM through NICEATM in promoting the development, validation, and regulatory acceptance of new and revised alternative toxicological methods.

Strengthening existing partnerships and forging new ones are important to achieve the goals of the NTP. Partnerships with sister federal agencies are increasing and the NTP continues to collaborate with the private sector. Examples include co-sponsorship of numerous workshops, establishment of the ICCVAM to oversee validation of alternative testing methods, and an interagency initiative to characterize occupational exposures. The NTP continues to support an effort to evaluate the phototoxicity of various compounds through the NTP Center for Phototoxicology (NCP) at NCTR/FDA. In addition, the NTP is contributing to toxicological assessments of emerging issues such as nanotechnology, drinking water contaminants, radiofrequency radiation emissions from cellular phones, and herbal medicines/dietary supplements and will provide this information to other agencies.

Regulatory agencies make decisions for the protection of public health based on scientific information from multiple sources (*e.g.*, toxicology, human studies, and basic research). The NTP plays a critical role in providing needed scientific data, interpretation, and guidance concerning the appropriate uses of these data to regulatory agencies as well as other groups involved in health-related research. The program is committed to using the best science available in setting priorities for future studies and in designing, conducting, and interpreting the findings of those studies. The American people and government agencies at state and federal levels rely on the NTP to provide a strong scientific basis for making credible decisions that will protect public health. Over the past two decades, the NTP has developed an increasingly interactive relationship with regulatory agencies which plays an important, although indirect, role in shaping public health policy. The program maintains an objective, science-based approach in dealing with critical issues in toxicology and is recognized by many groups for its scientific rigor, objectivity, and open approach in the continuing dialogue on the appropriate application of scientific advances to applied toxicology research and testing.

COMMUNICATION AND PUBLIC OUTREACH

Maintaining open communications and ensuring dialogue with federal and state agencies, industry, stakeholders, academia, and the public are goals of the NTP. NTP advisory groups (see page 2) provide regular scientific and public peer review and input. NTP conferences and workshops remain a priority and are designed to bring researchers, regulators, policy

makers, and the public together to examine issues and achieve consensus on future directions in toxicology and risk assessment.

Distribution of NTP study results, program plans, initiatives, announcements, press advisories, and publications is accomplished in a variety of ways to communicate as much as possible with the public. Information is routinely distributed through both regular postal and web-based mailings to interested parties and Federal Register announcements. With the ever-increasing number of people gaining access, the Internet is a major source for distributing and receiving information for the NTP. For example, the NTP established a list-serv several years ago to take advantage of this medium and regularly sends news and updates to subscribers. To subscribe to this list-serv go to (*http://ntp.niehs.nih.gov*).

The NTP homepage (*http://ntp.niehs.nih.gov*) offers access to information about the program that details and highlights ongoing and future initiatives, announcements, NTP centers, the Report on Carcinogens, NTP Technical Reports, and study data. The NTP website was established in 1995 when the Internet was just becoming more readily accessible by the public. Over time, as new web tools were developed, many new file types and graphics were added to the site and it became clear that it was time to completely redesign and organize the website. At the end of 2004, the NTP launched its revised website. The information on this site is the same as on the previous site, but with a new format and reorganization to improve navigation and file retrieval. Some new features include an improved site search capability and new applications to view and download individual animal study data from the NTP databases.

The NIEHS/NIH Central Data Management (CDM) Office oversees distribution (upon request) of specific, chemical study information, and printed NTP documents – the NTP Study Status Reports, final and draft peer reviewed copies of NTP Technical Reports, and background documents for substances nominated to the NTP.

On-line, searchable access is available for the Report on Carcinogens (*http://ehponline.org*) and the NTP Technical, Toxicity, and Genetically Modified Models Reports (*http://ntp.niehs.nih.gov* or *http://ehp.niehs.nih.gov/ntp/docs/ntp.html*) and printed copies of NTP publications are available from the CDM (*CDM@niehs.nih.gov* or 1-919-541-3419).

The NTP is interested in and welcomes stakeholder input into its programs and priorities. Nominations, inquiries, and comments from the public and other interested parties are encouraged at any time. The NTP Liaison and Scientific Review Office at the NIEHS/NIH under the direction of Dr. Mary S. Wolfe serves as the focal point for receiving input to the program and for overseeing the distribution of information about programs, workshops, initiatives, etc.

NTP Liaison and Scientific Review Office
NIEHS/NIH
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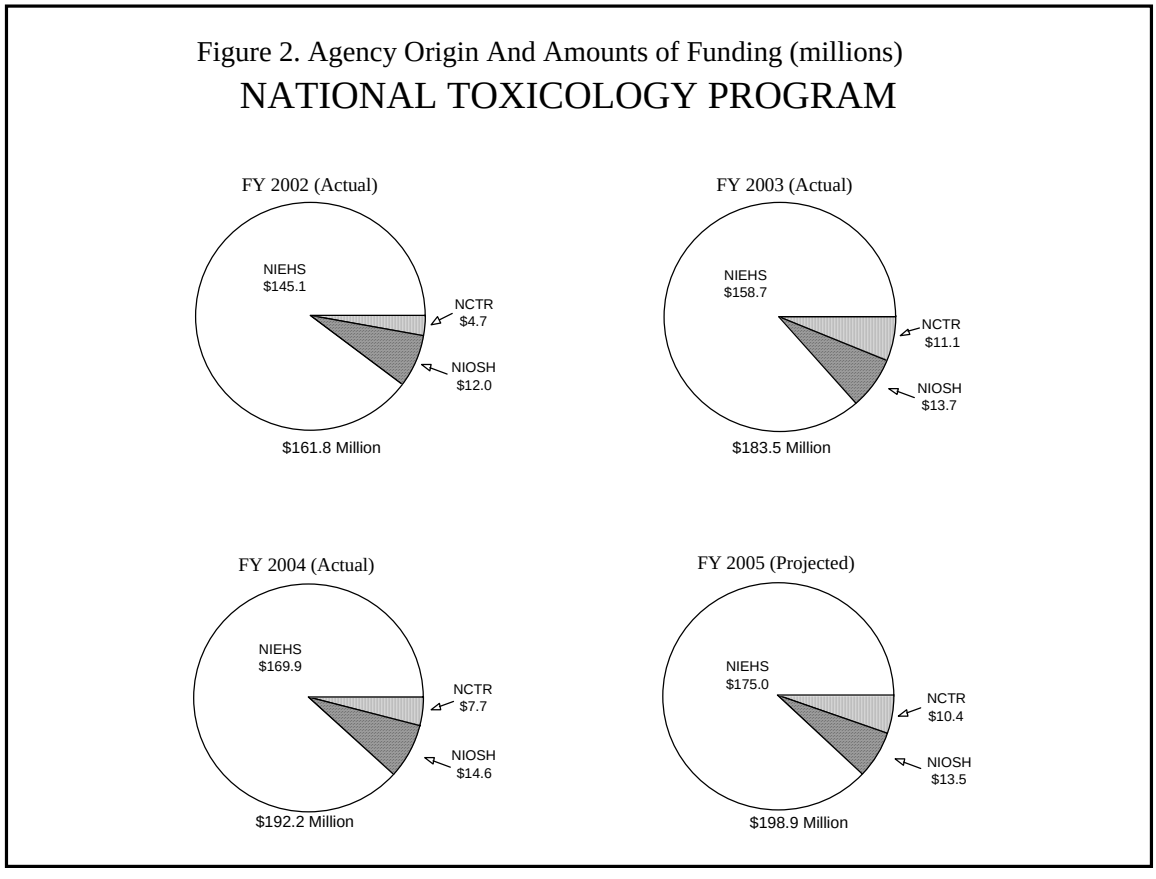
Central Data Management
NIEHS/NIH
P.O. Box 12233
79 T.W. Alexander Drive
Phone: (919) 541-3419
cdm@niehs.nih.gov

RESOURCES AND PLANNING

CURRENT AND PROJECTED RESEARCH CAPACITY

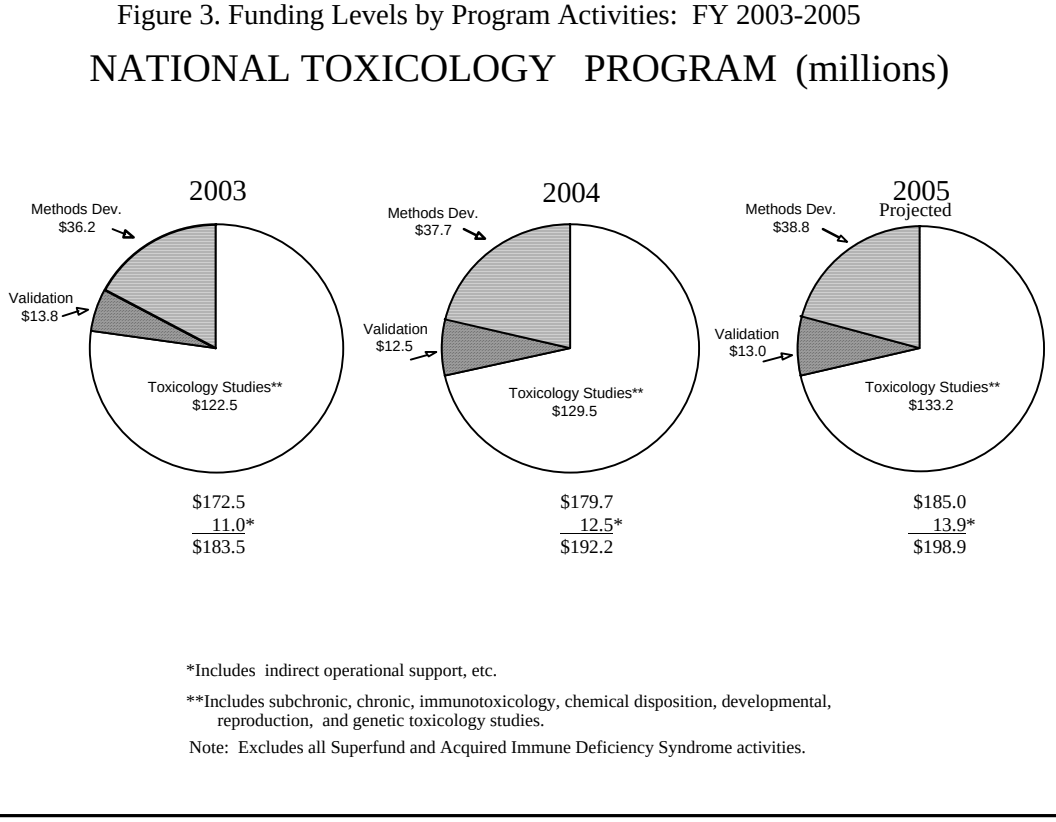
The NTP relies on voluntary allocations from the program's three core agencies (NIEHS/NIH, NCTR/FDA, and NIOSH/CDC) for supporting its various programs and initiatives. These allocations are specified following the determination of yearly appropriations. As shown in Figure 2, the actual allocations from the principals toward the NTP have steadily increased over the past three years (2002-2004) and are projected to provide a total funding level of $198.9M (direct plus indirect) in FY 2005. The NTP primarily conducts its research studies in-house at the core agencies or through contract laboratories, but also supports cooperative and/or collaborative agreements with other federal agencies. Funds are also used to sponsor workshops and conferences and produce and disseminate printed programmatic materials.

Figure 2. Agency Origin And Amounts of Funding (millions)



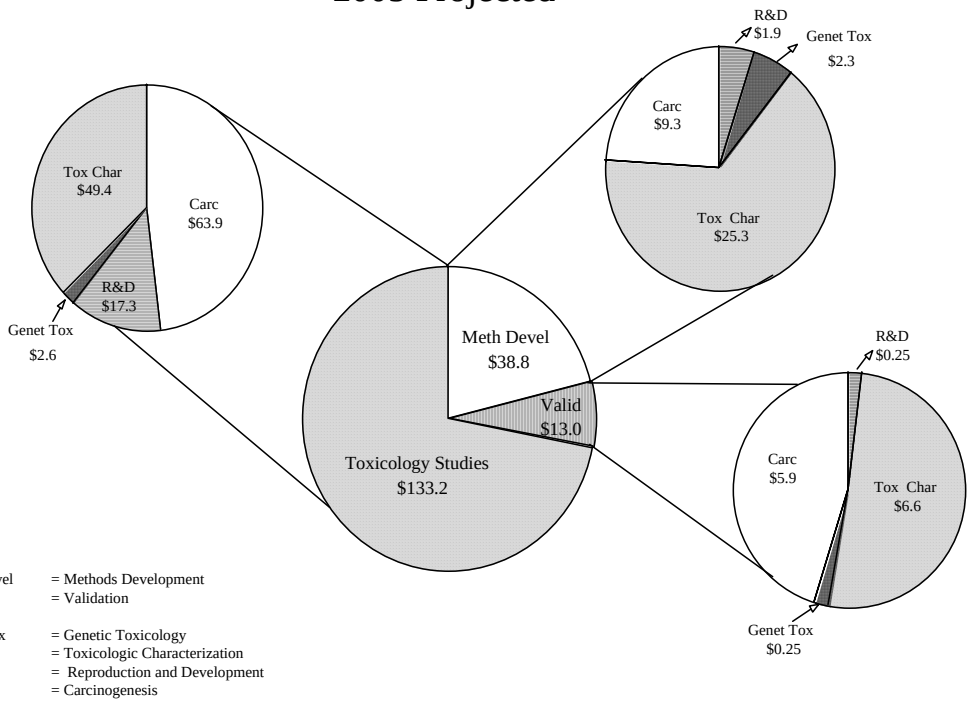
The NTP maintains an objective, science-based approach in dealing with critical issues in toxicology. The program continually sets priorities to improve the nation's ability to evaluate human health effects from environmental exposures and focuses its resources on three major program activities: toxicology studies, methods development, and validation. As shown in Figure 3, approximately three-fourths (72%) of the NTP's allocations (direct only) in FY 2004 were directed toward program activities in basic and applied research (toxicology studies) and a similar level of effort is projected for FY 2005 (72%). The NTP also has ongoing activities for the development and validation of improved research tools for carrying out its research studies. Approximately 28% of the NTP allocations are budgeted in FY 2005 for methods development and validation. These include NTP initiatives such as transgenic and/or alternative models, biomathematical modeling, and genomics.

Figure 3. Funding Levels by Program Activities: FY 2003-2005



Within each of the major program activities, the NTP targets multiple program areas broadly represented as genetic toxicology, toxicological characterizations (including immuno-toxicology, neurotoxicology, epidemiology and exposure assessment, and general toxicology), reproduction and development, and carcinogenesis. Figure 4 shows the projected FY 2005 NTP allocations for each of these areas within individual program activities. For toxicology studies, the primary single focus remains on carcinogenesis although total projected funding for research on non-cancer end points (toxicological characterizations plus reproduction and development) is projected at 52%. Methods development and validation address strategies for both cancer and non-cancer end points. The majority of the funds for both methods development and validation ($25.3M or 65% and $6.6M or 51%, respectively) are designated for technologies that will improve the NTP's ability to characterize toxicities.

Figure 4. Funding Levels by Program Area



Meth Devel = Methods Development
Valid = Validation

Genet Tox = Genetic Toxicology
Tox Char = Toxicologic Characterization
R & D = Reproduction and Development
Carc = Carcinogenesis

For each program activity (toxicology studies, methods development and validation), the projected allocated funds for FY 2005 are given for each major program area (genetic toxicology, toxicological charaterizations, reproduction and development, and carcinogenesis).

In totality, the NTP is a comprehensive interagency research program whose core agencies are committed to providing resources for continuing the program's research efforts and for communicating the knowledge learned to all stakeholders, public and private. The program's efforts in toxicity testing and risk assessment are directed toward obtaining the best scientifically valid data that can be used by health, regulatory, and research agencies for making appropriate decisions about potential human risk(s) from exposure to environmental toxicants. Toward that end, the NTP is continually evolving to remain at the cutting edge of scientific research and the development and application of technology.

PROGRAM FOR THE 21ST CENTURY

In its more than 25 years of existence, the NTP has fulfilled its mandate by becoming a world leader in providing scientific information that improves the nation's ability to evaluate potential human health effects from chemical and physical exposures. While the NTP has studied over 500 compounds in depth, more than 80,000 chemicals are presently registered in the United States for use in such items as foods, personal care products, prescription drugs, and household cleaners. During the past quarter of a century, the NTP has provided extensive and useful data for predicting human health hazards using a battery of toxicology tests and cancer bioassays. However, relatively few of the existing and new chemicals brought to market can be fully evaluated for their potential to cause toxicity because these traditional toxicity testing methods, while of great value in predicting biological responses, are time consuming and resource-intensive. Thus, in August of 2003, the NTP decided it was time to review its activities and consider how to modify its program to address this deficiency.

With this in mind, the NTP began a yearlong process to create a vision and subsequent roadmap for the NTP ("NTP Roadmap") available at *http://ntp-server.niehs.nih.gov* select "NTP Vision and Roadmap." The NTP Vision for the 21st Century is directed 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. To assess potential changes in its program, the NTP will evaluate its key activities to determine how best to incorporate new scientific technological advances into its present research and testing strategies. The NTP Roadmap - developed with input from leading researchers in academia, industry, government, and advocacy groups - grew in complexity and scope during its development and addresses the goals of the NTP Vision. It provides a framework for setting NTP research priorities to achieve the most efficient and effective research portfolio possible. The NTP Roadmap identifies the challenges and opportunities confronting the program today and discusses the directions envisioned for the NTP in the 21st century in three main areas: (1) refining traditional toxicology assays, (2) developing rapid, mechanism-based predictive screens for environmentally induced diseases, and (3) improving the overall utility of NTP products for public health decisions.

Over the last two decades, scientists have increasingly studied critical cellular and molecular events (mechanisms) that lead to adverse responses to toxicants. Mechanistic information may be useful in the identification of biomarkers of exposure and effects 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, for the future, the NTP plans to identify and incorporate more mechanistic approaches into its toxicology assessments and undertake a systematic and continuing evaluation of the data derived from these new approaches to determine their value for providing improved information for making public health decisions. 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. Thus, the NTP will continue to conduct long-term bioassays. 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.

The NTP envisions that over the next decade utilization of our rapidly expanding knowledge of the physiological, biochemical, and molecular basis 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. Through sustained leadership in creating and applying these mechanistic toxicology tools, the NTP will generate the scientific information and understanding necessary for public health decision-makers to use for risk assessment that will reduce the burden of environmental disease.

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 generation of mechanistic information in short or medium high-throughput assays (i.e., gene and protein expression, DNA damage/repair, disruptions in cell cycle, and use of non-mammalian models such as *Caenorhabditis elegans*) will create databases of biological observations that can be examined for their predictive value and use in priority setting. The results of these screening studies could also potentially stimulate the conduct of more extensive, agent-specific, mechanistic studies. 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 response, and provide better and more targeted scientific guidance for making public health decisions aimed at preventing or reducing adverse health effects. 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 plans to incorporate these screening data into publicly accessible databases available to the scientific community for addressing questions about the molecular basis of environmentally induced disease. The NTP Roadmap offers hope that at some point predictive models could be utilized in reaching public health decisions.

Additional information about the NTP Roadmap is available at *http://ntp-server.niehs.nih.gov* select "NTP Vision and Roadmap."

Contact Information: NTP Liaison and Scientific Review Office, Dr. Mary S. Wolfe, Director, NIEHS/NIH, P.O. Box 12233, MD A3-01, 111 T.W. Alexander Dr., Research Triangle Park, NC 27709; T: (919) 541-7539; *wolfe@niehs.nih.gov*.

REPORT ON CARCINOGENS

The Biennial Report on Carcinogens (RoC) is a Congressionally mandated listing of substances (i) that either are known to be human carcinogens or may reasonably be anticipated to be human carcinogens; and (ii) to which a significant number of persons residing in the United States are exposed. The Secretary, HHS, delegated responsibility for its preparation to the NTP who prepares the draft with assistance from other federal health and regulatory agencies. The RoC is an informational, scientific, and public health document that identifies and discusses agents, substances, mixtures, or exposure circumstances that may pose a carcinogenic hazard to human health. It serves as a meaningful and useful compilation of data for listed compounds on (1) the carcinogenicity, genotoxicity, and biological mechanisms in humans and/or animals, (2) the potential for exposure, and (3) any relevant regulations promulgated by federal agencies. Dr. C.W. Jameson, NIEHS/NIH, oversees preparation of the RoC.

The nomination of substances for listing in or removal from the RoC is open to all interested individuals and groups. As shown in Figure 5 the process for review of nominations to the report is a multi-step, formal, and open process. The scientific review of nominations to the 11th edition involved three separate reviews (NIEHS/NTP Review Group, NTP Executive Committee Interagency Working Group, NTP Board of Scientific Counselors RoC Subcommittee) followed by review and comment by the NTP Executive Committee. Public comments were solicited multiple times during the process and provided to each review group as available. The NTP Director received the input from all reviews plus the public comments and made his recommendations on the nominations to the Secretary, HHS, for review and approval. Additional information about the RoC is available on the NTP website: *http://ntp.niehs.nih.gov* select "Report on Carcinogens."

Figure 5 Report on Carcinogens Review Process for the 11th Report

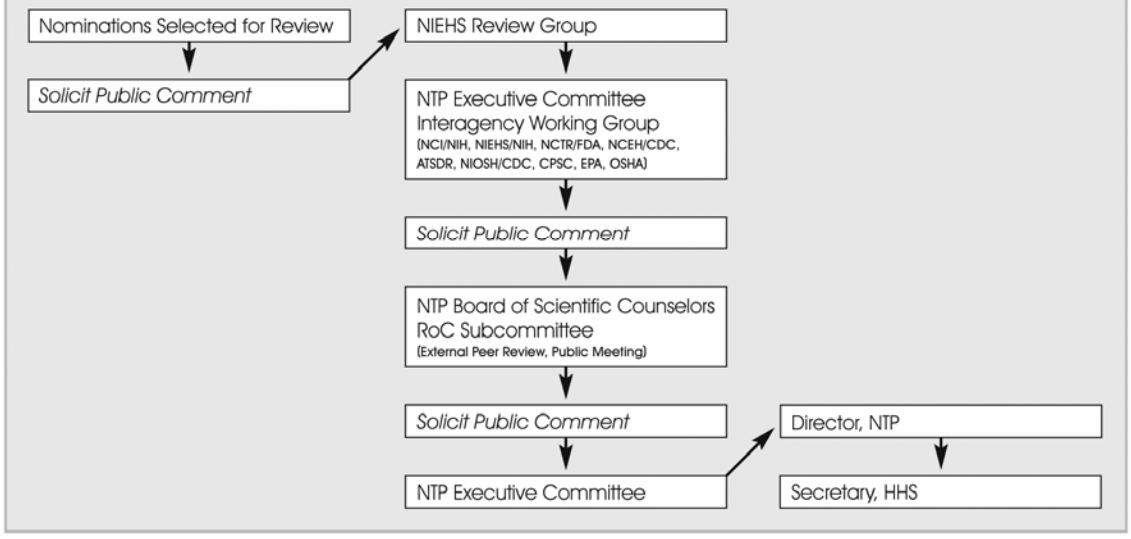


Table 3 lists the nominations completed for review for listing in the 11th RoC. The preparation and review process for each RoC extends over approximately a three-year period. The scientific review of nominations to the 12th RoC is underway. Table 4 lists the nominations under consideration for the 12th RoC.

Contact information: Report on Carcinogens, Dr. C.W. Jameson, Head, NIEHS/NIH, P.O. Box 12233 EC-14, 79 T.W. Alexander Dr., Research Triangle Park, NC 27709; T: (919) 541-4096; e-mail: *jameson@niehs.nih.gov*. RoC website: *http://ntp.niehs.nih.gov/* select "Report on Carcinogens."

Table 3. Summary of New Listings to the Eleventh Edition of the Report on Carcinogens (Released January 31, 2005)

Nomination	CAS Number	Primary Uses or Exposures	Listing Status
1-Amino-2,4-dibromoanthraquinone	81-49-2	1-Amino-2,4-dibromoanthraquinone is an anthraquinone-derived vat dye that is used in the textile industry.	Listed as *reasonably anticipated to be a human carcinogen*
Certain Heterocyclic Amines (three nominations): (1) 2-Amino-3,4-dimethylimidazo[4,5-*f*]quinoline (MeIQ) (2) 2-Amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (MeIQx) (3) 2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP)	(1) 77094-11-2 (2) 77500-04-0 (3) 105650-23-5	MeIQ, MeIQx, and PhIP are heterocyclic amines that are formed during heating or cooking and are found in cooked meat and fish.	Listed as *reasonably anticipated to be a human carcinogen*
Cobalt Sulfate	10124-43-3	Cobalt sulfate is used in electroplating and electrochemical industries. It is also used as a coloring agent for ceramics, a drying agent in inks, paints, varnishes and linoleum, and has been added to animal feed as a mineral supplement.	Listed as *reasonably anticipated to be a human carcinogen*
Diazoaminobenzene (DAAB)	136-35-6	DAAB is used as an intermediate, complexing agent, polymer additive and also to promote adhesion of natural rubber to steel.	Listed as *reasonably anticipated to be a human carcinogen*
Diethanolamine (DEA)	111-42-2	DEA is used in the preparation of surfactants used in liquid laundry, dishwashing detergents, cosmetics, shampoos, and hair conditioners. DEA is also used in metal working fluids, in textile processing, industrial gas purification and as an anticorrosion agent.	Not recommended for listing
Hepatitis B Virus (HBV)		HBV is a small enveloped DNA virus that is transmitted by percutaneous or permucosal exposure to infectious blood or body fluids that contain blood.	Listed as *known to be a human carcinogen*
Hepatitis C Virus (HCV)		HCV is an enveloped RNA virus that is transmitted mainly by percutaneous exposure to infectious blood and less efficiently by permucosal exposure to infectious blood or body fluids that contain blood.	Listed as *known to be a human carcinogen*
Human Papillomaviruses (HPVs)		The HPVs are small, non-enveloped viruses that infect oral and genital mucosa. HPV infections are common throughout the world.	Listed as *known to be a human carcinogen*
X-Radiation and Gamma (γ)-Radiation		The major exposures of concern for cancer from X- and γ-radiation are from the past use of atomic weapons and from medical uses of radiation.	Listed as *known to be a human carcinogen*
Neutrons		Exposure to neutrons normally occurs from a mixed irradiation field in which neutrons are a minor component. The exceptions are exposure of patients to neutron radiotherapy beams and exposures of aircraft passengers and crew.	Listed as *known to be a human carcinogen*
Lead and Lead Compounds		Major occupational exposures are in the lead smelting and refining industries, battery-manufacturing plants, steel welding or cutting operations, construction, and firing ranges.	Listed as *reasonably anticipated to be a human carcinogen*
Naphthalene	91-20-3	Naphthalene is used as an intermediate in the synthesis of many industrial chemicals, an ingredient in some moth repellants and toilet bowl deodorants, as an antiseptic for irrigating animal wounds and to control lice on livestock and poultry.	Listed as *reasonably anticipated to be a human carcinogen*

Nomination	CAS Number	Primary Uses or Exposures	Listing Status
Nitrobenzene	98-95-3	Nitrobenzene is used mainly in the production of aniline, itself a major chemical intermediate in the production of dyes.	Listed as *reasonably anticipated to be a human carcinogen*
Nitromethane	75-52-5	Nitromethane is used in specialized fuels, in explosives and in the synthesis of nitromethane derivatives, pharmaceuticals, agricultural soil fumigants and industrial antimicrobials. In the past it was used as a chemical stabilizer to prevent the decomposition of various halogenated hydrocarbons such as metal degreasers and aerosol propellants.	Listed as *reasonably anticipated to be a human carcinogen*
4,4'-Thiodianiline	139-65-1	4,4'-Thiodianiline has been produced commercially since the early 1940's as an intermediate of several diazo dyes.	Listed as *reasonably anticipated to be a human carcinogen*

Table 4. Nominations Being Reviewed for the Twelth Report on Carcinogens (as of December 2005)

Nomination	CAS Number	Primary Uses or Exposures	Nominator	Basis of Nomination
Aristolochic Acid	313-67-7	Aristolochic acid, the principle extract from Aristolochia, is a mixture of nitrophenanthrene carboxylic acids.	NIEHS	Naturally occurring mixtures of aristolochic acids: IARC[2] finding of sufficient evidence of carcinogenicity in animals and limited evidence in humans (IARC Monograph Vol. 82, 2002).
Herbal Remedies Containing Aristolochic Acid[1]		Several *Aristolochia* species (notably *A. contorta, A. debilis, A. fangchi* and *A. manshuriensis*) have been used in traditional Chinese medicine as anti-rheumatics, as diuretics, in the treatment of edema and for other conditions such as hemorrhoids, coughs and asthma.	NIEHS	Herbal remedies containing the plant genus *Aristolochia*: IARC[2] finding of sufficient evidence of carcinogenicity in humans (IARC Monograph Vol. 82, 2002).
Captafol	2425-06-01	Captafol is a fungicide that has been widely used since 1961 for the control of fungal diseases in fruits, vegetables and some other plants. Use of captafol in the United States was banned in 1999.	NIEHS	IARC[2] finding of sufficient evidence of carcinogenicity in animals (IARC Monograph Vol. 53, 1991). IARC also noted that captafol is positive in many genetic assays, including the *in-vivo* assay for dominant lethal mutation.
Cobalt–Tungsten Carbide Powders and Hard Metals[1]		Cobalt-tungsten carbide hard-metals are manufactured by a process of powder metallurgy from tungsten and carbon (tungsten carbide), and small amounts of other metallic compounds using cobalt as a binder. They are used to make cutting and grinding tools, dies, and wear products for a broad spectrum of industries including oil and gas drilling, and mining..	NIEHS	Recent human cancer studies on the hard metal manufacturing industry showing an association between exposure to hard metals (cobalt tungsten-carbide) and lung cancer.

Nomination	CAS Number	Primary Uses or Exposures	Nominator	Basis of Nomination
Di-(2-ethylhexyl) Phthalate (DEHP)	117-81-7	DEHP is mainly used as a plasticizer in polyvinyl chloride (PVC) resins for fabricating flexible vinyl products. PVC resins have been used to manufacture toys, dolls, vinyl upholstery, tablecloths and many other products.	Aekyung Petrochemical Co., LTD of Seoul, Korea (for delisting)	Currently listed in the RoC as *reasonably anticipated to be a human carcinogen.* IARC[2] reclassified as not classifiable as to its carcinogenicity to humans (Group 3) (IARC Monograph Vol.77, 2000). IARC stated that there was sufficient evidence for the carcinogenicity in experimental animals; however, the mechanism for liver tumor involves peroxisome proliferation that is not relevant to humans.
Etoposide in Combination with Cisplatin and Bleomycin		Etoposide in combination with cisplatin and bleomycin is used to treat testicular germ cell cancers.	NIEHS	IARC[2] finding of sufficient evidence of carcinogenicity in humans (IARC Monograph Vol. 76, 2000).
Etoposide	33419-42-0	Etoposide is a DNA topoisomerase II inhibitor used in chemotherapy for non-Hodgkin's lymphoma, small-cell lung cancer, testicular cancer, lymphomas and a variety of childhood malignancies.	NIEHS	IARC[2] finding of limited evidence of carcinogenicity in humans (IARC Monograph Vol. 76, 2000).
Formaldehyde	50-00-0	Formaldehyde is primarily used in the production of resins that are used in the production of many different products, including plastics, adhesives and binders for wood products, pulp and paper, synthetic fibers, and in textile finishing. It is also used as a disinfectant and preservative and as an intermediate for many industrial chemicals.	NIEHS	Formaldehyde (gas) is currently listed in the RoC as *reasonably anticipated to be a human carcinogen* Nominated for reconsideration based on the 2004 IARC[2] review, which concluded that there was sufficient evidence for the carcinogenicity of formaldehyde in humans (IARC Monograph Vol. 88, 2004).
Certain Glass Wool Fibers[1] *NIEHS recommended that the nomination be defined as "certain glass wool fibers" because of the considerable differences in the composition of glass wool fibers		Glass wool fibers, which are a type of synthetic vitreous fibers, are an inorganic fibrous material manufactured primarily from glass and processed inorganic oxides. The composition of these fibers may vary substantially because of differences in end-use, manufacturing requirements and biopersistence considerations. The major uses of glass wool are in thermal, electrical, and acoustical insulation, weatherproofing, and filtration media. Some glass wool fibers (special purpose fibers) are used for high-efficiency air filtration media, and acid battery separators.	North American Insulation Manufacturers Association nominated glass wool (respirable size) for delisting	Glass wool (respirable size) is currently listed in the RoC as *reasonably anticipated to be a human carcinogen*. Insulation glass wool: IARC[2] finding of limited evidence of carcinogenicity in animals and evaluation as not classifiable as to its carcinogenicity to humans (Group 3) (IARC Monograph Vol. 81, 2002). Special-purpose glass fibers: IARC[2] finding of sufficient evidence of carcinogenicity in animals (IARC Monograph Vol. 81, 2002).
Metal Working Fluids		Metal working fluids are complex mixtures that may contain mixtures of oil, emulsifiers, anti-weld agents, corrosion inhibitors, extreme pressure additives, buffers biocides and other additives. They are used to cool and lubricate tools and working surfaces in a variety of industrial machining and grinding operations.	NIEHS	Recent human cancer studies of metal working fluids that show an association between exposure to these materials and cancer at several tissue sites.
ortho-Nitrotoluene	88-72-2	*ortho*-Nitrotoluene is used to synthesize agricultural and rubber chemicals, azo and sulfur dyes, and dyes for cotton, wool, silk, leather, and paper.	NIEHS	Results of a NTP bioassay (NTP Technical Report 504, 2002)[3], which reported *clear evidence of carcinogenicity* in rats and mice.
Riddelliine	23246-96-0	Riddelliine is found in class of plants growing in western United States. Cattle, horses and sheep ingest these toxic plants. Residues have been found in, milk, and honey.	NIEHS	Results of a NTP bioassay (NTP Technical Report 508, 2003)[3], which reported *clear evidence of carcinogenicity* in male and female rats and mice.

Nomination	CAS Number	Primary Uses or Exposures	Nominator	Basis of Nomination
Styrene	100-42-5	Styrene is used in the production of polystyrene, acrylonitrile-butadiene-styrene resins, styrene-butadiene rubbers and latexes, and unsaturated polystyrene resins.	Private Individual	IARC[2] finding of limited evidence of carcinogenicity in animals and limited evidence of carcinogenicity in humans (IARC Monograph Vol. 82, 2002).
Teniposide	29767-20-2	Teniposide is a DNA topoisomerase II inhibitors used mainly in the treatment of adult and childhood leukemia.	NIEHS	IARC[2] finding of limited evidence of carcinogenicity in humans (IARC Monograph Vol. 76, 2000).

[1] Nomination has been redefined based on public comments received from earlier Federal Register Notices and/or review of the literature. The review of several nominations has been deferred until the 13th RoC (asphalt fumes, atrazine, benzofuran, oxazepam, vinyl mono-halides as a class). The nomination of talc (cosmetic and occupational exposure) was withdrawn from review. For additional information on the rationales for deferring or withdrawing a nomination see *http://ntp.niehs.nih.gov/* see "Federal Register Notices" [October 18, 2005 (Vol. 70, No. 200) pages 60548-60544]

[2] International Agency for Research on Cancer (IARC). IARC Monographs are available from *http://monographs.iarc.fr/.*

[3] NTP Technical Reports are available at *http://ntp.niehs.nih.gov/* see "NTP Study Reports."

NTP CENTERS

NTP CENTER FOR THE EVALUATION OF RISKS TO HUMAN REPRODUCTION

The NTP Center for the Evaluation of Risks to Human Reproduction (CERHR) was established in 1998 to serve as an environmental health resource to the public and regulatory and health agencies. The CERHR is located at the NIEHS/NIH and Dr. Michael Shelby serves as the Director. The CERHR publishes monographs that assess the potential for substances to cause adverse effects on reproduction and development and whether these substances are hazardous for humans. The NTP Board (see page 2) advises the CERHR on its processes, priorities, and direction.

The CERHR follows a formal process for nomination, selection, and review of substances that includes evaluation by an *ad hoc* panel of scientists with topic-specific expertise and three formal solicitations of public comment. The CERHR selects substances for review based on several factors including production volume, extent of human exposures, public concern about the chemical hazard, and the extent of published data from reproductive or developmental toxicity studies. Expert panel meetings are open to the public. CERHR held three expert panel meetings during fiscal years 2003 and 2004. Other substances have been selected for evaluation but expert panel meetings are not yet scheduled (see list below). Following completion of an expert panel report and receipt of public comments on the report, the CERHR prepares an NTP-CERHR Monograph that is transmitted to federal and state agencies, interested parties, the public, and are published in MEDLINE. Each CERHR Monograph includes the expert panel's report, the NTP Brief, and any public comments received on the expert panel report. The NTP Brief provides in plain language:

- background information on the chemical
- the findings of the expert panel report
- discussion of any relevant data received after the expert panel meeting
- the NTP's conclusions on the potential for the chemical to cause adverse reproductive and/or developmental effects in exposed humans

A summary of conclusions on substances evaluated between 1998 and 2004 is presented in Table 5. Additional details about the CERHR process, CERHR expert panel evaluations, and monographs are available at the CERHR website (*http://cerhr.niehs.nih.gov*). The CERHR website also contains information covering common questions and concerns regarding a healthy pregnancy and the potential of various exposures to adversely affect fertility or the development of children

FY 2003 and 2004 CERHR Expert Panel Evaluations:

- Ethylene Glycol [CAS No. 107-21-1] - February 11-13, 2003
- Propylene Glycol [CAS No. 57-55-6] - February 11-13, 2003
- Fluoxetine (Prozac®) [CAS No. 54910-89-3] - March 3-5, 2004
- Acrylamide [CAS No. 79-06-1] - May 17-19, 2004

Contact Information: NTP Center for the Evaluation of Risks to Human Reproduction, Dr. Michael Shelby, Director, NIEHS/NIH, P.O. Box 12233 EC-32, 79 T.W. Alexander Dr., Research Triangle Park, NC 27709; T: (919) 541-3455; *shelby@niehs.nih.gov*. CERHR website: *http://cerhr.niehs.nih.gov*

Table 5. Summary of NTP-CERHR Monographs and/or Expert Panel Evaluations

Chemical	CAS Number	Use	NTP Conclusions for Effect on Human Reproduction	NTP Conclusions for Effect on Human Development
Acrylamide	79-06-1	Used in the production of polyacrylamide, which is used in water treatment, pulp and paper production, mineral processing, and scientific research; and in the synthesis of dyes, adhesives, contact lenses, soil conditioners, cosmetics and skin creams, food packaging materials, permanent press fabrics. Acrylamide has recently been found to be produced in some starchy foods cooked at high temperatures.	*Negligible concern* for adverse reproductive and developmental effects in the general population. *Minimal concern* for acrylamide-induced heritable effects in the general population. *Some concern* for adverse reproductive and developmental effects, including heritable effects, for exposures in occupational settings.	*Negligible concern* for adverse reproductive and developmental effects in the general population. *Minimal concern* for acrylamide-induced heritable effects in the general population. *Some concern* for adverse reproductive and developmental effects, including heritable effects, for exposures in occupational settings.
1-Bromopropane	106-94-5	Used as a solvent for fats, waxes and resins, and as an intermediate in the synthesis of pharmaceuticals, insecticides, flavors, and fragrances. Used as a vehicle in spray adhesives and as a cold bath degreaser.	*Serious concern* for reproductive effects at the upper end of the human occupational exposure range (18-381 ppm). *Minimal concern* for reproductive effects when humans are exposed at the lower end of the human occupational exposure range (0.04-0.63 ppm).	*Serious concern* for developmental effects at the upper end of the human occupation exposure range (18–381 ppm) (concurs with expert panel). *Minimal concern* for developmental effects when humans are exposed at the lower end of the human occupational exposure range (0.04–0.63 ppm).
2-Bromopropane	75-26-3	Used as an intermediate in the synthesis of pharmaceuticals, dyes and other organic chemicals. In Asia, used as a replacement for chlorofluorocarbons and 1,1,1-trichloroethane and as a solvent/cleaner for micro-electronics. In the US, 2-BP is a contaminant (<0.1%) of 1-bromopropane.	*Some concern* for adverse reproductive effects when people are exposed to concentrations of 2-bromopropane at the high end of the occupational exposure range. *Minimal concern* for adverse reproductive effects when people are exposed to 2-bromopropane at the lower end of the occupational exposure range.	*Insufficient evidence* to assess the developmental effects of 2-bromopropane exposure.
Butyl Benzyl Phthalate [BBP]	85-68-7	Primarily used in the production of vinyl tiles. Also used in food conveyor belts, artificial leather, automotive trim and traffic cones.	*Negligible concern* for adverse reproductive effects in exposed men; data are insufficient to reach conclusions for exposed women.	*Minimal concern* for developmental effects in fetuses and children.
Di-*n*-butyl Phthalate [DBP]	84-74-2	Used as a component of latex adhesives. Used in cosmetics and other personal care products, as a plasticizer in cellulose plastics, and as a solvent for dyes.	*Negligible concern* for reproductive toxicity in exposed adults.	*Minimal concern* for developmental effects on the male reproductive tract when pregnant women are exposed to levels of 2-10 µg/kg bw/day; *Some concern* when pregnant women are exposed to higher levels.

Chemical	CAS Number	Use	NTP Conclusions for Effect on Human Reproduction	NTP Conclusions for Effect on Human Development
Di(2-ethylhexyl) Phthalate [DEHP]*	117-81-7	Used in polyvinyl chloride medical devices such as blood bags and IV tubing. Used in a wide variety of products, including flooring, vehicle upholstery, raincoats, toys, and food packaging. It is not used in toys intended for mouthing, such as nipples or teething rings.	*Minimal concern* for reproductive toxicity in exposed adults (Concurs with expert panel). [Expert panel conclusions are presented. NTP conclusions have not yet been determined.]	*Concern* for developmental effects on the reproductive tract of male infants and/or toddlers exposed to DEHP at levels several fold higher than the general population. *Serious concern* that certain medical treatments of critically ill male infants may result in DEHP exposures adversely affecting male reproductive tract development. [Expert panel conclusions are presented. NTP conclusions have not yet been determined.]
Di-*n*-hexyl Phthalate [DHP]	84-75-3	A component of industrially important phthalates such as di-isohexyl phthalate (up to 25%) and C6-10 phthalate (up to 1%). It may occur in a variety of commercial products including dip-molded products such as tool handles or dishwasher baskets, flooring, vinyl gloves, flea collars and conveyer belts used in food processing.	*Insufficient data* on hazard and/or exposure.	*Insufficient data* on hazard and/or exposure.
Di-isodecyl Phthalate [DIDP]	26761-40-0 68515-49-1	Used in a wide variety of products, including insulation of wires and cables, artificial leather, toys, carpet backing, and pool liners. Has only limited use in food packaging and handling.	*Negligible concern* for adverse reproductive effects in exposed adults.	*Minimal concern* for developmental effects in fetuses and children.
Di-isononyl Phthalate [DINP]	28553-12-0 68515-48-0	Used in a wide variety of products, including garden hoses, pool liners, flooring tiles, tarps, and toys. Has limited use in food packaging.	*Minimal concern* for adverse reproductive effects in exposed adults	*Minimal concern* for developmental effects in fetuses and children.
Di-*n*-octyl Phthalate [DnOP]	117-84-0	No commercial uses. Makes up approximately 20% of the industrially important C6-10 phthalate mixture used in the manufacture of commercial products.	*Negligible concern* for adverse reproductive effects in exposed adults	*Insufficient data* on hazard and/or exposure.
Ethylene Glycol	107-21-1	Used as a chemical intermediate in the production of polyester compounds. Also found in automotive anti-freeze, industrial coolants, hydraulic and deicer fluids.	*Negligible concern* for adverse reproductive effects in exposed adults	*Negligible concern* of adverse developmental effects from ethylene glycol at exposures below 125 mg/kg bw.

Chemical	CAS Number	Use	NTP Conclusions for Effect on Human Reproduction	NTP Conclusions for Effect on Human Development
Fluoxetine Prozac®; Sarafem™	59333-67-4	A widely prescribed pharmaceutical, used in the treatment of depression. Recently approved for use in 7–17 year-olds. Sarafem™, is now being prescribed to treat premenstrual dysphoric disorder, potentially increasing the number of exposures for women of childbearing age.	*Minimal concern* for adverse reproductive effects in exposed adults	*Some concern* for shortened gestational length and poor neontal adaptation at therapeutic doses (20–80 mg/day). *Insufficient evidence* to assess effects on pregnancy loss and fetal growth, on infant exposure through breast milk, or on children on fluoxetine therapy.
Methanol	67-56-1	Used in chemical syntheses and as an industrial solvent. In a variety of consumer products such as paints, antifreeze, cleaning solutions, and adhesives. Produced as a by-product of fermentation, sewage treatment, and paper production. Used as a racing car fuel with potential for expanded use as a vehicle fuel.	*Negligible concern* for adverse male reproductive effects when exposed to methanol levels that result in a low blood methanol level (<10 mg/L blood). *Insufficient evidence* to assess the effects of methanol on female reproduction.	*Concern* for adverse developmental effects in fetuses if pregnant women are exposed to methanol at levels that result in high blood methanol concentrations. *Minimal concern* for adverse developmental effects when humans are exposed to methanol levels that result in low blood methanol concentrations (<10 mg/L blood).
Propylene Glycol	57-55-6	Used as a chemical intermediate in the production of unsaturated polyester resins. Used in liquid detergents, deicing fluids, antifreeze/engine coolant, paints and coatings. Used in foods, cosmetics, tobacco products and pharmaceuticals.	*Negligible concern* for adverse reproductive effects in exposed adults	*Negligible concern* for adverse developmental effects from propylene glycol exposure in humans.

* NTP CERHR Monograph not yet available

NTP Interagency Center for the Evaluation of Alternative Toxicological Methods

The development, validation, acceptance, and harmonization of new, revised, and alternative toxicological test methods are coordinated in the federal government through the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). NIEHS established ICCVAM in 1997 to implement directives in the 1993 NIH Revitalization Act - to develop a process to achieve the regulatory acceptance of scientifically valid alternative testing methods. Alternative methods are those that reduce, refine, or replace the use of animals. The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) was established in 1998 to administer ICCVAM and provide scientific support for ICCVAM activities. Dr. William Stokes (CAPT, USPHS) is the NICEATM Director. The ICCVAM Authorization Act of 2000 (Public Law [P.L.] 106-545) established ICCVAM as a permanent committee and directed ICCVAM to carry out technical evaluations of new, revised, and alternative methods. ICCVAM is composed of designated representatives of the heads of 15 federal regulatory and research agencies (ATSDR, CPSC, Departments of Agriculture, Defense, Energy, Interior, and Transportation, EPA, FDA, NIOSH/CDC, OD/NIH, NCI/NIH, NIEHS/NIH, NLM/NIH and OSHA). These agencies generate, use, or provide information from toxicity test methods for risk assessment purposes. Dr. Leonard Schechtman, NCTR/FDA, serves as chair of ICCVAM.

The Scientific Advisory Committee for Alternative Toxicological Methods (SACATM, see page 4) was chartered on January 9, 2002, to fulfill mandates specified in the ICCVAM Authorization Act of 2000 (P.L. 106-545). The SACATM provides advice to ICCVAM, NICEATM, and the Director of the NIEHS and NTP regarding statutorily mandated duties of the ICCVAM and activities of the NICEATM.

ICCVAM and NICEATM work to promote the validation and regulatory acceptance of new, revised, and alternative toxicological test methods that are more predictive of human and ecological effects than those currently available and that refine, reduce, and replace animal use whenever possible. The desired outcomes from these new methods are an improvement in agencies' abilities to assess risk and make regulatory decisions, more humane animal use, and the reduction and replacement of animals. Workshops and expert panels may be convened for various purposes, such as to evaluate the adequacy of existing methods, identify promising test methods for further development and validation, evaluate the interim validation status of methods, and evaluate proposed validation studies. On behalf of ICCVAM, NICEATM convenes scientific peer review panels to evaluate the validation status of proposed alternative testing methods for which there is evidence of scientific validity. ICCVAM then develops formal test method recommendations for consideration of acceptance by agencies.

Contact information: NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, Dr. William Stokes, Director, NIEHS/NIH, P.O. Box 12233, MD EC-17, 79 T.W. Alexander Dr., Research Triangle Park, NC 27709, T: (919) 541-2384, e-mail: *iccvam@niehs.nih.gov*. NICEATM/ICCVAM website: *http://iccvam.niehs.nih.gov*.

Current Nomination, Evaluation, and Validation Activities

NICEATM receives proposed test method nominations or submissions intended for ICCVAM consideration and review. Test methods can be nominated for validation studies or technical reviews. The ICCVAM evaluation process involves an initial assessment by NICEATM of the adequacy and completeness of the proposed test method nomination or submission, and a determination by ICCVAM of the priority of the proposed method for technical evaluation or

validation studies. Once a proposed test method is accepted for evaluation or validation, ICCVAM assembles an interagency working group of scientists with appropriate scientific and regulatory expertise to collaborate with NICEATM on the evaluation process. Depending on the validation status of the proposed test method, ICCVAM, in conjunction with NICEATM, develops recommendations and priorities for further efforts. Such efforts might include an expert workshop, an expert panel meeting, a peer review meeting, an expedited peer review process, or a validation study. Information and status for the following NICEATM activities, including meeting reports, and background documents, are available on the NICEATM/ICCVAM website. Recent NICEATM publications and test methods currently under review are presented in Tables 6 and 7 respectively.

Table 6. Recent NICEATM Publications

Title	Date
Publications	
ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods	September 2003
ICCVAM Biennial Progress Report	December 2003
ICCVAM Mission, Vision, and Strategic Priorities	February 2004
Agency Responses to ICCVAM Test Recommendations for the Revised Up-and-Down Procedure for Determining Acute Oral Toxicity and *In Vitro* Methods for Assessing Acute Systemic Toxicity	March 2004
Recommended Performance Standards for *In Vitro* Test Methods for Skin Corrosion	May 2004
Updated Standardized *In Vitro* Cytotoxicity Test Method Protocols for Estimating Acute Oral Systemic Toxicity	October 2004

Table 7. Summary of Nominations or Submissions Under Review by NICEATM/ICCVAM

Test Method Nomination or Submission	Status of Nomination
Xenobiotic Detection Systems (XDS) LUMI-CELL™ - Stably transfected recombinant cell-based estrogen receptor transcriptional method	Initializing protocol optimization and validation study – expected 2005
Ocular and dermal toxicity test methods/ approaches for antimicrobial cleaning products	Published call for data and nominees to serve on scientific expert panel – expected March 2005
IA, Inc. - Biosensor system that can assess estrogen receptor binding and transcriptional activation	Received letter of intent. Awaiting submission.
Otsuka Pharmaceutical Company, Ltd. – Androgen receptor transcriptional activation assay	Received pre-validation data. NICEATM reviewed and is awaiting notice of Otsuka's intent to submit for possible validation study
CertiChem, Inc. - MCF-7 cell proliferation assay	Received letter of intent. NICEATM currently reviewing draft submission
IRAS, The Netherlands - H295R cell line screening assay	Received letter of intent. NICEATM currently reviewing draft submission
EPA – ER and AR binding assays	EPA validation studies in progress; submission pending
International Life Sciences Institute (ILSI)/ Health and Environmental Science Institute (HESI) Biomarkers Committee – developing validation study plans for inhibin B, serum cardiac troponins, and nephrotoxicity biomarkers	ILSI/HESI studies in progress; ICCVAM providing comments on study plans; submissions pending

NTP CENTER FOR PHOTOTOXICOLOGY

The NTP Center for Phototoxicology (NCP) was established in 2000 at the NCTR/FDA in Jefferson, Arkansas, to conduct mechanism-based research on the potential toxic or carcinogenic effects of a test substance in combination with electromagnetic radiation from several light sources. In general, these studies investigate the effects on gene expression, toxicity, and carcinogenicity of exposure to sunlight combined with either topically applied or systemically applied administered substances to the SKH-1 hairless mouse. Many of the

substances under study are high priority and regulatory interest to the FDA. These studies generate critically important scientific data for use in determining potential human health risks from the effects of these agents on light-induced skin toxicity and skin cancer. Dr. Paul Howard, NCTR/FDA, serves as NCP Director.

The NCP's state-of-the-art laboratory is equipped with two six-inch zenon arc lamps that operate at 6,500 watts. The visible and UV radiation emitted from each lamp, when filtered through glass designed to simulate the earth's atmosphere, closely mimics the spectrum of solar light. About 5,000 mice can be exposed per day to the simulated solar light making this facility unique for handling the large number of animals required for carcinogenicity studies. The facility also has a portable fluorescent lamp assembly that can be equipped with most of the available fluorescent lamps (*e.g.*, UV-B lamps, tanning lamps, and germicidal lamps) for use in studying the biological effects of these light sources.

Substances are nominated to the NTP for testing by FDA centers and offices within the FDA Commissioner's Office. The FDA Phototoxicology Chemical Selection Working Group prioritizes the nominations and forwards them to the Interagency Committee for Chemical Evaluation and Coordination (ICCEC) for entry into the NTP nomination and selection process (see page 25). The Toxicology Study Selection and Review Committee, composed of scientists with expertise in this area from FDA, NIEHS/NIH, other federal agencies, and academia, meets periodically to review the design of protocols and progress of ongoing studies.

Phototoxicology studies are in progress at the NCP for topically applied chemoexfoliating acids (α- and β-hydroxy acid) and aloe vera. These lotions or creams are often used in cosmetics to correct or improve the appearance of "sun-aged" skin so that it appears smoother and less wrinkled. The impact on skin cancer from their continuous use in combination with exposure to sunlight is not known. Studies underway at the NCP are using glycolic acid and salicylic acid as representatives of the α- and β-hydroxy acids, respectively. The NCP is also investigating the effect on acute toxicity and photocarcinogenesis of topically applied plant fractions of the aloe vera plant in combination with simulated sunlight. Numerous products including cosmetics and dietary supplements include portions of the aloe vera plant. Additional chemicals in the phototoxicity program include retinyl palmitate (a vitamin A derivative in cosmetics), padamate O (lime oil), D&C 27 and 28 (cosmetics), tattoo ink chemicals, and fluorescein-based dyes. The end points of these studies are time-to-tumor and pathology of the tumor.

Animal models for testing the role of specific UV wavelengths and substances in the development of human malignant skin melanoma do not exist at this time. As a result, the effects of substances combined with exposure to sunlight on melanoma development are not understood. The NCP is investigating the suitability of a transgenic mouse [TP-*ras* (+) p16/INK4a (+/-)] as a surrogate animal for studying melanoma.

Future NCP plans include the development of a digital imaging capability for documentation of skin lesions on the mouse. Digital analysis of the lesions will decrease personnel time and the tracking of lesions on each mouse should be more accurate. The NCP also plans to use multiplex polymerase chain reaction (PCR) to study 20 genes and perform gene array studies on skin tumors for development of a database that can be used to predict the type of pathological lesion in the skin.

Contact information: NTP Center for Phototoxicology, Dr. Paul C. Howard, Director, NCTR/FDA, HFT-110, 3900 NCTR Road, Jefferson, Arkansas, 72079; T: (870) 543-7137; *phoward@nctr.fda.gov*.
NCP website: *www.fda.gov/nctr/sciences/phototox.htm*

NTP TESTING PROGRAM

NOMINATION, SELECTION, EVALUATION, AND REVIEW

Nominations for Study

The NTP seeks to maintain a balanced research and testing program that provides data addressing a wide variety of issues important to public health. The NTP actively solicits the nomination of studies that permit the testing of hypotheses to enhance the predictive ability of future NTP studies, address mechanisms of toxicity, or fill significant gaps in the knowledge of the toxicity of chemicals or classes of chemicals. Nominations considered appropriate for NTP study follow the principles listed in Table 8.

Table 8. Nomination Principles for NTP Studies

1.	Chemicals found in the environment not closely associated with a single commercial organization
2.	Biological or physical agents that may not be adequately evaluated without federal involvement
3.	Commercial chemicals with significant exposure that were first marketed prior to current testing requirements or those that generate too little revenue to support further evaluations
4.	Potential substitutes for existing chemicals or drugs that might not be developed without federal involvement
5.	Substances that occur as mixtures for which evaluations cannot be required of industry
6.	Chemicals or agents that will aid our understanding of chemical toxicities, or our understanding of the use of test systems to evaluate potential toxicities
7.	Chemicals that should be evaluated to improve the scientific understanding of structure-activity relationships and thereby help limit the number of chemicals requiring extensive evaluations
8.	Emergencies or other events that warrant immediate government evaluation of a chemical or agent

The nomination process is open to the public. The NTP routinely solicits nominations at conferences and workshops; through the NTP newsletter, Federal Register notices, and NTP homepage (*http://ntp.niehs.nih.gov*), and from academia, federal and state regulatory and health agencies, industry, labor unions, environmental groups, and the general public. In addition, standing nomination committees within the NCI/NIH, FDA, NIOSH/CDC, and NIEHS/NIH routinely select and forward nominations to the NTP. The NTP also reviews environmental occurrence and human exposure databases and scientific literature reports to identify substances of potential interest.

Contact Information: Office of Chemical Nomination and Selection, Dr. Scott Masten, NIEHS/NIH, P.O. Box 12233 MD A3-07, 111 T.W. Alexander Dr., Research Triangle Park, NC 27709; T: (919) 541-5710; *masten@niehs.nih.gov*. Nomination website: *http://ntp.niehs.nih.gov/* select "Nominations to the Testing Program."

Review and Selection Process

Nominations undergo a multi-step, formal process of review prior to selection for study (Figure 6). During the entire process, the NTP works actively with regulatory agencies and interested parties to supplement information about nominated substances and ensure that the nomination and selection process meets regulatory and public health needs. The ICCEC plays a central role in recommending substances for NTP study and coordinating NTP testing efforts with other relevant agency activities.

Public comments are solicited on nominated substances and those received are considered at all stages through study selection and design. At the final step of the formal process, the NTP Executive Committee reviews the nominations and makes a final recommendation as to whether the nominated substances are accepted for study by the NTP. The NTP Executive

Committee reviewed nominations for NTP toxicological studies at its August 2003 meeting and its recommendations are summarized in Table 9.

The selection of a nomination for study by the NTP does not automatically commit the NTP to its evaluation. The nominations selected for study and the toxicology and carcinogenicity study designs are carefully considered to ensure that the resources invested in NTP research are wisely spent. A chemical or study may be withdrawn if applicable research data or higher priority studies are identified or if a study proves impractical.

Figure 6 NTP Toxicology Study Nomination and Selection Process

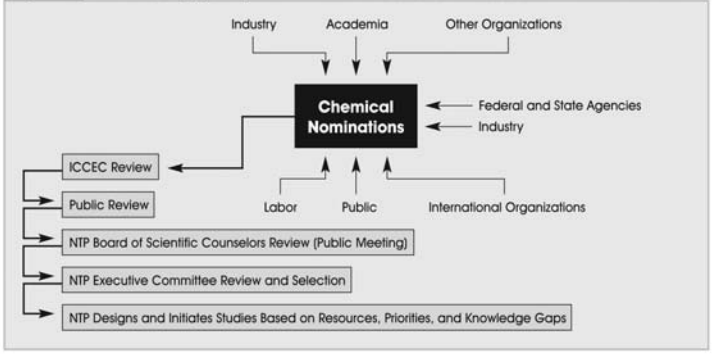


Table 9. Study Nominations Reviewed by the NTP Executive Committee During FY 2003 – FY 2004[1]

Substance	CAS Number	Nominator	Basis of Nomination	Study Recommendations[2]
Acrylamide and Glycidamide	79-06-1 5694-00-8	FDA	Inadequate information available to accurately assess human health risks from exposure to acrylamide in foodstuffs; a properly designed well-conducted bioassay with appropriate ancillary studies is needed to provide dose response information and account for the food matrix through which humans are exposed	Toxicological characterization; toxicokinetics; mechanistic (i.e., hemoglobin adducts); carcinogenicity; bioavailability from food and drinking water
Antimony Trisulfide	1345-04-6	NCI	Significant human exposure in occupational settings and suspicion of carcinogenicity	Chronic toxicity and carcinogenicity
Cadmium Telluride	1306-25-8	DOE, Brookhaven National Laboratory, National Renewable Energy Laboratory, First Solar, Inc.	Potential for widespread applications in photovoltaic energy generation; anticipated increase in human exposures; further data needed to address health and safety issues related to manufacture and use	Toxicological characterization; chemical disposition (oral and inhalation)
Cedarwood Oil, Virginia	8000-27-9	NCI	Widespread occupational and consumer exposure; lack of basic toxicology data	Toxicological characterization; developmental toxicity
Chondroitin Sulfate	9007-28-7	NCI	Widespread long-term use as a dietary supplement and inadequate data to assess safety	Chronic toxicity/ carcinogenicity; carcinogenicity of chondroitin sulfate and glucosamine combined

Substance	CAS Number	Nominator	Basis of Nomination	Study Recommendations[2]
Dimethylethanolamine (DMAE)	108-01-0	NIEHS	Potential for widespread human exposure to DMAE through its use in industrial and consumer products; inadequate toxicological database; some ethanolamines can interfere with choline uptake and utilization and may also generate nitrosamines	Metabolism
Drugs positive for QT Interval Prolongation/Induction of Torsade Proarrhythmia		FDA	QT interval prolongation and *torsade de pointes* is a high priority cause for concern in drug development and regulatory safety evaluation; a clear definition of the strengths, limitations, and future performance characteristics of the canine telemetry model for pre-clinical safety assessment is needed	Initiate a study program to develop *in vitro* and *in vivo* test systems for assessing QT interval prolongation
Glucosamine	3416-24-8	NCI	Widespread long-term use as a dietary supplement and inadequate data to assess safety	Chronic toxicity/ carcinogenicity; carcinogenicity of chondroitin sulfate and glucosamine combined
Nanoscale Materials		Rice University Center for Biological and Environmental Nanotechnology	Intense current and anticipated future research and development focus; further studies and development of appropriate toxicological methods are needed to adequately assess health effects	Size- and composition-dependent biological disposition of nanocrystalline fluorescent semiconductor materials; toxicological characterization of high aspect ratio carbon nanomaterials; role of particle core and surface composition in the immunotoxicity of the above listed materials; phototoxicity of representative metal oxide nanoparticles
4-Phenylcyclohexene	4994-16-5	Private Individuals	Present in indoor environments primarily from carpet emissions; concern that it has not been adequately tested for potential health effects	No toxicological studies at this time due to low suspicion of hazard based on available human exposure and toxicity information
trans-Resveratrol	501-36-0	NIEHS	Widespread human exposure from natural dietary sources and use of dietary supplements; suspicion of toxicity based on estrogenic and genotoxic activity; insufficient data available to characterize safety	Toxicological characterization; carcinogenicity; reproductive toxicity
Tetrabromobisphenol A	79-94-7	NIEHS	High production volume, widespread human exposure and suspicion of thyroid toxicity/tumorigenicity	Toxicological characterization; neurodevelopmental toxicity; carcinogenicity
Tetrabromobisphenol A bis(2,3-dibromopropyl ether)	21850-44-2	NIEHS	High production volume; little toxicity data available; suspicion of carcinogenic potential due to 2,3-dibromo-1-propanol substructure	Toxicological characterization; i*n vivo* genotoxicity; metabolism; carcinogenicity

Substance	CAS Number	Nominator	Basis of Nomination	Study Recommendations[2]
Tungsten	7440-33-7	NCEH/CDC	Important industrial materials; insufficient data to assess human health implications of elevated urinary tungsten levels	Toxicological characterization; carcinogenicity; studies should focus on a representative soluble tungsten compound

[1] Testing status and study results for completed studies can be found at *http://ntp.niehs.nih.gov/* select "Testing Status of Agents at NTP" and "Study Results & Research Projects

[2] Study recommendations are developed by the ICCEC and the NTP Board of Scientific Counselors

Evaluation

In carrying out its mission, the NTP provides toxicological evaluations on substances of public health concern. Unfortunately, the NTP can initiate bioassays to characterize potential carcinogenicity of only a small fraction of the thousands of substances for which there is little or no information. Many more substances are also studied to assess a variety of non-cancer health-related effects including, but not limited to, reproductive and developmental toxicities, immunotoxicity, neurotoxicity, and genotoxicity. Other biological parameters are often assessed such as quantifying the disposition and excretion of substances, identifying and correlating biochemical markers with exposure and metabolism, and examining genetic polymorphisms in human drug metabolizing enzymes to understand the susceptibility of individuals and populations to xenobiotic-induced toxicity.

An NIEHS/NTP project review committee reviews and evaluates a study's project plan (*e.g.*, design, methods, hypothesis, etc.) and proposes the funding format for execution (*e.g.*, grant, contract, etc.). The toxicological evaluation for carcinogenicity is generally conducted through repeated administration of a substance to groups of laboratory animals for variable periods of time generally one to two years. Many short-term studies are designed to provide dose-setting information for chronic exposure studies and address specific deficiencies in the toxicology database. The adverse health effects from short- or long-term exposures of different dose levels of the substance are evaluated clinically, by histopathology, and by a variety of toxicology end points through comparison with groups of animals not administered the substance. Many substances are also studied using protocols specifically designed to address issues pertaining to the mechanism by which a substance causes a particular toxic outcome(s). The NTP has specific requirements for the testing laboratories to comply with the Laboratory Animal Welfare Act of 1966 and adhere to the principles enunciated in the "Guide for the Care and Use of Laboratory Animals" NRC, 1996. General information about the objectives and procedures of NTP study protocols is available on the NTP website (*http://ntp.niehs.nih.gov/* select "Descriptions of NTP Study Types"). Current testing status can be found at *http://ntp.niehs.nih.gov/* select "Testing Status of Agents at NTP."

Support activities and contact staff at the core agencies:

- Animal production and care (King-Herbert, NIEHS/NIH; Martin, NCTR/FDA)
- Archives (Maronpot, NIEHS/NIH)
- Biological monitoring and health assessment (DeBord, NIOSH/CDC)
- Chemistry/biochemistry (Beland/Siitonen, NCTR/FDA; Smith/Collins/Burka/Cunningham, NIEHS/NIH; Snawder, NIOSH/CDC)
- Chemical disposition contracts (Cunningham, NIEHS/NIH); chemical metabolism (Burka, NIEHS/NIH)
- Clinical pathology (Travlos, NIEHS/NIH)
- Genetic toxicity testing (Caspary, NIEHS/NIH)
- Information retrieval and analysis (Tatken, NIOSH/CDC; Wright, NIEHS/NIH)

- Information systems and central files (Eastin, NIEHS/NIH), database management (Rowley, NIEHS/NIH), NTP website (Soward, NIEHS/NIH)
- Mass spectrometry (Tomer, NIEHS/NIH)
- Microbiology (Cerniglia, NCTR/FDA; King-Herbert, NIEHS/NIH)
- Pathology (Hailey/Herbert, NIEHS/NIH; Witt, NCTR/FDA; Hubbs, NIOSH/CDC)
- Quality assurance (Culp, NCTR/FDA; Bristol, NIEHS/NIH; Benson, NIOSH/CDC)
- Statistical services (Kodell, NCTR/FDA; Kissling/Dunson, NIEHS/NIH; Krieg, NIOSH/CDC)
- Study coordination/oversight (Weis, NCTR/FDA; Bucher, NIEHS/NIH; Toraason, NIOSH/CDC)
- Toxicogenomics: microarray (Walker/Paules, NIEHS/NIH); proteomics (Merrick, NIEHS/NIH)
- Technical report preparation (Alden, NIEHS/NIH; Schulte, NIOSH/CDC)
- Toxicology and carcinogenicity testing (Roycroft/Orzech, NIEHS/NIH)
- Toxicity testing (Chhabra/Vallant, NIEHS/NIH)
- Transgenic mouse colonies (King-Herbert/French, NIEHS/NIH)

NTP contracts that facilitate support activities:

- NTP toxicity study report preparation support (Alden, NIEHS/NIH)
- Animal husbandry support services for the NIEHS (Boyd, NIEHS/NIH)
- Quality assurance audit and inspection support resource contract (Bristol, NIEHS/NIH)
- Conducting comprehensive toxicological assessments (Bucher, NIEHS/NIH)
- Chemistry support for the Environmental Toxicology Program (Collins, NIEHS/NIH)
- Research development and planning (DeBord, NIOSH/CDC)
- Carcinogenic potency database (Eastin, NIEHS/NIH)
- Website design and content management (Eastin, NIEHS/NIH)
- Inhalation facility for animal exposures (Goldsmith, NIOSH/CDC)
- Pathology support for the NTP quality assessment (Hailey, NIEHS/NIH, Malarky, NIEHS/NIH)
- NTP database summarization and evaluation (Haseman, NIEHS/NIH)
- Statistical analysis and computational support for the NIEHS experimental studies (Haseman, NIEHS/NIH)
- Pathology support for the NIEHS (Herbert, NIEHS/NIH)
- Support for the preparation of the Report on Carcinogens (Jameson, NIEHS/NIH; Lunn, NIEHS/NIH)
- DNA isolation and molecular analysis (Juras, NIEHS/NIH)
- Genetic analyses for epidemiologic studies of respiratory disease (London, NIEHS/NIH)
- Rodent production center (Maronpot, NIEHS/NIH)
- NIEHS/NTP archives and specimen repository (Maronpot, NIEHS/NIH)
- Genetic monitoring of inbred rodents (Maronpot, NIEHS/NIH)
- Molecular oncology support (Maronpot, NIEHS/NIH)
- Rodent disease diagnostic laboratory (Maronpot, NIEHS/NIH)
- Magnetic resonance imaging and multimodality imaging support for NIEHS and NTP research (Maronpot, NIEHS/NIH)

- Literature search and summary support for the Environmental Toxicology Program (Masten, NIEHS/NIH)
- Research on the inhalation toxicology of environmental chemicals (Moorman, NIEHS/NIH)
- Genetics adjudication resource project (Newton, NIEHS/NIH)
- NIEHS-central computing support for the NTP and the Division of Intramural Research (Rowley, NIEHS/NIH)
- NTP CERHR (Shelby, NIEHS/NIH)
- Developmental toxicity test data (Shelby, NIEHS/NIH)
- Record creation and maintenance of the developmental and reproductive toxicology (DART) database (Shelby, NIEHS/NIH)
- Chemistry support for the ETP (Smith, NIEHS/NIH)
- Inhalation facility for animal exposures (Goldsmith, NIOSH/CDC)
- CDM and information systems contract (Soward, NIEHS/NIH)
- Breeding and rederivation of transgenic animals (Stasiewicz, NIEHS/NIH)
- Genotyping of transgenic animals for NIEHS (Stasiewicz, NIEHS/NIH)
- Support contract for the NICEATM (Stokes, NIEHS/NIH)
- NTP Coordination: occupational health exposures (Toraason, NIOSH/CDC)
- Conduct of studies to evaluate the toxicologic potential of selected chemicals for the NTP (Vallant, NIEHS/NIH)

The NTP carries out toxicology and carcinogenesis research through two primary mechanisms: laboratory studies conducted in contract laboratories and in-house studies conducted at its core agencies: NIEHS/NIH, NCTR/FDA, and NIOSH/CDC. In addition, the NTP leverages resources through cooperative and/or collaborative agreements with other Federal agencies, academia, and industry. The NIEHS/NIH Division of Extramural Research and Training supports research on methods development.

The NIEHS/NIH has supported an interagency agreement with the Lawrence Livermore National Laboratory in collaboration with the University of California at Berkeley to develop, maintain, update, and upgrade a comprehensive database of laboratory animal carcinogenicity study results taken from the literature, including carcinogenesis studies conducted by the NTP. The Carcinogenic Potency Database contains the results of chronic, long-term animal cancer tests, both positive and negative.

In addition to toxicology research of compounds and exposures, the NTP supports the development of new techniques and methods for improving the ability to identify and assess potential environmental toxicants and the development and validation of novel and alternative testing methods that will reduce, replace, or refine animal use. The NTP also supports development of improved statistical methods for toxicology studies.

Review and Dissemination

The results of toxicology and carcinogenesis studies undergo rigorous peer review and are published in several NTP report series:

- *Technical Reports* (TR). This series presents the results of long-term, generally 2-year, toxicology and carcinogenicity studies, typically conduced in two rodent species, rats and mice. Results of chemical disposition and physiologically based pharmacokinetic (PBPK) studies are often included in TRs. The Technical Reports

Review Subcommittee of the NTP Board (see Advisory Boards and Committees, page 2) evaluates TRs in an open, public meeting.

- *NTP Toxicity Reports* (TOX). TOX reports are prepared for studies where the substance exposure period is short-term, generally up to 13-weeks. TOX reports are typically peer-reviewed through letter review.
- *Genetically Modified Models Reports* (GMM). NTP initiated the GMM report series in May 2003. This report series presents the results of substances evaluated by NTP in transgenic strains (e.g., p53+/-heterozygous and Tg.AC). The Technical Reports Review Subcommittee of the NTP Board (see Advisory Boards and Committees, page 2) evaluates GMM reports in an open, public meeting.

Abstracts of the TR, TOX, and GMM series are posted on the NTP website and PDF files of completed reports are available free-of-charge at the NTP website (*http://ntp.niehs.nih.gov/* select "NTP Study Reports"). Hardcopies of NTP reports can by obtained by contacting Central Data Management (919-541-3419, *cdm@niehs.nih.gov*). TR and TOX report series are also catalogued in MedLine. Study summaries for other types of studies, such as immunotoxicity, developmental, and reproductive studies, are also available at "NTP Study Reports." All types of NTP studies may also be published in peer-reviewed scientific journals.

Table 10. Technical Reports Completed During FY 2003-2004: Rodents

Chemical	CAS Number	Technical Report Number	Use	Levels of Evidence of Carcinogenicity			
				Male Rat	Female Rat	Male Mice	Female Mice
Conventional Models							
Anthraquinone	84-65-1	TR 494	Intermediate in dye manufacture	Some	Clear	Clear	Clear
Leucomalachite Green	129-73-7	TR 527	Dye; antifungal for fish	Equivocal	Equivocal	Not tested	Some
Malachite Green Chloride	569-64-2	TR 527	Dye; antifungal for fish	Not tested	Equivocal	Not tested	No evidence
2-Methylimidazole	693-98-1	TR 516	Chemical and pharmaceutical intermediate	Some	Clear	Some	Some
PCB-126 (3,3',4,4',5-Pentachlorobiphenyl)	57465-28-8	TR 520	No longer used commercially; persistent polyhalogenated aromatic hydrocarbons present in the environment	Not tested	Clear	Not tested	Not tested
PeCDF (2,3,4,7,8-Pentachlorodibenzofuran)	57117-31-4	TR 525	No longer used commercially; persistent polyhalogenated aromatic hydrocarbons present in the environment	Not tested	Some	Some	Not tested
Propylene Glycol Mono-*t*-butyl Ether	57018-52-7	TR 515	Solvent	Equivocal	No evidence	Clear	Clear
Stoddard Solvent (Type IIc)	64742-88-7	TR 591	Paint and dry cleaning solvent	Some	No evidence	No evidence	Equivocal
TCDD (2,3,7,8-Tetrachlorodibenzo-*p*-dioxin)	1746-01-6	TR 521	No longer used commercially; persistent polyhalogenated aromatic hydrocarbons present in the environment	Not tested	Clear	Not tested	Not tested

Chemical	CAS Number	Technical Report Number	Use	Levels of Evidence of Carcinogenicity			
				Male Rat	Female Rat	Male Mice	Female Mice
TCDD, PCB 126, and PeCDF Mixture	1746-01-6; 57465-28-8; 57117-31-4	TR 526	No longer used commercially; persistent polyhalogenated aromatic hydrocarbons present in the environment	Not tested	Clear	Not tested	Not tested
Triethanolamine	102-71-6	TR 518	Large variety of industrial and manufacturing applications	Not tested	Not tested	Equivocal	Some
Genetically-Modified Mouse Models - p53 Haploinsufficient Mice							
Aspartame	22839-47-0	GMM 1	Artificial sweetener	N/A	N/A	No evidence	No evidence
Acesulfame Potassium	55589-62-3	GMM 2	Artificial sweetener	N/A	N/A	Clear	No evidence

Table 11. Technical Reports Completed During FY 2003-2004: Fish

Chemical	CAS Number	Technical Report Number	Use	Response in Rodents	Species	Male	Female
Nitromethane	75-52-5	TR 528	Rocket and engine fuel; synthesis intermediate for agricultural fumigants, biocides, and other products; solvent; explosive in mining, oil-well drilling, and seismic exploration	No evidence in male rats; clear evidence in female rats and male and female mice	Medaka	No evidence	No evidence
					Guppy	Inadequate experiment	No evidence
2,2-bis-(Bromomethyl)-1,3-Propanediol	3296-90-0	TR 528	Fire retardant	Clear evidence in male and female rats and mice	Medaka	Clear	No evidence
					Guppy	Clear	Inadequate experiment
1,2,3-Trichloropropane	96-18-4	TR 528	Paint and varnish remover, solvent, and degreasing agent, and as a crosslinking agent in the	Clear evidence in male and female rats and mice	Medaka	Clear	Clear
					Guppy	Clear	Clear

HIGHLIGHTED CURRENT NTP INITIATIVES

The NTP has a broad mandate to provide toxicological characterizations for substances and agents of public health concern. This has resulted in a diverse research program, but with emphasis on synthetic chemicals, metals and 40 dietary supplements. The following section highlights some current NTP initiatives: several areas that have received inadequate attention in the past, i.e., cardiovascular toxicity, photoactive chemicals, endocrine disrupting agents, and certain occupational exposures; and research addressing potential safety issues associated with radiofrequency radiation emissions from cellular telephones, herbal medicines, drinking water contaminants, and DNA-based therapies. In addition, the NTP is also addressing the emerging issue of nanotechnology. In general, these initiatives are broad-based and include various health-related end points.

Nanotechnology

Nanotechnology has become an increasing focus of U.S. and global research and development efforts. As with many technological advances, new materials are created, and as a result, the potential exists for new and unanticipated human exposures for which the impact on human health is unknown. The NTP is developing a broad-based research program to address potential human health hazards associated with the manufacture and use of nanoscale materials. This research program will apply existing toxicology testing methods to the study of nanoscale materials and also explore the development of novel toxicological methods to assess potential health effects (Walker, NIEHS/NIH, Howard, NCTR/FDA, Castranova, NIOSH/CDC).

Nanoscale materials are a broadly defined set of substances where at least one critical dimension is less than 100 nanometers. Ultrafine particulate matter is a well-known example of ambient nanoscale particles; however, the NTP's research program will initially focus on manufactured nanoscale materials of current or projected commercial importance. Nanoscale materials can exist in many forms including semiconductor nanocrystals, organic dendrimers, carbon fullerenes and carbon nanotubes. They are already appearing in commerce as industrial and consumer products and as novel drug delivery formulations.

The intent of the NTP's research program is to evaluate the toxicological properties of major classes of nanoscale materials which represent a cross-section of composition, size, surface coatings, and physico-chemical properties. These model systems will be used to investigate fundamental questions concerning if and how nanoscale materials can interact with biological systems. Some of these fundamental questions include: What are the appropriate methods for detection and quantification of nanoscale particles in tissues? How are nanoscale materials absorbed, distributed in the body and taken up by cells? Are there novel toxicological interactions? As part of this research program, studies have been initiated to evaluate the biological disposition of nanoscale crystalline fluorescent semiconductors ("quantum dots"), long-term toxicology studies of carbon-based nanoscale materials (*e.g.*, single- or multi-walled nanotubes, fullerenes), and phototoxicology studies of representative nanoscale metal oxide particles used in industrial settings and consumer products (*e.g.*, titanium dioxide).

Persistent Polyhalogenated Compounds

Dioxin-like compounds. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and dioxin-like compounds (DLCs) comprise a large class of structurally related environmental contaminants including polychlorinated dibenzodioxins (PCDD), polychlorinated dibenzofurans (PCDF), and some polychlorinated biphenyls (PCBs). Because DLCs are persistent, they remain in human tissues for extended periods of time. Both the NTP and the International Agency for Research on Cancer have concluded that TCDD, the most potent dioxin, is a known human carcinogen. Although the manufacture and use of PCBs was halted in the United States in

1977, PCBs continue to be released into the environment through the use and disposal of products containing these compounds, as by-products from the manufacture of certain organic chemicals, and during combustion of some waste materials.

Because TCDD is a known human carcinogen and other DLCs bind to the same aryl hydrocarbon receptor (AhR), public health officials are concerned that PCBs and other compounds that bind to this receptor may also be human carcinogens. Human exposure to DLCs always occurs as a complex mixture; therefore, a method known as the Toxic Equivalency Factor (TEF) was developed as a mathematical tool to assess the health risk posed by mixtures of these compounds. The TEF methodology is a relative potency scheme that ranks the dioxin-like activity of a compound relative to TCDD , the most potent congener. This method allows for the estimation of the potential dioxin-like activity of a mixture of chemicals, based on a common mechanism of action involving initial binding to the AhR.

The toxic equivalency of DLCs was nominated for evaluation to the NTP because of the widespread human exposure to DLCs and the lack of data on the adequacy of the TEF methodology for predicting relative potency for cancer risk. To address this request, the NTP conducted a series of chronic toxicity and carcinogenicity assays of DLCs and mixtures of these compounds in female Harlan Sprague-Dawley rats (Walker, NIEHS/NIH). Three PCB congeners were selected for evaluation singly (PCB 118, 126 and 153) and in combination with each other, TCDD, and a polychlorinated dibenzofuran. Studies are also in progress to examine the chronic toxicity of compounds with weak dioxin-like activity to which humans are exposed. These include polychlorinated naphthalenes, tetrachloroazobenzene, hexachlorobenzene, and indole-3-carbinol.

Polybrominated flame retardants. The NTP is studying how exposure to brominated flame retardants might effect human health (Dunnick, NIEHS/NIH). One class of brominated flame retardants, polybrominated diphenyl ethers (PBDE), is structurally similar to PCBs and there is evidence that PBDEs bioaccumulate in human and animal tissues. Presently, the NTP is studying the PBDE isomers found in DE-71, the most widely used commercial formulation of a PBDE-based flame retardant. Although the manufacturer of DE-71 recently announced plans to stop its production, people will still be exposed to PBDE isomers and decomposition products of other brominated flame retardants that are still in use, and they will continue to accumulate in the environment. Previous NTP studies of brominated chemicals and/or brominated flame retardants, such as 2,2-bis(bromomethyl)-1,3-propanediol (FR-1138), have shown that these chemicals have the potential to cause cancer in model systems. Other flame retardants being studied include tetrabromobisphenol A (TBBPA) and tetrabromobisphenol A- bis(2,3-dibromopropyl) ether.

Perfluorinated compounds. Over the past five years, perfluorinated compounds such as perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), and similar substances have been found globally in humans and the environment. Perfluorinated compounds are characterized by their persistence, resistance to heat and chemical stress, as well as their insolubility in both water and oil. Because of this unusual combination of physical properties, these compounds or their chemical precursors have been used since the 1950s as surfactants and emulsifiers in commercial products including stain or water protectors for carpets, textiles, auto interiors, camping gear and leather, and in food packaging and other paper containers. Although a considerable amount of toxicity information exists for PFOS and PFOA, this class of perfluorinated compounds is quite large and includes straight chain as well as branched chain compounds. For this reason, the NTP is collaborating with the EPA to conduct a class study of the perfluorinated sulfonates and carboxylic acids as well as fluorotelomeric alcohol derivatives (potential precursors of perfluorinated carboxylic acids) (Melnick, NIEHS/NIH). Initial efforts will include studies on reproduction and development, pharmacokinetics, and mechanistic studies to better understand the potential for common modes of action by this class of compounds.

Cardiovascular Toxicity

Heart disease is the leading cause of mortality in the United States. and the NTP is working to further understand the contribution of environmental exposures to this disease. To achieve this goal, the NTP is studying how environmental exposures may contribute to heart disease, elucidate mechanisms of heart toxicity, understand gene changes in heart toxicity, and translate basic information into prevention strategies. Recent findings from this project show that a combination of the herbal supplement ephedrine with caffeine can cause rapid death by inducing heart toxicity. Other findings indicate that certain compounds, such as 3'-azido-thymidine (AZT) and bis(2-chloroethoxy)methane, can cause heart toxicity via mitochondrial damage. Further work is ongoing to understand gene changes induced by heart toxicants (Murphy, NIEHS/NIH).

In a separate initiative, the NTP is investigating QT interval prolongation and an associated life-threatening ventricular arrhythmia because it is a high priority concern in drug development and regulatory safety evaluation (Hooth, NIEHS/NIH). The QT interval is a reflection of the duration of the ventricular action potential and represents the time during which the ventricles depolarize and repolarize. One of the most common causes of drugs being removed recently from the U.S. market is QT interval-related cardiac toxicity. Given the medical and economic consequences of this issue, a recommendation has been made to incorporate preclinical models predictive of QT interval prolongation and proarrhythmia into drug development. The conscious canine radiotelemetry model is the most common *in vivo* model used to determine if a drug causes QT prolongation; however, the sensitivity and specificity of this model are unknown. Consequently, the FDA requested that the NTP evaluate both QT-prolonging and non-prolonging drugs in the conscious canine telemetry model. The objective of these studies will be to better establish the sensitivity and specificity of this *in vivo* model system for evaluating the ability of a test agent to prolong the QT interval.

Radiofrequency Radiation Emissions from Cellular Phones

Over 100 million Americans currently use wireless communication devices with thousands of new users added daily. Personal (cellular) telecommunications is a rapidly evolving technology that uses microwave radiation to communicate between a fixed base station and a mobile user. Most systems employ a hand-held cellular phone where the radiation antenna is close to the user's head. Cellular phones and other wireless communication devices are required to meet the radiofrequency radiation exposure guidelines of the Federal Communication Commission. These guidelines are based on protecting the user from acute injury from thermal effects produced by radiofrequency radiation. Current data are insufficient to draw definitive conclusions concerning the adequacy of these guidelines for protecting against potential adverse health effects from chronic exposure.

Studies in laboratory animals are considered crucial for understanding whether chronic exposure to radiofrequency radiation may pose a danger to human health. Through an interagency agreement with the National Institute of Standards and Technology, studies were conducted that demonstrated the feasibility of using reverberation exposure chambers to study long-term health effects of cellular phone radiofrequency radiation in laboratory animals. Subsequently, the NTP developed a research project aimed at evaluating the toxic and carcinogenic potential of cellular phone radiofrequency radiation in rats and mice exposed in reverberation chambers. By using radiofrequency signals that simulate exposures of cellular phone users it is expected that results from these studies will clarify any potential health hazard for the U.S. population. This project will begin in FY 2005 (Melnick, NIEHS/NIH).

Herbal Medicines and Dietary Supplements[1]

Medicinal herbs are among the oldest medicines, and their increasing use in recent years is evidence of public interest in alternatives to conventional medicine. Approximately one-third of the U.S. population is believed to use some form of alternative medicine including herbal remedies. The use of herbal medicines and other dietary supplements has increased substantially since passage of the 1994 Dietary Supplement Health and Education Act. Although approximately 1,500 botanicals are sold as dietary supplements or ethnic traditional medicines, herbal formulations are not subjected to FDA pre-market approval to ensure their safety or efficacy.

The NTP is planning or conducting research (listed in Table 12) on numerous medicinal herbs, compounds found in herbs, and dietary supplements that focus on carcinogenicity, reproductive toxicity, neurotoxicity, immunotoxicity, and toxic effects associated with acute exposures to high doses and chronic exposures to low doses (Burka, NIEHS/NIH; Boudreau, NCTR/FDA).

[1] Congress defined the term "dietary supplement" in the Dietary Supplement Health and Education Act (DSHEA) of 1994. A dietary supplement is a product taken by mouth that contains a "dietary ingredient" intended to supplement the diet. The "dietary ingredients" in these products may include: vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites. Dietary supplements can also be extracts or concentrates, and may be found in many forms such as tablets, capsules, softgels, gelcaps, liquids, or powders. They can also be in other forms, such as a bar, but if they are, information on their label must not represent the product as a conventional food or a sole item of a meal or diet. Whatever their form may be, DSHEA places dietary supplements in a special category under the general umbrella of "foods," not drugs, and requires that every supplement be labeled a dietary supplement.

Table 12. Herbal Ingredients and Dietary Supplements[1]

Compound	CAS Number	NTP Studies (completed, ongoing or planned)
S-Adenosylmethionine	29908-03-0	Genetic toxicity (*Salmonella*)
Aloe Vera Charcoal Filtered Whole Leaf Extract		Chronic toxicity/carcinogenicity (dermal)
Aloe Vera Whole Leaf Extract (Native)		Subchronic (drinking water), chronic toxicity/carcinogenicity (dermal)
Aloe Vera Gel	8001-97-6	Chronic toxicity/carcinogenicity (dermal), genetic toxicity (*Salmonella*)
Androstenedione	63-05-8	Subchronic (gavage and topical studies), chronic toxicity/carcinogenicity (gavage), chemical disposition (dogs, humans, mice, rats - gavage, *in vitro*, intravenous), genetic toxicity (*Salmonella* and micronucleus)
Berberine Chloride	633-65-8	Genetic toxicity (*Salmonella* and micronucleus)
Berberine Chloride Dihydrate	5956-60-5	Teratology (gavage and feed)
Bilberry Fruit Extract	84082-34-8	Genetic toxicity (*Salmonella*)
Bitter Orange Extract		Testing planned
Black Cohosh	84776-26-1	Genetic toxicity (*Salmonella*), other studies planned
Black Walnut Extract/Juglone		Chemical disposition (rat - topical), genetic toxicity (*Salmonella*)
Blue-Green Algae		Genetic toxicity (*Salmonella*), other studies planned
Chitosan	9012-76-4	Subchronic (feed)
Chromium Picolinate Monohydrate	27882-76-4	Subchronic (feed), chronic toxicity/carcinogenicity (feed); chemical disposition (rat - gavage, intraperitoneal injection, intravenous), genetic toxicity (micronucleus)
Chondroitin Sulfate	9007-28-7	Testing planned
Echinacea Purpurea Extract	90028-20-9	Immunotoxicity, other studies planned
Ephedrine Alkaloid Dietary Supplements		Testing planned
Folic Acid	59-30-3	Genetic toxicity (*Salmonella*)
Ginkgo Biloba Extract	90045-36-6	Subchronic (gavage), chronic toxicity/carcinogenicity (gavage), chemical disposition (human - *in vitro*), genetic toxicity (micronucleus)
Ginseng	50647-08-0	Subchronic (gavage), chronic toxicity/carcinogenicity (gavage), genetic toxicity (*Salmonella* and micronucleus)
Glucosamine	3416-24-8	Testing planned
Goldenseal Root Powder		Subchronic (feed), chronic toxicity/carcinogenicity (feed), chemical disposition (human - *in vitro*), teratology (feed), genetic toxicity (micronucleus)
Grape Seed Extract		Genetic toxicity (*Salmonella*)
Grape Seed and Pine Bark Extracts		Chemical disposition (human - *in vitro*)

Compound	CAS Number	NTP Studies (completed, ongoing or planned)
Green Tea Extract		Testing planned
Hydrastine	118-08-1	Genetic toxicity (*Salmonella*)
Indole-3-carbinol	700-06-1	Subchronic (gavage), chronic toxicity/carcinogenicity (gavage), genetic toxicity (*Salmonella* and micronucleus)
Juglone	481-39-0	Chemical disposition (rat - topical), genetic toxicity (*Salmonella*)
Kava Kava Extract	9000-38-8	Subchronic (gavage), chronic toxicity/carcinogenicity (gavage), chemical disposition (human - *in vitro*, rat - gavage, intravenous), genetic toxicity (*Salmonella*)
α-Lipoic Acid	1077-28-7	Genetic toxicity (*Salmonella*)
Melatonin	73-31-4	Subchronic (gavage), teratology (gavage)
Milk Thistle Extract	84604-20-6	Subchronic (feed), chronic toxicity/carcinogenicity (feed), chemical disposition (human - *in vitro*), genetic toxicity (*Salmonella* and micronucleus)
Pulegone	89-82-7	Subchronic (gavage), chronic toxicity/carcinogenicity (gavage), chemical disposition (rat - gavage, intravenous), genetic toxicity (*Salmonella* and micronucleus)
trans-Resveratrol	501-36-0	Testing planned
Senna (Powdered)	8013-11-4	Transgenic model, genetic toxicity (*Salmonella*)
Silymarin	65666-07-1	Genetic toxicity (*Salmonella*)
Silybin	22888-70-6	Genetic toxicity (*Salmonella*)
α-Thujone	546-80-5	Subchronic (gavage), genetic toxicity (*Salmonella*)
α/β-Thujone Mixture		Subchronic (gavage), chronic toxicity/carcinogenicity (gavage), genetic toxicity (*Salmonella* and micronucleus)
l-Tryptophan	73-22-3	Subchronic (feed), chronic toxicity/carcinogenicity (feed), genetic toxicity (*Salmonella*, micronucleus, chromosome aberration, sister chromatid exchange, mouse lymphoma)

[1] Testing status and study results for completed studies can be found at *http://ntp.niehs.nih.gov/* select "Testing Status of Agents at NTP" and "Study Results & Research Projects"

Safe Drinking Water Program

More than 200 million Americans are estimated to use municipally treated drinking water, so the availability of safe drinking water is of enormous importance to public health. NTP research under the safe drinking water program is broad in scope with some studies being conducted at NIEHS/NIH and others being done through agreements with the U.S. Army and EPA.

Although chlorination is one of the major public health advances of the 20th century, by-products of chlorination or other disinfection processes (disinfection by-products, DBPs) may cause health problems such as adverse reproductive effects or cancer. The EPA is responsible for setting water standards for DBPs under the Safe Drinking Water Act. To provide scientific data for setting sound standards for water quality, the NTP is collaborating with the EPA on a research program to assess potential risks from human exposure to DBPs. This program includes a systematic, mechanism-based evaluation of DBPs focusing on reproductive toxicity, immunotoxicity, neurotoxicity, and carcinogenicity. The program selected DBPs for study based on their presence in drinking water, occurrence with different disinfection processes, chemical structures, and class: trihalomethanes, haloacetic acids, and haloacetonitriles.

Besides DBPs, many agents occur (1) naturally (*e.g.*, arsenic, aluminum) in water, (2) because of contamination (*e.g.*, methyl tert-butyl ether and other gasoline additives, pesticides, organic tin compounds), or (3) with environmental changes (*e.g.*, cyanobacterial toxins from algal blooms in surface waters). The NTP is designing long-term toxicology and toxicokinetic studies on several of these agents including aluminum complexes, organic tin compounds, and the two most common cyanobacterial toxins (microcystin-LR and cylindrospermopsin). Table 13 lists DBPs and other water-related agents under study by the NTP.

Table 13. Water Contaminants[1]

Chemical	CAS Number	NTP Studies (Completed, Ongoing or Planned)
Disinfection by-products, DBPs		
Bromochloroacetic Acid	5589-96-8	Subchronic (water), chronic toxicity/carcinogenicity (water), genetic toxicity (*Salmonella* and micronucleus), reproductive toxicity (water)
Bromodichloromethane	75-27-4	Subchronic (water, gavage, topical), chronic toxicity/carcinogenicity (water, gavage), transgenic models (water, gavage), genetic toxicity (*Salmonella*, micronucleus and mouse lymphoma), chemical disposition (rat – gavage, intravenous), toxicokinetic (mouse – gavage), reproduction/development (water)
Chloramine	10599-90-3	Chronic toxicity/carcinogenicity (water),
Chloroform	67-66-3	Subchronic (gavage), chronic toxicity/carcinogenicity (gavage), genetic toxicity (*Salmonella*, micronucleus, chromosome aberration, sister chromatid exchange, mouse lymphoma), chemical disposition (rat – water, intraperioneal injection), reproduction/development (gavage)
Dibromoacetic Acid	631-64-1	Subchronic (water), chronic toxicity/carcinogenicity (water), genetic toxicity (*Salmonella* and micronucleus), immunotoxicity (water), neurotoxicity (water), spermiation inhibition (rat – gavage), toxicokinetics (mice – gavage)
Dibromoacetonitrile	3252-43-5	Subchronic (water), chronic toxicity/carcinogenicity (water), genetic toxicity (*Salmonella*, micronucleus and Drosphila), chemical disposition (rat – gavage, intravenous), neurotoxicity (water), reproduction/development (water)
Dichloroacetic Acid	79-43-6	Subchronic (water, topical), chronic toxicity/carcinogenicity (water), genetic toxicity (*Salmonella* and micronucleus), spermiation inhibition (rat – gavage), immunotoxicity (water), transgenic models (water, topical)
Sodium Bromate	7789-38-0	Subchronic testing completed, genetic toxicity (micronucleus), toxicokinetic (mice – gavage, topical), reproduction/development (water), immunotoxicity (water), transgenic models (water, topical)
Sodium Chlorate	7775-09-9	Subchronic (water), chronic toxicity/carcinogenicity (water), genetic toxicity (*Salmonella* and micronucleus), teratology (gavage)

Chemical	CAS Number	NTP Studies (Completed, Ongoing or Planned)
Sodium Chlorite	7758-19-2	Immunotoxicity (water)
Other Water Contaminants		
Microcystin-LR	101043-37-2	Chronic toxicity/carcinogenicity planned
Cylindrospermopsin	143545-90-8	Chronic toxicity/carcinogenicity planned

[1] Testing status and study results for completed studies can be found at *http://ntp.niehs.nih.gov/* select "Testing Status of Agents at NTP" and "Study Results & Research Projects

Endocrine Disrupting Compounds

Endocrine disrupting compounds (EDCs) are naturally occurring or man-made substances that may mimic or interfere with natural hormones in the body. Endocrine disruptors may turn on, shut off, or modify hormone signals and thus affect the normal functions of tissues and organs. The NTP is involved in several efforts to strengthen the scientific knowledge within this field (Table 14).

The NIEHS/NIH is examining the cellular and molecular mechanisms through which natural and synthetic estrogenic compounds might interact with target tissues (*e.g.*, developing genital tract, gonads, and mammary gland) and cause permanent alterations that potentially could affect sexual differentiation or induction of hormone-sensitive cancers (*e.g.*, cervix, uterus, vagina, breast, testis, and prostate). Diethylstilbestrol is being used as the model compound to compare its effects with naturally occurring substances (genistein and daidzein found in soy), drugs (Tamoxifen), pesticides (methoxychlor) and xenoestrogens (bisphenol A). Other studies include identifying stem cells in target tissues, investigating the role of the estrogen receptor in induction and/or progression of neoplasms, identifying potentially altered growth factor pathways, and defining markers of pre-neoplasia. This group of investigators is also interested in developing assays to determine estrogenicity of environmental chemicals that can be used as sensitive markers of exposure (Newbold, NIEHS/NIH). Another area of study at NIEHS/ NIH is investigating mechanisms through which environmental and synthetic antiandrogenic agents interact with the developing male reproductive system in experimental animals that could model human testicular dysgenesis syndrome (a collection of adverse reproductive responses with an *in utero* origin including decreased sperm parameters and increased incidence of cryptorchidism, hypospadias, and testicular cancer). Efforts are primarily focused on the environmental contaminant di-*n*-butyl phthalate and the pharmaceutical androgen receptor antagonist flutamide as model compounds (Foster, NIEHS/NIH).

Several NIEHS/NIH epidemiology studies are examining the potential effects of endocrine disrupting agents in human populations. One project is investigating the impact of exposure to hormonally active compounds in soy formula on estrogen-responsive tissues in infants and sexual differentiation (Rogan, NIEHS/NIH). Another project is focusing on the effects of early-life exposure to a DDT degradation product DDE (an antiandrogen) in relation to anogenital distance in newborn males among a highly exposed population in Southern Mexico (Longnecker, NIEHS/NIH). *In utero* exposure to bisphenol A, an estrogenic compound, is being studied to assess whether it is associated with body weight in children in Rotterdam, the Netherlands (Longnecker, NIEHS/NIH. This same population will be used to assess early exposure to phthalates in relation to respiratory outcomes and possibly anogenital distance. Another NIEHS/NIH epidemiology study will examine *in utero* exposure to perfluorinated alkyl compounds (such as perfluorooctanesulfate) in relation to thyroid function in neonates in Norway (Longnecker, NIEHS/NIH).

Table 14. Endocrine Disruptors[1]

Chemical	CAS Number	Primary use	NTP Studies (Completed, Ongoing or Planned)
Di(2-ethylhexyl) Phthalate	117-81-7	Used as a plasticizer, agaracide, and ingredient in pesticides, cosmetics, detergents	Subchronic (feed), chronic toxicity/carcinogenicity (feed), genetic toxicity (*Salmonella*, chromosome aberration, sister chromatid exchange, mouse lymphoma and Drosophila), chemical disposition (rat – topical), mechanism (rat – gavage)
Ethinyl Estradiol	57-63-6	Nonsteroidal semi-synthetic estrogen used in the treatment of breast and prostate cancer	Genetic toxicity (*Salmonella* and micronucleus), reproduction/development (gavage), multigenerational study with carcinogenicity (feed), immunotoxicity (feed), behavioral toxicity (feed), transgenic models (gavage, topical)
Flutamide	13311-84-7	Androgen antagonist used as an antineoplastic therapy for prostate cancer	Reproduction/development (gavage)
Flutamide and Dibutyl Phthalate Mixture	13311-84-7; 84-74-2	Used as a plasticizer, solvent and textile lubricant	Reproduction/development (gavage)
Genistein	446-72-0	Antineoplastic agent; growth inhibitor; naturally-occurring phytoestrogen found in several plants including soy products. Nutritional and pharmaceutical applications	Subchronic (feed), multigeneration study with carcinogenicity (feed), immunotoxicity (feed), behavioral toxicity (feed)
Methoxychlor	72-43-5	Insecticide	Subchronic (feed), chronic toxicity/carcinogenicity (feed), genetic toxicity (*Salmonella*, chromosome aberration, sister chromatid exchange, mouse lymphoma), reproduction/development (gavage), range finding (feed), immunotoxicity (feed), behavioral toxicity (feed)
Nonylphenol	84852-15-3	Used extensively as non-ionic detergent surfactant in industrial applications	Reproduction/development (feed), multigenerational study with carcinogenicity (feed), immunotoxicity (feed), behavioral toxicity (feed)
Phenobarbital	50-06-6	Pharmaceutical thyroid-active agent used as a anticonvulsant and sedative	Genetic toxicity (*Salmonella*, chromosome aberration, sister chromatid exchange, mouse lymphoma), reproduction/development (gavage),
Propylthiouracil	51-52-5	Used since the 1940s as an antithyroid agent for the treatment of hyperthyroidism	Genetic toxicity (*Salmonella*), reproduction/development (water), neurotoxicity (water)
Vinclozolin	50471-44-8	Fungicide, bactericide, wood preservative; used on fruits, vegetables, ornamental plants and vines	Reproduction/development (gavage), range finding (feed), immunotoxicity (feed), behavioral toxicity (feed)

[1] Testing status and study results for completed studies can be found at *http://ntp.niehs.nih.gov/* select "Testing Status of Agents at NTP" and "Study Results & Research Projects

EDCs are of interest to the FDA, and through an interagency agreement the NIEHS/NIH supports toxicology studies being conducted at the NCTR/FDA. Chemicals under study include the phytoestrogen genistein, the pesticides vinclozolin and methoxychlor, the drug ethinyl estradiol, and the industrial chemical nonylphenol. These studies assess effects on reproduction, development of hormone-sensitive organs, and cancer in rodents over multiple generations (Delclos, NCTR/FDA). The NCTR/FDA scientific staff is also interested in evaluating neuroanatomical, neurobehavioral, and immunological end points associated with exposure to endocrine disrupting chemicals (Ferguson, NCTR/FDA; Slikker, NCTR/FDA; Scallet, NCTR/FDA). These are critical parallel studies to the multigeneration toxicology studies. Two of the compounds (genistein and ethinyl estradiol) are also being investigated for chronic exposure effects including neoplasia (Newbold, NIEHS/NIH; Delclos, NCTR/FDA).

Studies at NIOSH/CDC are exploring how exposure to occupational chemicals impacts normal testicular function *in vitro* at different stages of maturation/development (fetal/neonatal, prepubertal, and adult). Primary cultures of rat cells that synthesize testosterone (Leydig cells) and help regulating spermatogenesis (Sertoli cells) from animals at different ages following exposure are being used. These studies target the testing of endocrine - disrupting chemicals (industrial surfactant additive - octylphenol and pesticides - methoxychlor and vinclozolin), which are reported to alter normal functioning of endogenous estrogens and androgens. Results from initial studies demonstrate age-dependent responses to chemical exposures. Future studies will focus on establishing possible mechanism(s) of action and comparing *in vitro* and *in vivo* responses (Murono, NIOSH/CDC). NIOSH/CDC is examining the relationship between female worker exposure to polychlorinated biphenyls and breast cancer. These compounds are suspected carcinogens because of their estrogenic and lipophilic properties (Whelan, NIOSH/CDC).

As required by the 1996 Food Quality Protection Act, the EPA is in the process of choosing appropriate assays to screen endocrine-active agents and develop standardized, validated protocols for those assays. NICEATM is currently evaluating several test methods nominated to assess endocrine activities of chemicals (see page 22).

Occupational Mixtures and Exposures

The NTP is coordinating an effort between NIEHS/NIH and NIOSH/CDC to better characterize worker exposures, educate workers, and identify occupational health research gaps. Current efforts are assessing worker exposures to 1-bromopropane (1-BP) and tungsten fibers. In addition, laboratory studies designed to address specific questions regarding workplace exposure to complex mixtures are being conducted or planned with welding fumes, abrasive blasting materials, and metal working fluids (Morgan, NIEHS/NIH; Toraason, NIOSH/CDC).

The EPA has approved 1-BP as an alternative to ozone-depleting solvents for metal cleaning, electronics cleaning, and precision cleaning. It is also acceptable for use as an aerosol solvent and as a carrier solvent for adhesives. This may result in a vast increase in the exposure of workers and the public to this compound. To characterize these exposures, NIOSH/CDC is conducting an industry-wide exposure assessment. Study sites are being assessed based on quantity and manner of 1-BP use, number of workers exposed, type of manufacturing process, and how representative the exposure is for the industry as a whole. Exposures are being characterized by monitoring breathing zones, exhaled breath, and biological measures. Results from this study will be used to (1) evaluate patterns of exposure, (2) develop and validate biomonitoring methods, (3) facilitate development of intervention recommendations for reducing exposures, and (4) aid establishment of exposure limits (Hanley, NIOSH/CDC).

Metallurgists create tungsten-trioxide or suboxide (WO) species as products of reduction reactions in processing tungsten containing ores to obtain useful chemical forms of tungsten. Recent studies in the Swedish hard-metal industry have shown that calcinations of WO, ammonium paratungstate, and ‘blue’ oxide result in the formation of asbestos-like WO whiskers that are thought to be more toxic than WO powder. Investigations into the existence of WO fibers in the U.S. hard-metal industry have not been conducted previously. NIOSH is embarking on a field study in the hard metal industry to define baseline exposure to WO fibers among U.S. hard-metal workers (Hooth, NIEHS/NIH; Mckernan, NIOSH/CDC).

Epidemiology suggests that pulmonary exposure to welding fumes may cause adverse health effects such as lung inflammation, cancer, and neurotoxicity. However, more information is required to determine causality, evaluate temporal and dose-response relationships, and elucidate mechanisms. NIOSH/CDC has designed and constructed a welding fume generation and inhalation exposure system that will be used to characterize the physical and chemical properties of generated welding fumes. The system will be used to evaluate

exposure conditions, generator parameters, and welding processes and materials that may cause acute biological responses in an animal model (Morgan, NIEHS/NIH; Antonini, NIOSH/CDC).

Alternatives to silica sand for abrasive blasting are frequently recommended to reduce workers' risk for developing fibrotic lung disease and cancer. Coal slag, garnet, steel grit, crushed glass, and specular hematite are frequently recommended as safe alternatives to silica sand. These abrasive blasting materials are being assessed to determine their relative potential for inducing lung fibrosis in experimental animals. Results will aid risk assessors in providing guidance for development of exposure limits (Suarez, NIEHS/NIH; Hubbs, NIOSH/CDC).

Millions of gallons of metal working fluids are used each day in industry for cutting, milling, drilling, stamping, and grinding. NIOSH has estimated that over a million workers are engaged in these activities and potentially are exposed dermally and via inhalation to a wide variety of formulations. Potential hazards of product formulations are typically identified by testing of individual constituents. To determine if inhalation exposure to metal working fluid formulations poses an unrecognized hazard, several commercial products will be tested in sub-chronic, and in some cases, chronic inhalation bioassays (Roycroft, NIEHS/NIH; Toraason, NIOSH/CDC).

DNA-Based Products

DNA-based therapies are being developed for the treatment of a wide range of human diseases. However, by their very nature, they pose a risk of interacting with the host genome or disrupting normal cellular processes in unexpected and unpredictable ways with potentially adverse consequences. Examples of DNA-based products include plasmid DNA encoding one or more antigenic proteins for vaccines against viral and bacterial pathogens, triplex forming synthetic oligonucleotides to modulate gene expression, and viral vectors for gene therapy. The FDA has only limited authority to require evaluation of non-acute, long-term safety risk associated with these therapies. In addition, the majority of the manufacturers of DNA-based products are small biotechnology companies and academic sponsors that lack the resources to perform long-term, large-scale studies on their products. Presently the NTP is collaborating with the FDA and sister NIH institutes to study the safety of DNA-based products and address life-long risks presented by their use and their potential for reproductive toxicities and transmission of altered genetic material to subsequent generations. In addition, the potential for DNA-based products to cause autoimmune disease or immune dysfunction will be evaluated (Irwin, NIEHS/NIH).

GENERAL TOXICOLOGY AND SUBCHRONIC STUDIES

Research Initiatives

In the area of general toxicology assessments, the scope and types of studies performed are dictated to a large degree by the data needs for the specific substance nominated for study. General toxicology studies usually fall into two categories: subchronic or prechronic studies and 2-year chronic toxicity and carcinogenicity studies. These studies are typically carried out as contracted studies at several commercial laboratories in the United States. The NTP performs subchronic toxicity studies in part to provide dose-setting information for chronic studies and also to address specific deficiencies in the toxicology database for the chemical.

Although designs are flexible, subchronic studies usually involve exposures of rats and mice of both sexes to substances for periods of 14 to 90 days. Assessments almost always include tissue histopathology, clinical pathology, and sperm motility or measurements of estrous cycle length. A determination of the frequency of micronucleated erythrocytes is conducted as an *in*

vivo measure of genotoxic potential, and, in some cases, a Functional Observational Battery is included as a neurotoxicology screen. The study protocol may include more detailed or focused studies when findings published in the existing scientific literature or identified in initial NTP studies suggest a target organ or system. Also, the study protocol may include separate studies of reproductive, genetic, or immunological toxicity based on the outcome of the toxicity screens.

In some cases, the NTP uses alternative models, including genetically modified mouse models and non-mammalian models, for subchronic studies. Such studies are presented in the section "Alternative Test Systems" (page 65). Table 15 lists the agents tested in subchronic studies during FY 2003-2004.

Table 15. Ongoing Subchronic Toxicity Studies During FY 2003-2004[1]

Chemical	CAS Number	Species/ Strain	Route	Study Length	Project Leader[2]
Acetaminophen (4-Hydroxyacetanilide)	103-90-2	Rats: Fischer 344	Gavage	2 days	Boorman
Acrolein	107-02-8	Mice: B6C3F1 Rats: Fischer 344	Gavage	14 days 90 days	Irwin
Acrylamide	79-06-1	Mice: B6C3F1 Rats: Fischer 344	Water, Feed	14 days 90 days	Beland (NCTR/FDA)
Adenoviral Vector (Ad-Hgh)		Rats: Fischer 344	Intraductal Cannulation	28 days	Irwin
Allyl Acetate	591-87-7	Mice: B6C3F1 Rats: Fischer 344	Gavage	14 days 90 days	Irwin
Allyl Alcohol	107-18-6	Mice: B6C3F1 Rats: Fischer 344	Gavage	14 days 90 days	Irwin
1-Bromopropane	106-94-5	Mice: B6C3F1 Rats: Fischer 344	Inhalation	14 days 90 days	Morgan
o-Chloropyridine	109-09-1	Mice: B6C3F1 Rats: Fischer 344	Topical	14 days	Chhabra
o-Chloropyridine	109-09-1	Mice: B6C3F1 Rats: Fischer 344	Water	90 days	Chhabra
Diethylamine	109-89-7	Mice: B6C3F1 Rats: Fischer 344	Inhalation	14 days 90 days	Morgan
N,N-Dimethyl-*p*-toluidine	99-97-8	Mice: B6C3F1 Rats: Fischer 344	Gavage	90 days	Dunnick
Ginkgo Biloba Extract	90045-36-6	Mice: B6C3F1 Rats: Fischer 344	Gavage	90 days	Chan
Ginseng	50647-08-0	Mice: B6C3F1 Rats: Fischer 344	Gavage	14 days 90 days	Chan
Glycidamide	5694-00-8	Mice: B6C3F1/NCTR BR Rats: Fischer 344	Water	14 days 90 days	Weis (NCTR/FDA)
Kava Kava Extract	9000-38-8	Mice: B6C3F1 Rats: Fischer 344	Gavage	14 days 90 days	Chan
Melatonin	73-31-4	Rats: Fischer 344 Rats: Long-Evans	Gavage	14 days 90 days	Boorman
Methyl *trans*-Styryl Ketone	1896-62-4	Mice: B6C3F1 Rats: Fischer 344	Feed	90 days	Cunningham
Milk Thistle Extract	84604-20-6	Mice: B6C3F1 Rats: Fischer 344	Feed	90 days	Dunnick
Polychlorinated Naphthalenes (PCN 66 and PDN67)	1034426-96-6; 1034426-97-7	Rats: Fischer 344 Rats: Sprague Dawley	Gavage	14 days 90 days	Hooth
β-Picoline	108-99-6	Mice: B6C3F1 Rats: Fischer 344	Water	90 days	Abdo
Pyrogallol	87-66-1	Mice: B6C3F1 Rats: Fischer 344	Topical	90 days	Wyde

Chemical	CAS Number	Species/ Strain	Route	Study Length	Project Leader[2]
Sodium Thioglycolate	367-51-1	Mice: B6C3F1 Rats: Fischer 344	Topical	14 days 90 days	Hooth
Styrene-Acrylonitrile Trimer		Rats: Fischer 344	Feed	7 weeks 18 weeks	Chhabra
α/β Thujone Mixture	546-80-5; 471-15-8	Mice: B6C3F1 Rats: Fischer 344	Gavage	90 days	Hooth
Triethylamine	121-44-8	Mice: B6C3F1 Rats: Fischer 344	Inhalation	14 days 90 days	Morgan

[1] Protocols for subchronic toxicity studies are described on the NTP website at *http://ntp.niehs.nih.gov/* see "Descriptions of NTP Study Types." Testing status and study results for completed studies can be found at *http://ntp.niehs.nih.gov/* select "Testing Status of Agents at NTP" and "Study Results & Research Projects

[2] Project Leader - NIEHS/NIH staff scientist (unless otherwise indicated) who oversees each chemical's evaluation

Research Projects (General Toxicology)

- Statistical methods and applications for laboratory animal studies (Dinse, NIEHS/NIH)
- Statistical methods for human studies (Dunson, NIEHS/NIH)
- Statistical methods for studying human fertility (Dunson, NIEHS/NIH)
- Statistical methods in toxicology (Dunson, NIEHS/NIH)
- Predicting skin penetration: mode and experiments (Frasch, NIOSH/CDC)
- The role of growth factors and inflammatory mediators in target-organ toxicity (Germolec, NIEHS/NIH)
- Metabolic activity of human recombinant cytochrome P450 enzymes (Ghanayem, NIEHS/NIH)
- Drug metabolizing enzymes in humans and animal models (Goldstein, NIEHS/NIH)
- Physiological effects of bitter orange in rats (Hansen, NCTR/FDA)
- Identifying and evaluating sources of variability in rodent studies (Haseman, NIEHS/NIH)
- Three dimensional atlas of mouse anatomy pathology (Maronpot, NIEHS/NIH)
- Nuclear receptors: action, functions, and roles in disease (Jetten, NIEHS/NIH)
- The roles of the cyclooxygenases (COXs) in normal physiology and pathological conditions (Langenbach, NIEHS/NIH)
- Development of gene single nucleotide polymorphisms (SNPs) as a web-accessible highly annotated relational database of human and mouse environmental response genes (Maull, NIEHS/NIH)
- Membrane transporters: critical determinats of AIDS antiviral drugs (Miller, NIEHS/NIH)
- Regulation of renal xenobiotic excretion (Miller, NIEHS/NIH)
- Biomarkers of cardiotoxicity (Murphy, NIEHS/NIH)
- NMR studies of the mechanisms of cell injury (Murphy, NIEHS/NIH)
- Asphalt fume chemical characterization and hazard identification (Olsen, NIOSH/CDC)
- Evaluation of methods: polycyclic aromatic hydrocarbons (PAH) determination in asphalt fumes (Olsen, NIOSH/CDC)
- Mapping tree coverage in Vietnam in the 1960s (Portier, NIEHS/NIH)
- Statistical models in toxicology and biochemistry (Portier, NIEHS/NIH)
- Role of membrane transport in the effectiveness and toxicity of AIDS therapeutics (Pritchard, NIEHS/NIH)

- Toxicology of AIDS therapeutics (Roycroft, NIEHS/NIH)
- Mechanisms of toxicity of redox reactive intermediates in skin (Shvedova, NIOSH/CDC)
- Environmental atherosclerosis studies (Sills, NIEHS/NIH)
- Developing healthy and dermatitis skin absorption models (Soderholm, NIOSH/CDC)
- Mass spectrometry and oxidative stress (Tomer, NIEHS/NIH)
- Statistical methods in human development/clinical studies (Umbach, NIEHS/NIH)
- Arachidonic acid metabolism by murine CYP2c isoforms (Zeldin, NIEHS/NIH)
- Characterization and functional significance of P450 arachidonate epoxygenases (Zeldin, NIEHS/NIH)

CHRONIC TOXICITY, CARCINOGENESIS, AND MUTAGENESIS

Research Initiatives

Two-year studies in rodents remain the primary laboratory method by which chemicals or physical agents are identified as having the potential to be hazardous to man. Studies in rodents along with studies in human populations (epidemiology studies) are the best means currently available for identifying potential human hazards. The chronic toxicology and carcinogenicity studies in conventional rodent models generally employ both genders of rats (Fisher 344) and mice (B6C3F1 hybrid) with three exposure levels plus untreated controls in groups of 50 animals for two years; genetically modified mouse and fish models are used occasionally. If adequate data exist in the literature for one rodent species, then typically only the remaining species is studied. The NTP interfaces its testing with regulatory agencies and the private sector in order to minimize duplication of effort. Table 16 lists the substances in the chronic phase of NTP study during FY 2003 and 2004.

Table 16. Ongoing Chronic Toxicity/Carcinogenicity Studies During FY 2003-2004[1]

Chemical Name	CAS Number	Species/ Strain	Route	Study Length	Project Leader[2]
Aloe-Emodin	481-72-1	Mice:SKH-1 Hairless	Topical	62 weeks	Boudreau (NCTR/FDA)
Aloe Vera Charcoal Filtered Whole Leaf Extract		Mice:SKH-1 Hairless	Topical	62 weeks	Boudreau (NCTR/FDA)
Aloe Vera Gel	8001-97-6	Mice:SKH-1 Hairless	Topical	62 weeks	Boudreau (NCTR/FDA)
Aloe Vera Whole Leaf Extract (Native)		Mice:SKH-1 Hairless	Topical	62 weeks	Boudreau (NCTR/FDA)
Androstenedione	63-05-8	Mice:B6C3F1 Rats:Fischer 344	Gavage	2 years	Eastin
Anthraquinone	84-65-1	Mice:B6C3F1 Rats:Fischer 344	Feed	2 years	Irwin
AZT (3'-Azido-3'-Deoxythymidine)	30516-87-1	Mice:B6C3F1 Mice:B6C3F1/NCTR BR	Gavage	2 year	Beland (NCTR/FDA)
AZT+ 3TC (2', 3'-Dideoxy-3'-thiacytidine)	30516-87-1; 134678-17-4	Mice:B6C3F1 Mice:B6C3F1/NCTR BR	Gavage	2 year	Beland (NCTR/FDA)
AZT + 3TC + NLFT (Nelfinavir Mesylate)	30516-87-1; 134678-17-4; 159989-65-8	Mice:B6C3F1 Mice:B6C3F1/NCTR BR	Gavage	2 year	Beland (NCTR/FDA)
AZT + 3TC + NVP (Nevirapine)	30516-87-1; 134678-17-4; 129618-40-2	Mice:B6C3F1 Mice:B6C3F1/NCTR BR	Gavage	2 year	Beland (NCTR/FDA)

Chemical Name	CAS Number	Species/ Strain	Route	Study Length	Project Leader[2]
AZT Transplacental Carcinogenesis Study	30516-87-1	Mice:Swiss CD-1	*In utero*	19 months	Dunnick
Benzophenone	119-61-9	Mice:B6C3F1 Rats:Fischer 344	Feed	2 years	Chhabra
Bromochloroacetic Acid	5589-96-8	Mice:B6C3F1 Rats:Fischer 344	Water	2 years	Melnick
Bromodichloromethane	75-27-4	Mice:B6C3F1 Rats:Fischer 344	Water	2 years	Melnick
1-Bromopropane	106-94-5	Mice:B6C3F1 Rats:Fischer 344	Inhalation	2 years	Morgan
bis (2-Chloroethoxy) Methane	111-91-1	Mice:B6C3F1 Rats:Fischer 344	Topical	2 years	Dunnick
Chromium Picolinate Monohydrate	27882-76-4	Mice:B6C3F1 Rats:Fischer 344	Feed	2 years	Abdo
Cresols	1319-77-3	Mice:B6C3F1 Rats:Fischer 344	Feed	2 years	Chhabra
Cumene	98-82-8	Mice:B6C3F1 Rats:Fischer 344	Inhalation	2 years	Chan
Dibromoacetic Acid	631-64-1	Mice:B6C3F1 Rats:Fischer 344	Water	2 years	Melnick
Dibromoacetonitrile	3252-43-5	Mice:B6C3F1 Rats:Fischer 344	Water	2 years	Melnick
1,2-Dibromo-2,4-dicyanobutane	35691-65-7	Mice:B6C3F1 Rats:Fischer 344	Topical	2 years	Dunnick
Diethylamine	109-89-7	Mice:B6C3F1 Rats:Fischer 344	Inhalation	2 years	Morgan
Diisopropylcarbodiimide	693-13-0	Mice:B6C3F1 Rats:Fischer 344	Topical	2 years	Chhabra
N,N-Dimethyl-*p*-toluidine	99-97-8	Mice:B6C3F1 Rats:Fischer 344	Gavage	2 years	Dunnick
Divinylbenzene	1321-74-0	Mice:B6C3F1 Rats:Fischer 344	Inhalation	2 years	Morgan
Formamide	75-12-7	Mice:B6C3F1 Rats:Fischer 344	Gavage	2 years	Irwin
Ginseng	50647-08-0	Mice:B6C3F1 Rats:Fischer 344	Gavage	2 years	Chan
Goldenseal Root Powder		Mice:B6C3F1 Rats:Fischer 344	Feed	2 years	Dunnick
β-Hydroxy Acids (Salicylic Acid)	69-72-7	Mice:SKH-1 Hairless	Topical	1 year	Howard (NCTR/FDA)
α-Hydroxy Acid (Glycolic Acid)	79-14-1	Mice:SKH-1 Hairless	Topical	1 year	Howard (NCTR/FDA)
5-(Hydroxymethyl)-2-Furfural	67-47-0	Mice:B6C3F1 Rats:Fischer 344	Gavage	2 years	Irwin
Isoeugenol	97-54-1	Mice:B6C3F1 Rats:Fischer 344	Gavage	2 years	Abdo
Leucomalachite Green	129-73-7	Mice:B6C3F1/NCTR BR Rats:Fischer 344	Feed	2 year	Culp (NCTR/FDA)
Malachite Green	569-64-2	Mice:B6C3F1/NCTR BR Rats:Fischer 344	Feed	2 year	Culp (NCTR/FDA)
Methylene Blue Trihydrate	7220-79-3	Mice:B6C3F1 Rats:Fischer 344	Gavage	2 years	Chhabra
2-Methylimidazole	693-98-1	Mice:B6C3F1 Rats:Fischer 344	Feed	2 years	Chan
4-Methylimidazole	822-36-6	Mice:B6C3F1 Rats:Fischer 344	Feed	2 years	Chan
Methyl Isobutyl Ketone	108-10-1	Mice:B6C3F1 Rats:Fischer 344	Inhalation	2 years	Suarez

Chemical Name	CAS Number	Species/ Strain	Route	Study Length	Project Leader[2]
α-Methylstyrene	98-83-9	Mice:B6C3F1 Rats:Fischer 344	Inhalation	2 years	Morgan
Methyl *trans*-Styryl Ketone	1896-62-4	Mice:B6C3F1 Rats:Fischer 344	Topical	2 years	Cunningham
Milk Thistle Extract	84604-20-6	Mice:B6C3F1 Rats:Fischer 344	Feed	2 years	Dunnick
β-Myrcene	123-35-3	Mice:B6C3F1 Rats:Fischer 344	Gavage	2 years	Chan
β-Picoline	108-99-6	Mice:B6C3F1 Rats:Fischer 344	Water	2 years	Abdo
Propargyl Alcohol	107-19-7	Mice:B6C3F1 Rats:Fischer 344	Inhalation	2 years	Hooth
Propylene Glycol Mono-*t*-butyl Ether	57018-52-7	Mice:B6C3F1 Rats:Fischer 344	Inhalation	2 years	Chhabra
Pulegone	89-82-7	Mice:B6C3F1 Rats:Fischer 344	Gavage	2 years	Chan
All-*trans*-Retinyl Palmitate	79-81-2	Mice:SKH-1 Hairless	Topical	1 year	Fu (NCTR/FDA)
Sodium Chlorate	7775-09-9	Mice:B6C3F1 Rats:Fischer 344	Water	2 years	Hooth
Sodium Dichromate Dihydrate (VI)	7789-12-0	Mice:B6C3F1 Rats:Fischer 344	Water	2 years	Abdo
Stoddard Solvent (Type IIC)	64742-88-7	Mice:B6C3F1 Rats:Fischer 344	Inhalation	2 years	Chhabra
Toxic Equivalency Factor TEF) Evaluation (Dioxin Mixture)		Rats:Sprague Dawley	Gavage	2 years	Walker
TEF Evaluation (Binary Mixture; PCB 126/ PCB 153	57465-28-8 35065-27-1	Rats:Sprague Dawley	Gavage	2 years	Walker
TEF Evaluation (PCB 118)	31508-00-6	Rats:Sprague Dawley	Gavage	2 years	Walker
TEF Evaluation (PCB Mixture; PCB 126/PCB 118)	57465-28-8 31508-00-6	Rats:Sprague Dawley	Gavage	2 years	Walker
TEF Evaluation (PCB 126)	57465-28-8	Rats:Sprague Dawley	Gavage	2 years	Walker
TEF Evaluation (TCDD)	1746-01-6	Rats:Sprague Dawley	Gavage	2 years	Walker
TEF Evaluation (Pentachlorodibenzofuran)	57117-31-4	Rats:Sprague Dawley	Gavage	2 years	Walker
3,3',4,4'-Tetrachloroazobenzene	14047-09-7	Mice:B6C3F1 Rats:Sprague Dawley	Gavage	2 years	Hooth
Tetralin	119-64-2	Mice:B6C3F1 Rats:Fischer 344	Inhalation	2 years	Chan
α/β-Thujone Mixture		Mice:B6C3F1 Rats:Fischer 344	Gavage	2 years	Hooth
TEF Evaluation (PCB 153-2,2'-4,4',5,5'-Hexachlorobiphenyl)	35065-27-1	Rats:Sprague Dawley	Gavage	2 years	Wyde
Triethanolamine	102-71-6	Mice:B6C3F1	Topical	2 years	Suarez
Trimethylolpropane Triacrylate	15625-89-5	Mice:B6C3F1 Rats:Fischer 344	Topical	2 years	Chhabra

[1] Protocols for chronic toxicity and carcinogenicity studies are described on the NTP website at *http://ntp.niehs.nih.gov/* see "Descriptions of NTP Study Types." Testing status and study results for completed studies can be found at *http://ntp.niehs.nih.gov/* select "Testing Status of Agents at NTP" and "Study Results & Research Projects

[2] Project Leader - NIEHS/NIH staff scientist (unless otherwise indicated) who oversees each chemical's evaluation

Mutagenesis and Genetic Toxicity

Genetic toxicity test results are used to make decisions about whether a substance should be tested for carcinogenicity in rodents; to aid in the interpretation of toxicity, carcinogenicity, or other *in vivo* test results; and to provide a database for use in structure-activity analyses. Testing is conducted at contract laboratories.

Analysis of the early, multi-test database showed that positive results for a chemical in the *Salmonella* gene mutation assay were highly correlated with carcinogenicity in multiple species/sexes of rodents and at multiple tissue sites; data from additional tests did not improve the correlation. Subsequently, studies of the correlation between mutagenicity test data and rodent carcinogenicity showed a strong association between clearly positive results in long-term mouse peripheral blood micronucleus tests and rodent carcinogenicity. The importance of genetic toxicity test data in assessing exposure hazard for NTP chemicals is underscored by the fact that most organic chemicals (other than hormones) identified by the International Agency for Research on Cancer as human carcinogens are genotoxic, and the vast majority of them are detected by both the *Salmonella* assay and rodent micronucleus tests. Additional assays may be conducted with certain chemicals to gain further insight into the types of DNA and chromosomal damage induced by a chemical.

Gene mutations and DNA damage are examined in most tissues; cytogenetic effects, measured as the induction of micronuclei, are generally examined in bone marrow cells or in peripheral erythrocytes. The erythrocyte studies are integrated with other toxicity evaluations to minimize the use of animals and to expand the toxicology information for the chemical in the same animals. Compounds tested for genetic toxicity during FY 2003 and 2004 are listed in Table 17.

Table 17. Ongoing and Completed Genetic Toxicity Studies During FY 2003-2004[1]

Chemical	CAS Number	Testing Battery
Abscisic Acid	14375-45-2	Salmonella
N-2-Acetylaminofluorene	53-96-3	Sister Chromatid Exchange
2-Acetylthiazole	24295-03-2	Salmonella
Acid Red 14 (C.I. 14720)	3567-69-9	Chromosome Aberrations
Acrylamide	79-06-1	Micronucleus
Acrylonitrile	107-13-1	Micronucleus
S-Adenosylmethionine	29908-03-0	Salmonella
β-Alanine	107-95-9	Salmonella
DL-Alanine	302-72-7	Salmonella
All-*trans*-Retinyl Palmitate	79-81-2	Salmonella
Aluminum Citrate	31142-56-0	Salmonella
Aluminum Fluoride	7784-18-1	Salmonella
2-Aminoanthracene	613-13-8	Salmonella
4-Androstene-3,17-dione	63-05-8	Micronucleus
Anthraquinone	84-65-1	Salmonella
Apigenin	520-36-5	Salmonella
Aspartame	22839-47-0	Micronucleus
AZT (3'-Azido-3'-deoxythymidine)	30516-87-1	Micronucleus
AZT + 2',3'-Dideoxyinosine	30516-87-1; 69655-05-6	Micronucleus
AZT + 3TC (2', 3'-Dideoxy-3'-thiacytidine)	30516-87-1; 134678-17-4	Micronucleus
Benzene	71-43-2	Micronucleus, Chromosome Aberrations
Benzo(a)pyrene	50-32-8	Chromosome Aberrations
Bisphenol A	80-05-7	Chromosome Aberrations
Bixin	6983-79-5	Salmonella
Black Cohosh	84776-26-1	Salmonella
Blackberry Extract	84787-69-9	Salmonella
1-Bromopropane	106-94-5	Micronucleus
Bupivacaine	38396-39-3	Salmonella
1,3-Butadiene	106-99-0	Chromosome Aberrations
2-Butanol	78-92-2	Salmonella
Cedarwood Oil	8000-27-9	Salmonella
Cefuroxime	55268-75-2	Salmonella
Cimperial 1070		Salmonella
Cimstar 3733		Salmonella
Cimtech 310		Salmonella
2-Chloro-l,3-butadiene (Chloroprene)	126-99-8	Chromosome Aberrations
Chlorodibromomethane	124-48-1	Chromosome Aberrations
2-(Chloromethyl)pyridine HC1	6959-47-3	Chromosome Aberrations
4-Chloronitrobenzene	100-00-5	Micronucleus
4-Chloro-o-phenylenediamine	95-83-0	Chromosome Aberrations
2-Chloropyridine	109-09-1	Salmonella, Micronucleus
Chromium Picolinate Monohydrate	27882-76-4	Micronucleus
Clearedge 6584		Salmonella
Colchicine	64-86-8	Micronucleus
Cumene Hydroperoxide	80-15-9	Micronucleus
Cyclophosphamide	50-18-0	Micronucleus
D&C Red 27	13473-26-2	Salmonella
D&C Red 28	18472-87-2	Salmonella
2,4-Decadienal	25152-84-5	Micronucleus
1,2-Dichlorobenzene	95-50-1	Micronucleus, Sister Chromatid Exchange
cis-l,2-Dichloroethylene	156-59-2	Chromosome Aberrations
2',3'-Dideoxyinosine (DDI)	69655-05-6	Micronucleus
2', 3'-Dideoxy-3'-thiacytidine (3TC)	134678-17-4	Micronucleus

Chemical	CAS Number	Testing Battery
Diethylamine	109-89-7	Micronucleus
Diethylformamide	617-84-5	Salmonella
Dimepranol (1-(dimethylamino)-2-propanol)	108-16-7	Salmonella
Dimethyl Hydrogenphosphite	868-85-9	Sister Chromatid Exchange
N,N-Dimethyl-*p*-toluidine	99-97-8	Salmonella, Micronucleus
Diphenolic Acid	126-00-1	Salmonella
Dodecyl Alcohol, Ethoxylated	9002-92-0	Sister Chromatid Exchange
Dong Quai		Salmonella
Drinking Water Contaminants Mixture	Numerous CAS Numbers	Chromosome Aberrations, Sister Chromatid Exchange
L-Ephedrine	299-42-3	Salmonella
1,2-Epoxypropane	75-56-9	Sister Chromatid Exchange
Ethyl Methanesulfonate	62-50-0	Micronucleus
2-Ethylhexyl-*p*-dimethylaminobenzoic Acid	21245-02-3	Salmonella
α-Fenchone	1195-79-5	Micronucleus
Ginseng and Ginsenosides	50647-08-0	Micronucleus
Glucono Delta Lactone	90-80-2	Salmonella
Glycidamide	5694-00-8	Salmonella
Glycidol	556-52-5	Micronucleus
Goldenseal Root Powder		Micronucleus
Grape Seed Extract		Salmonella
2,2',4,4',5,5'-Hexabromodiphenyl Ether	68631-49-2	Salmonella
2,4-Hexadienal	142-83-6	Micronucleus
Hydergine	8067-24-1	Salmonella
1-Hydroxyanthraquinone	129-43-1	Salmonella
2-Hydroxyanthraquinone	605-32-3	Salmonella
Indole-3-carbinol	700-06-1	Salmonella, Micronucleus
Iso-E Super	54464-57-2	Salmonella
Kava Kava Extract	9000-38-8	Micronucleus
Lime oil	8008-26-2	Salmonella
D-Mannitol	69-65-8	Sister Chromatid Exchange
2-Methyl-2-ethoxypropane (*t*-Butyl Ethyl Ether)	637-92-3	Micronucleus
Methyl Soyate	67784-80-9	Salmonella
2-Methyl Tetrahydrofuran	96-47-9	Salmonella
Milk Thistle Extract	84604-20-6	Micronucleus
Mitomycin C	50-07-7	Chromosome Aberrations
Monobutyltin Trichloride	1118-46-3	Salmonella
Monomethyltin Trichloride	993-16-8	Salmonella
1-Nitroanthracene	54738-93-1	Salmonella
2-Nitroanthracene	3586-69-4	Salmonella
9-Nitroanthracene	602-60-8	Salmonella
Nitrogen Trifluoride	7783-54-2	Salmonella
Norbixin	542-40-5	Salmonella
Oleid Acid Diethanolamine Condensate	93-83-4	Micronucleus
4,4'-Oxydianiline	101-80-4	Chromosome Aberrations
2,2',4,4',5-Pentabromodiphenyl Ether	60348-60-9	Salmonella
Pentabromodiphenyl Oxide	32534-81-9	Salmonella
Pentachloroethane	76-01-7	Sister Chromatid Exchange
Phenolphthalein	77-09-8	Micronucleus
3-Picoline	108-99-6	Micronucleus
Pimenta Oil	8006-77-7	Salmonella
Pine Bark Extract		Salmonella
Polybrominated Biphenyl Mixture (Firemaster FF1)	67774-32-7	Sister Chromatid Exchange
Prilocaine	721-50-6	Salmonella
Primaclone	125-33-7	Micronucleus
Pyrogallol	87-66-1	Micronucleus
Resveratrol	501-36-0	Salmonella

Chemical	CAS Number	Testing Battery
Scutellaria		Salmonella
Senna, Powdered	8013-11-4	Salmonella
Sodium Azide	26628-22-8	Salmonella
Sodium Dichromate Dihydrate (VI)	7789-12-0	Micronucleus
Sodium (2-Ethylhexyl)alcohol Sulfate	126-92-1	Sister Chromatid Exchange
Styrene	100-42-5	Micronucleus
Sulfisoxazole	127-69-5	Sister Chromatid Exchange
Superedge 6768		Salmonella
Syntilo 1023		Salmonella
Tetrabromobisphenol A-bis(2,3-dibromopropyl ether)	21850-44-2	Salmonella
2,2'4,4'-Tetrabromodiphenyl Ether	5436-43-1	Salmonella
1,1,1,2-Tetrachloroethane	630-20-6	Sister Chromatid Exchange
Tetrahydrofuran	109-99-9	Sister Chromatid Exchange
Thioglycolic Acid, Na^+ Salt	367-51-1	Micronucleus
α, β- Thujone Mixture	546-80-5; 471-15-8	Salmonella, Micronucleus
p-Toluenesulfonamide	70-55-3	Salmonella
Triethylamine	121-44-8	Micronucleus
Trim 229		Salmonella
Trim SC210		Salmonella
Trim VX		Salmonella
Turpentine	8006-64-2	Salmonella
Urethane (Ethyl Carbamate)	51-79-6	Micronucleus
Valerian	8008-88-6	Salmonella
Vincristine Sulfate	57-22-7	Micronucleus

[1] Protocols for genetic toxicity studies are described on the NTP website at *http://ntp.niehs.nih.gov/* see "Descriptions of NTP Study Types." Testing status and study results for completed studies can be found at *http://ntp.niehs.nih.gov/* select "Testing Status of Agents at NTP" and "Study Results & Research Projects

Research Projects

- Genetic susceptibility to carcinogens (Bell, NIEHS/NIH)
- Mechanism of carcinogens—genetic alterations in rodent and human tumors (Devereux, NIEHS/NIH)
- Biochemical mechanisms related to risk factors of mammary carcinogenesis (DiAugustine, NIEHS/NIH)
- Molecular mechanisms of UV-induced carcinogenesis (Ding, NIOSH/CDC)
- Genotoxicity, mutagenicity, and exposure biomarkers of acrylamide and its metabolite, glycidamide, in rodents (Doerge, NCTR/FDA)
- Anti-carcinogenic activity of nonsteroidal anti-inflammatory drugs (NSAID) mediated by a new TGF-β superfamily gene (Eling, NIEHS/NIH)
- Effect of topically applied skin creams containing retinyl palmitate on the photocarcinogenicity of simulated solar light in SKH-1 mice (Fu, NCTR/FDA)
- Molecular mechanisms of cadmium carcinogenesis (Joseph, NIOSH/CDC)
- Role of cytochrome P450-mediated oxidation in chemical-induced toxicity/carcinogenicity (Ghanayem, NIEHS/NIH)
- Effect of COX-1 or COX-2 deficiency on epidermal differentiation (Langenback, NIEHS/NIH)
- *In vivo* mammalian mutagenesis (Malling, NIEHS/NIH)

- Identification of single nucleotide polymorphisms (SNPS) in disease susceptibility genes (Maull, NIEHS/NIH)
- Recombination and DNA divergence (Resnick, NIEHS/NIH)
- Mechanisms of genome instability (Resnick, NIEHS/NIH)
- Regulation of human carcinoma cell adhesion (Roberts, NIEHS/NIH)
- Genetic alterations in rodent cancer—prospective and retrospective studies (Sills, NIEHS/NIH)
- Mechanisms of carcinogenesis caused by occupational exposure to metals (Shi, NIOSH/CDC)
- Silica carcinogenicity: use of susceptible mouse models (Vallyathan, NIOSH/CDC)
- Studies of breast cancer incidence in occupational cohorts exposed to PCB and ethylene oxide (ETO) (Whelan, NIOSH/CDC)

IMMUNOTOXICOLOGY

Research Initiatives

NTP immunotoxicity studies address adverse effects on the immune system that may result from exposure to environmental chemicals, biological materials, or therapeutic agents. The identification of substances that have potential to cause injury to the immune system is of considerable public health significance as alterations in immune function can lead to increased incidence of hypersensitivity disorders, autoimmune or infectious disease, or neoplasia. Immunotoxicity can be divided into two broad research areas: (1) studies of altered hematopoietic (blood cell development) or immunologic events associated with exposure of humans and animals to chemicals and (2) studies of immune-mediated hypersensitivity (allergy and autoimmunity) resulting from exposure to environmental chemicals or therapeutics. In the former case, the immune system acts as a passive target (nonspecific) for the xenobiotic, and the result may be an increased incidence or severity of infectious disease or neoplasia because of the inability to respond adequately to the invading agent. In hypersensitivity (i.e., allergy), the immune system responds to small molecular weight compounds that bind to host tissue, recognizing the complex as foreign antigen. This immune response to the chemical-host tissue complex may lead to a disease, such as respiratory tract allergies (e.g., asthma, rhinitis) or allergic contact (skin) dermatitis. Autoimmunity, another form of immune-mediated disease, is characterized by an immune response against constituents of the body's own tissues (autoantigens). Table 18 lists the substances in undergoing immunotoxicity assessment during FY 2003 and 2004. The NCTR/FDA is evaluating the effects of endocrine disrupting chemicals on the immune system in multigenerational studies (see page 41).

Table 18. Ongoing Immunotoxicity Studies During FY 2003-2004[1]

Chemical Name	CAS Number	Species/ Strain	Route	Testing Battery[2]
5-Amino-*o*-cresol	2835-95-2	Mice: B6C3F1	Topical	HY
Annatto	1393-63-1	Mice: BALB/C	Topical	HY
AZT (3'-Azido-3'-deoxythymidine)	30516-87-1	Mice: B6C3F1	Gavage	IM, MG
Cadmium Chloride	10108-64-2	Rats: Brown-Norway	Gavage/Water	AI
Chloroform	67-66-3	Mice: B6C3F1	Water	IM
Dibromoacetic Acid	631-64-1	Mice: B6C3F1	Water	IM
1,3-Dichloropropene (Telone II)	542-75-6	Mice: B6C3F1	Water	IM
Echinacea Purpurea, Extract	90028-20-9	Mice: B6C3F1	Gavage	IM, AI

Chemical Name	CAS Number	Species/ Strain	Route	Testing Battery[2]
Elmiron (Sodium Pentosanpolysulfate)	37319-17-8	Mice: B6C3F1	Gavage	IM
Itraconazole	84625-61-6	Mice: B6C3F1	Gavage	IM
Nevirapine	129618-40-2	Mice: B6C3F1	Gavage	IM, MG
Phenol	108-95-2	Mice: B6C3F1 Rats: Fisher 344	Water	IM
Pyrogallol	87-66-1	Mice: BALB/C	Topical	HY
Rifamycin	6998-60-3	Mice: BALB/C	Topical	HY
Saquinavir Mesylate	149845-06-7	Mice: B6C3F1	Gavage	IM
Sodium Dichromate Dihydrate (VI)	7789-12-0	Mice: B6C3F1 Rats: Fischer 344/ Sprague Dawley	Water	IM
Trichloroethylene	79-01-6	Rats: Brown-Norway	Gavage	AI
Urethane	51-79-6	Mice: B6C3F1	Subcutaneous Injection	AI

[1] Protocols for immunotoxicity studies are described on the NTP website at *http://ntp.niehs.nih.gov/* see "Descriptions of NTP Study Types." Testing status can be found at *http://ntp.niehs.nih.gov/* select "Testing Status of Agents at NTP." Project Leader - Dr. Germolec (NIEHS/NIH) serves as the staff scientist who oversees each chemical's evaluation.

[2] Testing Battery Abbreviations
AI = Automimmunity
HY = Hypersensitivity
IM = Immunomodulation
MG = Multiple generations, assess effects on immunologic function and cancer end points for multiple generations

Research Projects

- Improving the sensitivity and predictability of testing strategies for immunotoxicity (Germolec, NIEHS/NIH)
- Immunotoxicity of workplace xenobiotics (Germolec, NIEHS/NIH)
- The role of cytokines in the developing immune system (Germolec, NIEHS/NIH)
- Potential for environmental and therapeutic agents to induce immunotoxicity (Germolec, NIEHS/NIH)
- Neuroimmunotoxicology: autoimmunity, viral, infections and environmental agents (Harry, NIEHS/NIH)
- Identification of occupational allergens (Beezhold, NIOSH/CDC)
- The role of innate immunity genes in viral infection and disease progression (Kleeberger, NIEHS/NIH)
- Investigations of hypersensitivity responses and mechanisms (Meade, NIOSH/CDC)
- Pathogenesis and genetic/environmental risk factors for autoimmune disease (Miller, NIEHS/NIH)
- Assessment and therapy of autoimmune disease (Miller, NIEHS/NIH)
- Is the immune system targeted by asphalt fumes? (Munson, NIOSH/CDC)

NEUROTOXICOLOGY

Research Initiatives

Behavioral and neurologic alterations in response to deleterious environmental agents often represent the earliest observable manifestation of toxicity. Neurotoxicology screening of NTP compounds often employs the EPA Neurobehavioral Screening Battery and Functional Observational Battery (FOB), with addition of locomotor activity measurements or the NIEHS Neurobehavioral Test Battery. The testing batteries examine the various

neurobehavioral systems: sensory, motor, autonomic, and peripheral nervous system. The FOB employs observational screening while the NIEHS test battery uses automated test systems to evaluate the various nervous system components. Table 19 lists substances being evaluated for neurotoxicity during FY 2003 and 2004.

Table 19. Completed Neurotoxicity Studies During FY 2003-2004[1]

Chemical Name	CAS Number	Species/ Strain	Route	Project Leader[2]
Carbonyl Sulfide	463-58-1	Rats: Fisher 344	Inhalation	Morgan/Sills
Molinate	2212-67-1	Rats: Long-Evans Hooded	Feed	Harry
6-Propyl-2-thiouracil	51-52-5	Rats: Long-Evans Hooded	Water	Harry
Tellurium	13494-80-9	Rats: Long-Evans Hooded	Feed	Harry
Trimethyltin Hydroxide	56-24-6	Mice: CD1	Injection	Harry

[1] Testing status can be found at *http://ntp.niehs.nih.gov/* select "Testing Status of Agents at NTP"
[2] Project Leader - NIEHS/NIH staff scientist who oversees each chemical's evaluation, unless otherwise indicated.

Research Projects

- Mechanisms of synaptic plasticity in the adult and developing nervous system (Dudek, NIEHS/NIH)
- Environmentally induced alterations in neuron and glia development (Harry, NIEHS/NIH)
- Cellular indicators of neuronal insult (Harry, NIEHS/NIH)
- Role of arachidonate cyclooxygenanse in inflammation-mediated neuronal death (Hong, NIEHS/NIH)
- Roles of brain neuroimmune system in neurodegeneration (Hong, NIEHS/NIH)
- Lead and other neurotoxins as risk factors for amyotrophic lateral sclerosis (Kamel, NIEHS/NIH)
- Bioactivity of neuropeptides (Lazarus, NIEHS/NIH)
- Neurotoxicity of inhaled carbonyl sulfide (Morgan, NIEHS/NIH)
- Signalling pathways associated with toxicant-induced gliosis (O'Callaghan, NIOSH/CDC)
- Developmental neurotoxicity: Assessment of acrylamide in rats: Long-term studies (Paule, NCTR/FDA)
- Developmental neurotoxicity: Assessment of acrylamide in rats: Range-finding studies (Paule, NCTR/FDA)
- A case-control study of primary intracranial gliomas among rural residents (Ruder, NIOSH/CDC)
- NMDA antagonist/GABA agonist-induced cell death in the developing rat brain (Wang, NCTR/FDA)
- Modulation of neuronal channels and receptors in the brain (Yakel, NIEHS/NIH)

DEVELOPMENTAL AND REPRODUCTIVE TOXICOLOGY

Research Initiatives

As part of its charge to test chemicals of concern for potential toxicity the NTP evaluates developmental and reproductive toxicity primarily by using teratology and Reproductive Assessment by Continuous Breeding (RACB) study designs. The RACB study design was developed by the NTP for use to identify potential hazards to toxic effects on male and/or female reproduction, characterize that toxicity, and define the dose-response relationships for

each compound. The study design has evolved over the years; initially the study employed predominantly mice as the test species and now almost exclusively uses rats. As our improved knowledge and use of sensitive end points has increased, they have been incorporated into revisions of the study design. Table 20 list chemicals undergoing developmental and reproductive toxicity assessment during FY 2003 and 2004.

Table 20. Ongoing Developmental and Reproductive Toxicity Studies During FY 2003-2004[1]

Chemical Name	CAS Number	Species/ Strain	Route	Project Leader[2]	Testing Battery[3]
Aniline	62-53-3	Mice: B6C3F1	Gavage	Bishop	Sperm Fish Aneuploidy
AZT (3'-Azido-3'-deoxythymidine) + 2',3'-Dideoxyinosine	30516-87-1; 69655-05-6	Mice: Swiss (CD-1)	Gavage	Bishop	RACB
AZT+ 3TC (2', 3'-Dideoxy-3'-thiacytidine)	30516-87-1; 134678-17-4	Mice: Swiss (CD-1)	Gavage	Bishop	RACB
AZT + Dapsone	30516-87-1; 80-08-0	Mice: Swiss (CD-1)	Gavage	Jahnke	TER
Benzene	71-43-2	Mice: B6C3F1	Gavage	Bishop	Sperm Fish Aneuploidy
1,2,3,4-Butanetetracarboxylic Acid	1703-58-8	Rats: Sprague Dawley	Water	Bishop	RACB
Cyclophosphamide Monohydrate	6055-19-2	Mice: B6C3F1	Gavage	Bishop	Sperm Fish Aneuploidy
Dibutyl Phthalate + Flutamide	84-74-2; 13311-84-7	Rats: Sprague Dawley & Wistar	Gavage	Bishop	RACB
Diazoaminobenzene	136-35-6	Mice: B6C3F1	Gavage	Bishop	Sperm Fish Aneuploidy
Di(2-ethylhexyl) Phthalate	117-81-7	Rats: Sprague Dawley	Feed	Bishop	RACB
Hexachlorobenzene	118-74-1	Rats: Sprague Dawley	Gavage	Bishop	RACB
Sodium Bromate	7789-38-0	Rats: Sprague Dawley	Water	Bishop	RACB
3,3',4,4'-Tetrachloroazobenzene	14047-09-7	Rats: Sprague Dawley	Gavage	Bishop	RACB

[1] Protocols for developmental and reproductive toxicity studies are described on the NTP website at *http://ntp.niehs.nih.gov/* see "Descriptions of NTP Study Types." Testing status and study results for completed studies can be found at *http://ntp.niehs.nih.gov/* select "Testing Status of Agents at NTP" and "Study Results & Research Project

[2] Project Leader - NIEHS/NIH staff scientist who oversees each chemical's evaluation, unless otherwise indicated.

[3] Testing Battery Abbreviations
RACB = Reproductive Assessment by Continuous Breeding
TER = Teratology

Research Projects

- Molecular detection of chromosome damage in rodent germ cells (Bishop, NIEHS/NIH)
- Human germ line effects from zidovudine and other dideoxynucleosides (Bishop, NIEHS/NIH)
- Molecular detection of aneuploidy in mouse germ cells (Bishop, NIEHS/NIH)
- Propylthiouracil (PTU) induced failure of tooth eruption in Sprague Dawley rats (Bishop, NIEHS/NIH)
- Mechanistic studies of female reproductive toxicants and carcinogens (Davis, NIEHS/NIH)
- Pathobiology of uterine leiomyomas (fibroids) (Dixon, NIEHS/NIH)
- Analysis of mechanisms of testicular toxicity using DNA microarray technology (Eddy, NIEHS/NIH)
- Gene expression in spermatogenic cells (Eddy, NIEHS/NIH)

- Sperm scoring using multi-spectral flow imaging and fluorescence *in situ* hybridization (Heindel, NIEHS/NIH; Small Business Innovation Research contract)
- Developmental toxicity of bitter orange in rats (Hansen, NCTR/FDA)
- Reproductive state, xenoestrogens, and work (Huffman, NIOSH/CDC)
- Methods for assessing reproductive potential in females (Kesner, NIOSH/CDC)
- Chemical receptor interactions in reproduction and hormonal toxicity (Korach, NIEHS/NIH)
- Evaluation of the toxicity of jet fuel during *in utero* development (Meade, NIOSH/CDC)
- Emerging reproductive hazards (Moorman, NIOSH/CDC)
- Acrylamide workers' reproductive and neurological health (Moorman, NIOSH/CDC)
- Reproductive toxicity of occupational chemicals (Murono, NIOSH/CDC)
- Developmental biology/toxicology of estrogenic environmental chemicals (Newbold, NIEHS/NIH)
- Methods assessing toxicity to four sites of male reproductive toxicity (Schrader, NIOSH/CDC)
- The source, concentration, and role of phytoestrogens in rodent diets (Thigpen, NIEHS/NIH)
- Reproductive disorders in female flight attendants: health effects (Whelan, NIOSH/CDC)

RESPIRATORY TOXICOLOGY

Research Initiatives

Inhalation exposure to environmental and occupational toxicants is a major contributing factor to human health problems. Several agents are also under consideration as causative agents for adult or childhood respiratory diseases through epidemiology studies (Tables 21 and 22).

Table 21. Ongoing Inhalation Toxicity Studies During FY 2003-2004[1]

Chemical	CAS Number	Study Design
Carbonyl Sulfide	463-58-1	Neurotoxicity
Cumene	98-82-8	Subchronic, chronic toxicity/carcinogenicity
Diethylamine	109-89-7	Subchronic, chronic toxicity/carcinogenicity
Divinylbenzene	1321-74-0	Subchronic, chronic toxicity/carcinogenicity, chemical disposition
Methyl Isobutyl Ketone	108-10-1	Chronic toxicity/carcinogenicity
α-Methylstyrene	98-83-9	Subchronic, chronic toxicity/carcinogenicity, chemical disposition
α-Pinene	80-56-8	Subchronic
Propargyl Alcohol	107-19-7	Subchronic, chronic toxicity/carcinogenicity, chemical disposition
Propylene Glycol Mono-*t*-Butyl Ether	57018-52-7	Chronic toxicity/carcinogenicity, toxicokinetics
Stoddard Solvent (Type IIC)	64742-88-7	Chronic toxicity/carcinogenicity, mechanism
Tetralin	119-64-2	Subchronic, chronic toxicity/carcinogenicity
Triethylamine	121-44-8	Subchronic
Vinylidene Chloride	75-35-4	Subchronic, chronic toxicity/carcinogenicity

[1] Testing status and study results for completed studies can be found at *http://ntp.niehs.nih.gov/* select "Testing Status of Agents at NTP" and "Study Results & Research Project

Research Projects

- Pulmonary, systemic and dermal effects of welding fume inhalation exposure (Antonini, NIOSH/CDC)
- Particle-induced lung injury in mixed exposures (Hubbs, NIOSH/CDC)
- Particle surface program: biological interactions (Keane, NIOSH/CDC)
- Particle-induced cardiopulmonary injury in mice: genetic susceptibility (Kleeberger, NIEHS/NIH)
- Genetic mechanisms of susceptibility to ozone-induced pulmonary inflammation (Kleeberger, NIEHS/NIH)
- Gene-environment interaction and pulmonary disease: translational studies (Kleeberger, NIEHS/NIH)
- Vibration effects on pulmonary responses to toxic agents (Lindsley, NIOSH/CDC)
- Occupational asthma: Inflammation and workplace disease (Luster, NIOSH/CDC)
- Pulmonary toxicity of diesel exhaust particles (Ma, NIOSH/CDC)
- Role of apoptosis in particle induced lung injury (Mercer, NIOSH/CDC)
- Toxicological evaluation of World Trade Center dust (Morgan, NIEHS/NIH)
- Mechanisms of indium phosphide pleural and pulmonary toxicity (Morgan, NIEHS/NIH)
- Uric acid and susceptibility to ozone-induced lung injury (Porter, NIOSH/CDC)
- Noninvasive measures of small animal response to inhalation exposure (Reynolds, NIOSH/CDC)
- Characterization of experimental trimelletic anhydride late-phase airway response (Siegel, NIOSH/CDC)
- Carbonyl sulfide Clean Air Act studies (Sills, NIEHS/NIH)
- Airways disease induced by low molecular weight agents (Weissman, NIOSH/CDC)
- Dermal particle exposure and granulomatous lung disease (Weston, NIOSH/CDC)
- Molecular genetics of granulomatous disease in beryllium workers (Weston, NIOSH/CDC)

EPIDEMIOLOGY AND EXPOSURE ASSESSMENT

Research Initiatives

The presence of toxicants in the environment is a potential threat to human health and the extent of that threat is unclear. Environmental toxicants may produce a variety of health effects depending upon the timing of exposure, dose, individual susceptibility, and other, yet unidentified, factors. Many of the studies currently underway or planned by the NTP investigate occupational or environmental exposure to toxicants as potential risk factors for specific health effects. Table 22 lists specific exposures and health effects presently under consideration.

In the past, environmental research often has studied the crudest, most easily measurable health effects (cancer or death). More subtle damage (*e.g.*, infertility, neurological function, or endocrine imbalance) is often harder to detect although such effects may be more common and impact a greater number of individuals. Increasingly, the NTP looks for ways to improve its ability to detect potential health effects from environmental exposures. Efforts are underway by the NTP to develop sensitive techniques for measuring the phenotypic effects of exposure and studying genetic changes associated with disease etiology, identify new genes involved in response to environmental toxicants, and identify genetic polymorphisms. Some

of the important tools in this effort come from recent advances in biotechnology that include more sensitive methods for measuring low dose exposures, detecting early stages of disease, determining genetic susceptibility, and evaluating illnesses for which the causes are largely unknown, but for which environmental etiology is plausible.

The NTP recognizes that accurate and complete exposure assessment is critical both to the success of epidemiology studies of toxicant exposure and the utility of such studies for risk assessment and public health policy. However, the availability of human data is often the weakest component of risk assessment and limits the effective utilization of experimental data for making decisions about chemical exposures. Increased knowledge about the mechanisms that are responsible for environmentally induced diseases coupled with both sensitive and specific biomarkers and tests of biological effect from exposure are important in detecting and monitoring the early insult(s) of environmental toxicants and evaluating those effects under low-dose exposure. Advances in analytical methodologies now enable the detection of environmental and occupational chemicals in small volumes of biological samples (*e.g.*, blood, urine, and hair).

In addition, the development of novel statistical tools is aiding epidemiologic investigations. Such tools are being applied to evaluations of gene-environment interactions and genetic susceptibility. Improvements in study designs and associated techniques for data analysis are facilitating the study of interactions between genetic susceptibility factors and environmental exposures.

Table 22. Exposures under Consideration as Risk Factors for Specific Human Health Effects

Exposure	Health Effect
Air pollution	Childhood respiratory diseases
Beryllium	Chronic beryllium disease
Diet	Nonmalignant respiratory disease in adults, lung cancer
Ionizing radiation	Female reproductive health and outcomes
Lead	Amyotrophic Lateral Sclerosis and reproductive disorders
Magnetic fields	Breast cancer
Mercury	Amyotrophic Lateral Sclerosis
Nickel	Reproductive effects in females
Organochlorines (DDT, PCBs, dioxin, PCDFs)	Birth term and size, childhood neurologic deficits, child development, Type 2 diabetes, breast cancer, thyroid function, and reproductive disorders
Pesticides (insecticides, herbicides, fungicides, and fumigants)	Childhood diabetes, systemic lupus erythematosus, macular degeneration, neurobehavioral function, Amyotrophic Lateral Sclerosis, adult neurologic deficits, attention deficit hyperactivity disorder, Parkinson's disease, primary intracranial gliomas, and reproductive health effects
Radon	Lung cancer and childhood leukemia
Ionizing radiation	Reproductive disorders
Silica	Systemic lupus erythematosis
Smoking and Environmental Tobacco Smoke	Nonmalignant respiratory disease in adults, asthma, chronic bronchitis, lung cancer
Soy	Child development
Uranium mining	Lung and other cancers

Research Projects

- Environmental effects on fertility (Baird, NIEHS/NIH)
- A method for simultaneous analysis of multiple pesticides (Biagini, NIOSH/CDC)
- Biomonitoring analyses for studies of dermal exposure (Cheever, NIOSH/CDC)
- Antineoplastic drug exposure: Effectiveness of guidelines (Connor, NIOSH/CDC)
- Systemic lupus erythmatosus and other autoimmune diseases (Cooper, NIEHS/NIH)
- Environmental and take-home pesticide exposures - farm families (Curwin, NIOSH/CDC)

- Environmental pollution in Eastern and Central Europe (Gladen, NIEHS/NIH)
- Organochlorines and their human health effects (Gladen, NIEHS/NIH)
- Bromopropanes: exposure assessment of general industry (Hanley, NIOSH/CDC)
- Estimation of exposure to oxidized terpene products (Harper, NIOSH/CDC)
- Agriculture Health Study, pesticide exposure among farmer applicators and their families (Hines, NIOSH/CDC)
- Identification of a cohort for a reproductive health study of phthalates (Hines, NIOSH/CDC)
- The Norwegian mother and child study: environmental specimen collection (Hoppin, NIEHS/NIH)
- Pesticides and Parkinson's disease in the Agricultural Health Study (Kamel, NIEHS/NIH)
- Pesticide exposure and neurologic function in farmworkers (Kamel, NIEHS/NIH)
- Genetic and environmental factors in cancer (London, NIEHS/NIH)
- Genetic and environmental factors in childhood respiratory health (London, NIEHS/NIH)
- Genetic and environmental factors in adult nonmalignant respiratory disease (London, NIEHS/NIH)
- The Generation R Cohort Study as an NIEHS resource (Longnecker, NIEHS/NIH)
- Human health effects of exposure to organochlorine compounds (Longnecker, NIEHS/NIH)
- Effect of diet on child development and the occurrence of chronic disease (Longnecker, NIEHS/NIH)
- Study of health effects of DDT in Mexico (Longnecker, NIEHS/NIH)
- National children's study with National Institute of Child Health and Development (Longnecker, NIEHS/NIH)
- Effect of the antiandrogen on anthropometric measures at birth (Longnecker, NIEHS/NIH)
- Health assessment of workers exposed to bromopropane (Lynch, NIOSH/CDC)
- Biomarker development exposure assessment (Lynch, NIOSH/CDC)
- Characterization of adverse effects of complex occupational exposures (Morgan, NIEHS/NIH)
- Characterization of adverse effects of complex occupational exposures (Morgan, NIEHS/NIH)
- US/Vietnamese study on the effects of Agent Orange (Portier, NIEHS/NIH)
- Implications of dioxin in the food supply (Portier, NIEHS/NIH)
- Toxicity of lead in children--clinical trial (Rogan, NIEHS/NIH)
- Human exposure to halogenated aromatic compounds (Rogan, NIEHS/NIH)
- Estrogenicity of soy formula (Rogan, NIEHS/NIH)
- Genetic and environmental risk factors for breast cancer: the Sister Study (Sandler, NIEHS/NIH)
- Risk factors for attention deficit hyperactivity disorder (Sandler, NIEHS/NIH)
- Health effects of exposures in agriculture (Sandler, NIEHS/NIH)
- Environmental exposures and risk for cancer and chronic diseases in adults (Sandler, NIEHS/NIH)
- Cancer risk in Czech uranium miners (Sandler, NIEHS/NIH)

- Exposure to radon and cancer risk (Sandler, NIEHS/NIH)
- Improved environmental exposure sampling for bioterrorism research (Schnorr, NIOSH/CDC)
- Biomonitoring methods for agricultural exposures (Striley, NIOSH/CDC)
- Genetic susceptibility and the environment in cancer risk (Taylor, NIEHS/NIH)
- Exposure specific mutation in critical target genes (Taylor, NIEHS/NIH)
- Statistical method for gene/environmental interaction and genetic susceptibility (Umbach, NIEHS/NIH)
- Indoor allergens and asthma (Zeldin, NIEHS/NIH)

CHEMICAL DISPOSITION, TOXICOKINETICS, AND PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELS

Research Initiatives

Complete dosimetry of a chemical or physical agent describes its absorption, distribution, metabolism, and elimination (ADME) at differing levels of exposure, over all ages, via multiple routes of exposure, and under varying genetic backgrounds in humans and test animals. Data from NTP chemical disposition, metabolism, and toxicokinetic studies are used in these efforts. Those substances evaluated during FY 2004 are listed in Table 23. Most studies are conducted in intact laboratory animals; some require incubations of human and rodent liver slices with the chemical. This information provides dosimetric data that can be integrated with other anatomical, biochemical, and physiological information into development of biochemical and Physiologically Based Pharmacokinetic models. Such models are used increasingly in risk assessment to extrapolate between species, across dose ranges, and across different routes of exposure.

Risk assessment involves using factual data to determine the plausibility and magnitude of health effects for individuals and populations from exposure to hazardous agents. Useful to risk assessment is the development of biologically based models for estimating human risk. These models are mathematical representations of physiological and biochemical processes that occur in laboratory animals and humans. They can provide a scientifically sound basis for evaluating data in animals and then extrapolating that information across species to determine if and how exposure to an agent might cause health effects in humans. The process of developing biologically based models is iterative. It relies upon first developing a simple model based upon available data, testing predictions of the model experimentally, and then making adjustments or expanding the model's complexity as more data become available from studies in cell culture, animals, and humans.

PBPK models are an improved and realistic description of key physiological processes and biochemical activities that affect both ADME of the parent compound and its metabolites. Substitution of estimates of human physiological and biochemical parameters into models characterized for laboratory animals provides a sound scientific basis for extrapolations of tissue dosimetry across species, extrapolation from high exposures to low exposures, and extrapolation across different routes of exposure. Because PBPK models use parameters measurable in human populations, these models can also be used to evaluate the impact of inter-individual variability. PBPK models have been created or are under development at the NIEHS/NIH to evaluate exposure-response relationships for carcinogenicity and developmental and reproductive toxicities (Table 24). Inclusion of PBPK models in the NTP Technical Reports is routine.

Table 23. Ongoing Chemical Disposition, Metabolism and Toxicokinetic Studies During FY 2003-2004[1]

Chemical	CAS Number	Test Type	Species/Strain	Route	Project Leader[2]
Acesulfame Potassium	55589-62-3	Toxicokinetics	Mice: C57BL/6	Feed, Gavage, Intravenous	Collins
5-Amino-*o*-Cresol	2835-95-2	Chemical Disposition	Mice: B6C3F1 (female) Rats: Fischer 344 (female) Rats: Fischer 344 (female)	Gavage Gavage Topical	Burka
Androstenedione	63-05-8	Chemical Disposition	Mice: B6C3F1 (male) Rats: Fischer 344 Dog: Beagle Human: Liver microsomes	*In vitro*, Gavage Intravenous, *In vitro*, Gavage Intravenous, Gavage *In vitro*	Cunningham
AZT Transplacental Carcinogenesis Study	30516-87-1	Toxicokinetics	Mice: Swiss CD-1 (female)	Intravenous, Water	Dunnick
1-Bromopropane	106-94-5	Chemical Disposition	Rats: Fischer 344 (male)	Inhalation, Topical Intravenous	Burka
Bisphenol A	80-05-7	Metabolism	Mice: B6C3F1 Rats: Fischer 344	Gavage Gavage	Cunningham
Di-N-Butyltin Dichloride	683-18-1	Chemical Disposition	Mice: B6C3F1 (male) Rats: Fischer 344 (male)	Gavage Gavage	Burka
N,N-Dimethyl-*p*-toluidine	99-97-8	Chemical Disposition	Mice: B6C3F1 (male) Rats: Fischer 344 (male)	Intravenous	Burka
Estragole	140-67-0	Chemical Disposition	Mice: B6C3F1 Rats: Fischer 344 Human: Liver microsomes	Gavage Gavage *In vitro*	Cunningham
Ethanone, 1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-	54464-57-2	Chemical Disposition	Mice: B6C3F1 (female) Rats: Fischer 344 (male)	Gavage Gavage	Burka
Ginkgo Biloba Extract	90045-36-6	Chemical Disposition	Human: Liver microsomes	*In vitro*	Burka
Goldenseal Root Powder		Chemical Disposition	Human: Liver microsomes	*In vitro*	Burka
Grape Seed and Pine Bark Extracts		Chemical Disposition	Human: Liver microsomes	*In vitro*	Burka
Kava Kava Extract	9000-38-8	Chemical Disposition	Rats: Fischer 344 (male) Human: Liver microsomes	Intravenous, Gavage *In vitro*	Burka
2-Methyltetrahydrofuran	96-47-9	Chemical Disposition	Mice: B6C3F1 (male) Rats: Fischer 344 (male)	Gavage Gavage	Burka
Milk Thistle Extract	84604-20-6	Chemical Disposition	Human: Liver microsomes	*In vitro*	Burka
Myristicin	607-91-0	Metabolism	Mice: B6C3F1 Rats: Fischer 344 Human: Liver microsomes	*In vitro* *In vitro* *In vitro*	Cunningham
Pentabromodiphenyl Oxide (Technical) (DE 71)	32534-81-9	Chemical Disposition	Rats: Fischer 344 (male)	Gavage	Burka
Sodium Tungstate Dihydrate	10213-10-2	Chemical Disposition	Mice: B6C3F1 (female) Rats: Fischer 344 (female)	Gavage, Water Gavage, Water	Burka
2,2'4,4'-Tetrabromodiphenyl Ether	5436-43-1	Chemical Disposition	Rats: Fischer 344 (male)	Gavage, Intravenous	Burka

[1] Protocols for chemical disposition, metabolism and toxicokinetic studies are described on the NTP website at *http://ntp.niehs.nih.gov/* see "Descriptions of NTP Study Types." Testing status and study results for completed studies can be found at *http://ntp.niehs.nih.gov/* select "Testing Status of Agents at NTP" and "Study Results & Research Project."

[2] Project Leader - NIEHS/NIH staff scientist who oversees each chemical's evaluation

Table 24. Completed or Ongoing Physiologically Based Pharmacokinetic Modeling During FY 2003-2004

Chemical	CAS Number	NTP Technical Report Number[1]
Anthraquinone	478-43-3	494
Bromochloroacetic Acid	5589-96-8	
Dibromoacetic Acid	631-64-1	537
Dichloroacetic Acid	79-43-6	
p,p'-Dichlorodiphenyl Sulfone	80-07-9	501
Divinylbenzene	1321-74-0	534
Isoprene	78-79-5	486
Melatonin	73-31-4	
Mercury (Pregnant Rat)	16056-34-1	
Methyleugenol	93-15-2	491
4-Methylimidazole	822-36-6	535
Naphthalene	91-20-3	500
PCB126	57465-28-8	520
PCB153	35065-27-1	529
PCB Mixtures	Multiple	530, 531
Primidone	125-33-7	476
Sodium Nitrite	7632-00-0	495
TCDD (2,3,7,8-Tetrachloro-dibenzo-*p*-dioxin)	1746-01-6	521

[1] Results for PBPK models without a Technical Report number will be presented in future NTP Technical Reports and/or in the peer reviewed literature

ALTERNATIVE TEST SYSTEMS

Considering the large number of chemicals in commerce, the NTP must continually set priorities and develop research strategies to characterize toxicants and identify hazards that make the best use of available resources. Implementing new strategies, which provide additional or more accurate information, can strengthen the science base on which regulatory decisions are based. Through the NTP, efforts are focused on the development and validation of new alternative test systems (sensitive, specific, rapid) for toxicological research that will reduce, replace, or refine animal use.

Many testing strategies focus on more rapid screening tests, alternative or complementary *in vivo* tests for rodent bioassays, and less use of two-year rodent studies to determine toxicities. Strategies include molecular screening methods, non-mammalian test species, genetically engineered animal models, genetically engineered *in vitro* cell systems, microchip-based genomic technologies, and computer-based predictive toxicology models. Such techniques can provide insight into the molecular and biological events associated with a chemical's toxic effect, as well as mechanistic information for assessing human risk. Data gleaned from these tests can help to clarify dose-response relationships, aid in species comparisons, and identify sources of variations among individuals. In addition, through the NICEATM a concerted and coordinated federal effort is being made to identify, validate, and promote regulatory acceptance of alternative test systems. Extramural researchers are also involved in alternative methods development and validation through the NIEHS/NIH grants program. Below are brief overviews of some current and emerging NTP initiatives that make use of these new research tools.

TOXICOGENOMICS

New molecular technologies have brought the NTP into the arena of toxicogenomics, a scientific field that examines how the entire genetic structure, or genome, is involved in an organism's response to environmental toxicants. Toxicogenomics applies genetic knowledge to environmental medicine by studying the effect of toxicants on gene activity and specific proteins encoded by genes. It combines information from studies of genomic-scale messenger RNA profiling (by microarray analysis), cell-wide or tissue-wide protein profiling (proteomics), genetic susceptibility, and computational models. This information aids in our understanding of the interactions between genes and the environment in disease etiology. This field could revolutionize environmental health, drug safety, and risk assessment.

To centralize activities in toxicogenomics, the NIEHS/NIH established the National Center for Toxicogenomics (NCT) in 2000. Complementary DNA microchip-based technology enables the NCT to assess the genetic impact of toxicants. Microarrays containing genes from common test animals and organisms including mice, rats, and yeast, are currently in use.

The NCT is evaluating gene arrays and building a database of gene expression information to determine the typical genetic changes or "signature" profiles produced by these toxicants. Identification of such changes in gene expression on a genome-wide basis could provide a global perspective on how an organism responds to a specific stress, drug, or toxicant. As this technology continues to improve, it will help NTP scientists evaluate and compare the toxic effects and molecular changes elicited by compounds under study. Such information could define cellular networks of responsive genes, identify target molecules of toxicity, provide future biomarkers and alternative testing procedures, and identify individuals who are sensitive to drugs or environmental agents.

Initial efforts by the NTP include profiling a classic liver toxicant, acetaminophen, by

studying the variables that affect gene expression in exposed and unexposed animals. In addition, the NTP is also collecting gene expression data from unexposed animals to establish which genes are expressed at different stages of life and which are expressed continuously.

GENETICALLY MODIFIED MOUSE MODELS

The conventional rodent bioassay has been used for over three decades and is accorded credibility in identifying carcinogens thought to pose risks for human health. An ongoing goal of the NTP is to seek other model systems for toxicology and carcinogenesis studies, especially those that can provide mechanistic information relative to understanding an agent's mode of action. The use of transgenic models holds promise for improving both the accuracy and efficacy of experimental assessment of the carcinogenic potential of chemicals. Genetically altered or "transgenic" mouse models carry activated oncogenes or inactivated tumor suppressor genes known to be involved in neoplastic processes both in humans and rodents. This trait may allow them to respond to carcinogens more quickly than conventional rodent strains. In addition, the neoplastic effects of agents can be observed in transgenic models within a time frame in which few, if any, spontaneous tumors would arise. The high incidences of spontaneous or background tumors, which occur most often late in the two-year rodent cancer studies, are among the most confounding factors for interpreting the findings of these chemical carcinogenesis studies and their implications for human health. The use of target or reporter genes also allows for direct molecular and cellular analysis of a chemical's effects in these models and can provide additional mechanistic information about its mode of action. A list of chemicals being evaluated in transgenic animals in subchronic and chronic studies during FY 2003 and 2004 are presented in Table 25.

The NTP has undertaken more than 100 studies with genetically modified mouse models (GMM) to assess the carcinogenicity of known human and rodent genotoxic and non-genotoxic agents since 1995. The NTP has sought input from its advisory groups and the public about the usefulness of a number of transgenic rodent models for short-term studies of carcinogenicity [p53(+/–), Tg.AC, (v-Ha-ras), and RasH2]. Overall there is a concordance of 70 to 85% between GMMs and conventional rodent bioassays. In general, there is more support for the p53(+/-) and RasH2 models than the Tg.AC model for evaluating the carcinogenic potential of chemical or physical agents. While these GMM models often detect *known* or *probable* human carcinogens, some were missed. In contrast, no *known* or *probable* human carcinogens were missed using the conventional bioassay. These findings have led the NTP to conclude that positive findings in GMM should be taken seriously, but chemicals with negative findings should be viewed with caution. The NTP's current approach is to employ GMM models to conduct studies that can not be easily addressed in the conventional 2-year bioassay, such as mixture studies or class studies (e.g., dioxin-like compounds), when response of the model to an index substance is known to develop relative potencies for other members of the class.

Table 25. Ongoing Subchronic and Chronic Toxicity Studies in Genetically Modified Mouse Models During FY 2003-2004[1]

Chemical Name	CAS Number	Species/ Strain	Route	Study Length	Project Leader[2]
Acesulfame Potassium	55589-62-3	Mice: p53 +/- (C57BL/6) Mice: Tg.AC (FVB/N) hemizygous	Feed	2 years	Irwin
Aspartame	22839-47-0	Mice: p53 +/- (C57BL/6) Mice: Tg.AC (FVB/N) hemizygous Mice: P16 (Ink 4A)+/- (C57BL/6)	Feed	2 years	Bucher
AZT+3TC (2', 3'-Dideoxy-3'-thiacytidine)	30516-87-1; 134678-17-4	Mice:P53 +/- (C57BL/6)	Gavage	6 month	Leakey (NCTR/FDA)
Bromodichloromethane	75-27-4	Mice: p53 +/- (C57BL/6) Mice: Tg.AC (FVB/N) hemizygous	Gavage, Water	26 weeks	Boorman
Dichloroacetic Acid	79-43-6	Mice: p53 +/- (C57BL/6) Mice: Tg.AC (FVB/N) hemizygous	Water, Topical	26 & 39 weeks	Boorman
Diisopropylcarbodiimide	693-13-0	Mice: Tg.AC (FVB/N) hemizygous Mice: p53 +/- (C57BL/6)	Topical	20 & 27 weeks	Chhabra
PCB 126	57465-28-8	Mice:Tg.AC (FVB/N) hemizygous	Topical	26 weeks	Walker
PeCDF (2,3,4,7,8-Pentachlorodibenzofuran)	57117-31-4	Mice:Tg.AC (FVB/N) hemizygous	Topical	26 weeks	Walker
PCB 126 + PeCDF	57465-28-8; 57117-31-4	Mice:Tg.AC (FVB/N) hemizygous	Topical	26 weeks	Walker
Sodium Bromate	7789-38-0	Mice: p53 +/- (C57BL/6) Mice: Tg.AC (FVB/N) hemizygous	Water, Topical	26 & 39 weeks	Hooth
TCDD (2,3,7,8-Tetrachlorobenzo-*p*-dioxin)	1746-01-6	Mice: Tg.AC (FVB/N) hemizygous	Topical	26 weeks	Walker

[1] Protocols for chronic toxicity and carcinogenicity studies are described on the NTP website at *http://ntp.niehs.nih.gov/* see "Descriptions of NTP Study Types." Testing status can be found at *http://ntp.niehs.nih.gov/* select "Testing Status of Agents at NTP."

[2] Project Leader - NIEHS/NIH staff scientist who oversees each chemical's evaluation

NON-MAMMALIAN MODELS

The NTP has initiated studies in non-mammalian species to explore the use of alternate or additional models for examining chemical toxicity and carcinogenicity. For example, the use of small fish species in carcinogenicity testing may offer advantages as a bioassay test system including significant savings in cost and time over rodent studies. Large numbers of small fish can be easily maintained in a limited area. Draft technical reports (see Table 11) have been released for three compounds [nitromethane, (2,2-bis(bromomethyl)-1,3-propanediol), (1,2,3-trichloropropane)] tested in two species of fish, the guppy (*Poecilia reticulata*) and medaka (*Oryzias latipes*). The guppy and medaka are hardy, easily maintained, and have a low occurrence of background lesions

The NTP is interested in developing rapid, sensitive, and specific tests for screening environmental agents. The NTP is investigating the utility of *Caenorhabditis elegans* (*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. Five compounds are currently planned for testing in *C. elegans*: cadmium (II) chloride hydrate, chlorpyrifos (Dursban), dimethyl sulfoxide, iron citrate, and methylcellulose (Freedman, Duke/NIEHS)

MAGNETIC RESONANCE IMAGING

Traditionally, in NTP toxicology and carcinogenicity studies, tissues are evaluated with conventional optical microscopy for histopathological changes. Representative samples are collected because examining numerous samples of each tissue is impractical. Because of recent advances in the technology for imaging, magnetic resonance imaging (MRI) of the entire body at microscopic resolution is now possible. The NTP is investigating MRI for imaging laboratory animals. MRI microscopy is three-dimensional, can examine the same specimens at different angles, and measures the volume of tissue and organs. MRI of live animals permits acquisition of imaging data at different times over an animal's lifetime. Because the images are digital, web-based viewing by pathologists anywhere in the world is possible.

MRI is a noninvasive technique that permits more complete and thorough examination of tissues and organs from test animals without destroying the samples and may also allow more information to be gathered from NTP studies than before. Anticipated uses include monitoring lesions and examining the morphology and functionality of genetically engineered mice. The NTP also plans to apply this technology in the future to studies of birth defects. This technology is being applied to NTP microarray studies of acetaminophen-induced hepatotoxicity.

SCANSCOPE–2D IMAGING TECHNOLOGY FOR PATHOLOGICAL EVALUATIONS

The NTP has now acquired a new technology for evaluation of lesions in tissues of animals exposed to potentially toxic substances. ScanScope scans entire histopathology slides at high resolution and compresses the large file using JPEG2000. The resulting image can be viewed over the Internet and one is able to

select any area for viewing and magnifing the image to the same degree as that seen with a microscope using a 10, 20, or 40X objective. The result is that the computer becomes equivalent to a microscope and one can examine any portion of the whole image at microscopic resolution. This technology provides the NTP pathologists a tool to share treatment-induced lesions with colleagues via the Internet and, as needed, obtain their diagnostic opinions.

Research Projects

- Discovery and genetics of environmental response genes (Bell, NIEHS/NIH)
- Environmental genomics (Bell, NIEHS/NIH)
- Microarray gene expression database (Bushel, NIEHS/NIH)
- Altered gene expression in response to toxicants (Cunningham, NIEHS/NIH)
- Carcinogen inactivation of tumor suppressor genes in p53 haploinsufficient mice (French, NIEHS/NIH)
- Mechanism(s) of leukemogenesis in genetically altered mouse models (French, NIEHS/NIH)
- Development of a database of genetic alterations from environmental chemicals: development of the NIEHS genetic alterations in cancer database (Heindel, NIEHS/NIH; Small Business Innovation Research contract)
- System for high-throughput proteome characterization (Heindel, NIEHS/NIH; Small Business Innovation Research contract)
- Development of microarray profiles for microbial toxicity (Heindel, NIEHS/NIH; Small Business Innovation Research contract)
- Hepatitis C virus: From gene expression profiling to biomarkers (Heindel, NIEHS/NIH; small business innovation research contract)
- Targeted antibody microarrays: A tool for toxicoproteomics (Heindel, NIEHS/NIH; small business innovation research contract)
- Mass spectrometry based high-throughput proteomics approach (Heindel, NIEHS/NIH; Small Business Innovation Research contract)
- The toxicity studies of combination of AIDS drugs in p53 (+/-) transgenic mice (Leakey, NCTR/FDA)
- Microarray technology to study molecular pathways in disease and apoptosis (Paules, NIEHS/NIH)
- NCT proteomics resource - toxicoproteomics expression and microarray resource databases (Stasiewicz, NIEHS/NIH)
- National Center for Toxicogenomics microarray resources - gene expression analysis (Stasiewicz, NIEHS/NIH)
- NCT proteomics resource - proteomics analysis/identification (Stasiewicz, NIEHS/NIH)
- A validation study for *in vitro* basal cytotoxicity testing (Stokes, NIEHS/NIH)
- Characterization of follicular stem cells in Tg.AC mice (Tennant, NIEHS/NIH)
- Global analysis of arsenic-induced gene expression profiles in yeast (Van Houten, NIEHS/NIH)

APPENDIX 1

AGENCY STAFF AND CONTACT INFORMATION

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APPENDIX 2

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