



National Toxicology Program

U.S. Department of Health and Human Services

Annual Report 2012



National Toxicology Program

ANNUAL REPORT

for

Fiscal Year 2012

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

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National Toxicology Program

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Letter from the NIEHS/NTP Director



The NTP, an interagency program, provides scientific knowledge and functions as a truly translational program to safeguard public health. The NTP is involved in activities to evaluate substances of potential concern for our health and to develop new methods to improve such evaluation procedures. For example, the NTP is taking on the challenge of studying mixtures instead of testing one chemical at a time. In addition, a current project is examining the effects of exposures throughout a life span, to expand our knowledge about effects of prenatal exposures and how they may link to adult disease. The NTP is also leading the Tox21 initiative with the National Institutes of Health's National Center for Advancing Translational Science, the United States Environmental Protection Agency, and the Food and Drug Administration. Tox21 is a high throughput-testing program that shows great promise for moving toxicology into a predictive science.

As it has done in the past, in fiscal year 2012 (FY 2012), the NTP through scientific collaborations with federal agencies continued to enhance our knowledge about substances that affect health in our homes, workplaces, and other environments. The NTP translated and communicated these findings to the public, industry, federal regulatory agencies, and others so the information could be used to protect public health. The NTP disseminated reports on studies of dietary supplements, skin care products, and widely used industrial chemicals through publication of nine NTP Technical Reports. The final *NTP Monograph on Health Effects of Low-level Lead* was published, providing an overview of the science to date and conclusions on the potential health effects from low-level exposures to lead. The NTP also carried out two widely attended workshops: (1) the *International Workshop on Alternative Methods for Human and Veterinary Rabies Vaccine Testing: State of the Science and Planning the Way Forward* and (2) the *International Workshop on Alternative Methods for Leptospira Vaccine Potency Testing: State of the Science and the Way Forward*.

Of broad interest both nationally and internationally, the NIEHS Office of Health Assessment and Translation initiated modifications in how it would conduct NTP literature-based analysis of existing studies to assess if a substance may be of concern for human health. This effort focuses on incorporating systematic review methodologies to increase transparency in conducting and communicating these assessments. In addition, revisions to the multi-step process used to prepare the Biennial Report on Carcinogens were put in place and the evaluation of substances for future reports has begun.

The ability of the NTP to stay on the cutting edge of scientific research and to pioneer the development and application of new technologies is the reflection of a staff truly dedicated to the NTP and its mission. I am pleased to share through this report some of our achievements in FY 2012.

A handwritten signature in black ink that reads "Linda S. Birnbaum". The signature is written in a cursive, flowing style.

Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S.



1. National Toxicology Program: Mission And Goals

Safeguarding public health depends upon identifying the effects of substances that are in contact with people and their environment and determining the levels of exposure at which they may become potentially hazardous. The Toxic Substances Control Act Chemical Substance Inventory of January 2013 (<http://www.epa.gov/oppt/newchems/pubs/invntory.htm>) lists more than 83,000 chemicals as being available for sale and use in the United States. New chemicals are continuously introduced into the United States market each year. According to the Board of Governors of the Federal Reserve System, chemical production in the United States increased 2.1-fold from 1972 to 2012 (<http://www.federalreserve.gov/datadownload/default.htm>). While the effects of many of these substances on human health are unknown, 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.

The Department of Health, Education, and Welfare (now the U.S. Department of Health and Human Services, HHS) established the National Toxicology Program (NTP) in 1978 as a focal point to coordinate toxicology testing in the Federal government. In carrying out its mission, the NTP has several goals:

1. Coordinate toxicology testing programs within the federal government.
2. Strengthen the science base in toxicology.
3. Develop and validate improved testing methods.
4. Provide information about potentially toxic chemicals to health, regulatory, and research agencies, scientific and medical communities, and the public.

To protect public health, regulatory agencies make decisions based on scientific information. The NTP plays a critical role in providing scientific data, interpretation, and guidance in the appropriate uses of these data to regulatory agencies and other health-related research groups (see Table X). 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.

In following government-wide efforts to increase access to the results of federally funded scientific research, the NTP maintains open communications and dialogue with Federal and state agencies, industry, nongovernment groups, academia, and the public. The NTP website (<http://ntp.niehs.nih.gov>) provides the public with a variety of information including *Federal Register* notices, status and data of NTP studies, lists of reports and journal publications, media releases, calendar of upcoming events, and the *NTP Update* quarterly newsletter.

The public and other interested parties can stay abreast of NTP activities and events by subscribing to the NTP Listserv, an email notification system (<http://ntp.niehs.nih.gov/go/getnews>). In addition requests for information can be made to the NIEHS/NTP Central Data Management Office (CDM@niehs.nih.gov or 919-541-3419) or through Freedom of Information Act requests (<http://www.niehs.nih.gov/about/od/ocpl/foia/contact/index.cfm>).

As always, the NTP welcomes input on its programs and priorities. This input can be through response to formal requests for public comment in *Federal Register* notices or informal submissions to the Office of Liaison, Policy and Review, within the Division of NTP, at the NIEHS (919-541-7539 or wolfe@niehs.nih.gov).

NTP MISSION:

**TO EVALUATE
AGENTS OF PUBLIC
HEALTH CONCERN
BY DEVELOPING
AND APPLYING THE
TOOLS OF MODERN
TOXICOLOGY AND
MOLECULAR BIOLOGY**



A. Organizational Structure and Oversight

Three agencies form the core for the NTP (Figure 1): the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health, the National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention, and the U.S. Food and Drug Administration (FDA), primarily through its National Center for Toxicological Research (NCTR).

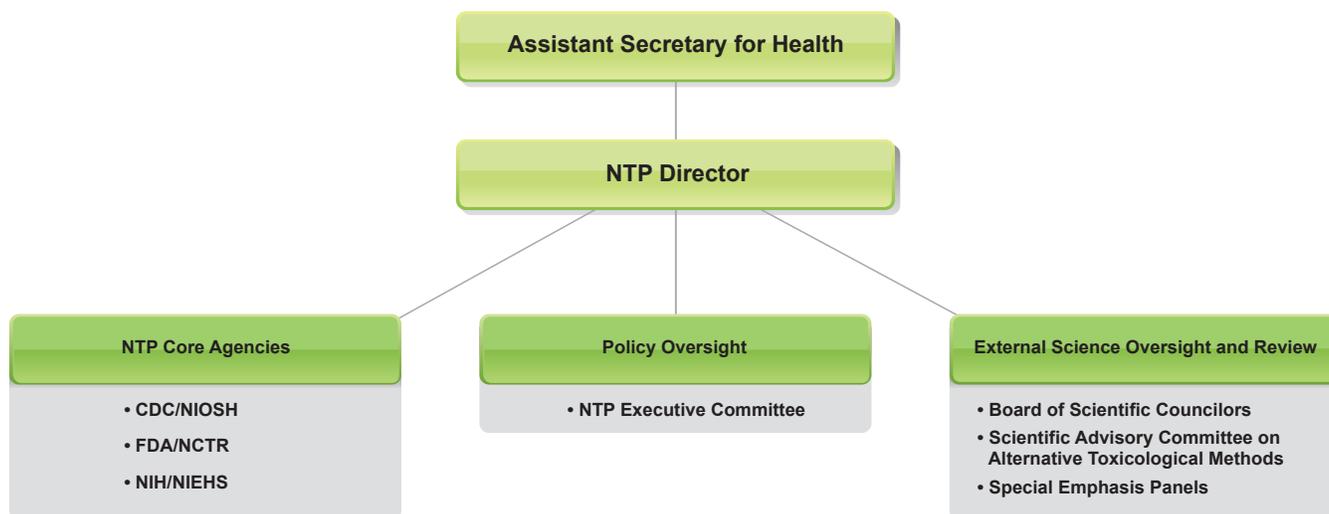
The NTP is located administratively at the NIEHS, and Linda Birnbaum, PhD, DABT, ATS, serves as the Director of the NIEHS and the NTP Director. John Bucher, PhD, serves as associate director of the NTP and director of the Division of the NTP at NIEHS, which is dedicated toward carrying out NTP activities. The NIEHS and NTP utilize best research practices and embrace developments in technology to discover how the environment affects people, and seek to lead the field of environmental health in innovation and the application of research to solve public health problems.

John Howard, MD, MPH, JD, LLM, is the director of NIOSH, and Gayle Debord, PhD, Chief, Biomonitoring and Health Assessment Branch, manages the NTP program at NIOSH. Staff within the following divisions participate in NTP activities: Division of Surveillance, Hazard Evaluations, and Field Studies; Division of Applied Research and Technology; Education and Information Division; Health Effects Laboratory Division.

The mission of NIOSH is to generate new knowledge in the field of occupational safety and health and to transfer that knowledge into practice for the betterment of workers. NIOSH's participation in the NTP is consistent with its mandate to protect workers' health and safety under the Occupational Safety and Health Act and the Federal Mine Safety and Health Act.

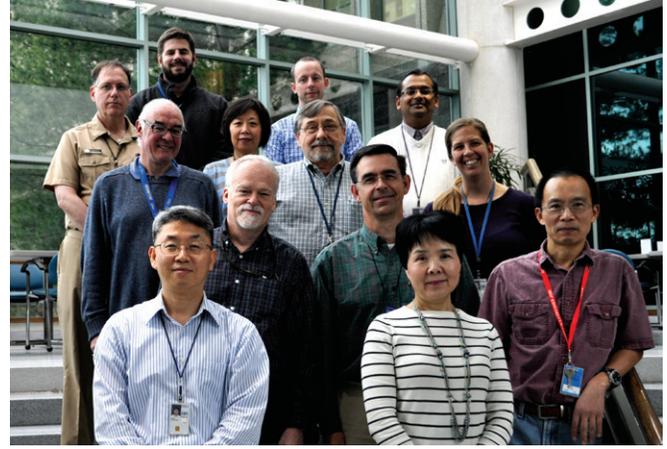
William Slikker, Jr., PhD, is the director of NCTR, and Paul Howard, PhD, Associate Director, Office of Scientific Coordination, manages the NTP program at NCTR. NCTR staff scientists, in partnership with researchers from elsewhere in FDA, other government agencies, academia, and industry, provide innovative technology, methods development, vital scientific training, and technical expertise. The NCTR conducts an array of studies that reflect the NTP mission statement and are critical in supporting FDA product centers and their regulatory roles.

Figure 1. Organizational Structure of NTP





NIEHS/NTP Staff



NIOSH Staff: Health Effects Laboratory Division



NIOSH Staff: Division of Applied Research and Technology and the Division of Surveillance, Hazard Evaluations, and Field Studies



NIOSH Staff: Education and Information Division



NCTR/NTP Staff



NCTR/NTP Staff



B. Training Programs

The NTP offers a limited number of postdoctoral training fellowships that prepare scientists for careers in pharmaceutical and chemical industries, regulatory agencies, and academia. Full details on opportunities, benefits, and applications can be found at <http://www.niehs.nih.gov/careers/research/postdoc-training/index.cfm>. The training program falls into the following six areas: applied toxicology and carcinogenesis, biomolecular screening and computational toxicology, health assessment and translation, laboratory animal medicine, systems and mechanistic toxicology, and toxicological pathology. In FY 2012, NTP staff mentored 19 postdoctoral fellows at the NIEHS.

Table 1. NTP Training Program Postdoctoral Fellows in FY 2012

Training Program	Fellow
Applied toxicology and carcinogenesis	Minerva Mercado-Feliciano
	Kristen Ryan
	In Ok Surh
	Sheetal Thakur
Biomolecular screening and computational toxicology	Rachel Goldsmith
	Julie Hall
	Jui-Hua Hsieh
	Yang Sun
Health assessment and translation	Katie Pelch
Laboratory animal medicine	Sheba Churchill
Systems and mechanistic toxicology	Xiaohua Gao
	Ntube Ngalame
	Ruben Orihuela-Garcia
	Rachel Person
	Yuanyuan Xu
Toxicological pathology	Sachin Bhusari
	Michael Boyle
	Michelle Cora
	Erin Quist

C. Advisory Boards and Committees

Three formal groups (NTP Executive Committee, NTP Board of Scientific Counselors, and Scientific Advisory Committee on Alternative Toxicological Methods) provide policy, or science oversight and peer review, to guide NTP activities.

i. 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:

- U.S. Agency for Toxic Substances and Disease Registry/National Center for Environmental Health (ATSDR/NCEH)
- U.S. Consumer Product Safety Commission (CPSC)
- U.S. Department of Defense (DOD)
- U.S. Environmental Protection Agency (EPA)
- U.S. Food and Drug Administration (FDA)
- National Cancer Institute (NCI)
- National Institute of Environmental Health Sciences (NIEHS)
- National Institute for Occupational Safety and Health (NIOSH)
- Occupational Safety and Health Administration (OSHA)

To enhance agency interactions, the NTP uses agency Points of Contact in lieu of formal committees to streamline communication and better utilize agency staff. Agency Points of Contact have a dedicated responsibility and time commitment, are knowledgeable about the NTP mission and programs and their agency's resources, and allow the most relevant agency expertise to be brought to bear on NTP issues.

ii. NTP Board of Scientific Counselors

The NTP Board of Scientific Counselors (BSC), a federally chartered advisory group, provides scientific oversight to the NTP on the merit of its programs and activities. The Secretary of HHS appoints members to the BSC. The BSC can consist of up to 35 scientists, primarily from the public and private sectors, with scientific expertise relevant to the NTP's activities. The BSC charter and current roster are available at <http://ntp.niehs.nih.gov/go/164>. Dr. Lori White, Designated Federal Officer, manages the BSC. Table 2 provides the BSC membership roster for FY 2012.



BSC members and NTP staff at the June 2012 BSC meeting.

The BSC met twice in FY 2012 (<http://ntp.niehs.nih.gov/go/9741>). At the meeting held on December 15, 2011, the BSC reviewed draft testing concepts for the study of sulfolane, phenolic benzotriazoles, and trimethylsilyldiazomethane. The BSC heard reports on an NTP Workshop: *Role of Environmental Chemicals in the Development of Diabetes and Obesity* and on a revised process for preparing the Report on Carcinogens (RoC). They reviewed a concept for a RoC workshop on permanent hair dyes and heard updates on NTP's progress since the April 2011 meeting from the NIEHS/ NTP Director and NTP Associate Director.



The second BSC meeting was held on June 21–22, 2012. The BSC voted unanimously to approve the concept for a contract for genetic toxicity testing. NTP staff presented an initiative to incorporate environmental enrichment into NTP studies and the recommendations for seven draft NTP Technical Reports from a peer-review panel convened on February 8-9, 2012. The BSC reviewed draft concepts on five substances nominated for review for the RoC: pentachlorophenol, cumene, trichloroethylene, ortho-toluidine, and 1-bromophenol. The NIEHS/NTP Director and NTP Associate Director provided reports, updating the BSC on NTP's progress since the December 2011 meeting.

The BSC formed a working group, which met on August 28–29, 2012, in Raleigh, NC, to evaluate the Draft NTP Approach for Reaching Conclusions for Literature-Based Evidence Assessments. The NIEHS Office of Health Assessment and Translation (OHAT), in concert with the Office of Liaison, Policy and Review, developed this approach during 2012 to incorporate elements of systematic review methodology into literature-based evaluations. The working group, chaired by Dr. Lynn Goldman, dean of the George Washington School of Public Health, prepared a report with recommendations for revisions to the approach. The BSC reviewed and approved the report, enabling formal transmittal to the NTP. NTP staff discussed changes to the draft approach based upon the working group's input and presented next steps toward finalization of the approach.

Table 2. NTP Board of Scientific Counselors Membership Roster FY 2012

Name and Title	Affiliation	Term Ends
Robert E. Chapin, PhD Laboratory Director	Pfizer Groton, CT	06/30/15
David C. Dorman, DVM, PhD Professor College of Veterinary Medicine	North Carolina State University Raleigh, NC	06/30/15
David A. Eastmond, PhD (chair) Professor and Chair Department of Cell Biology and Neuroscience	University of California Riverside, CA	12/27/12
Elaine M. Faustman, PhD Professor and Director Institute for Risk Analysis and Risk Communication Department of Environmental and Occupational Health Sciences	University of Washington Seattle, WA	12/27/12
Miguel C. Fernández, MD, FACEP, FAAEM, FACMT, FAACT Professor of Surgery Division of Emergency Medicine Director, South Texas Poison Center	University of Texas Health Science Center San Antonio, TX	06/30/13
Jack R. Harkema, DVM, PhD, DACVP Distinguished Professor Department of Pathobiology and Diagnostic Investigation	Michigan State University East Lansing, MI	06/30/15
Dale Hattis, PhD Research Professor George Perkins Marsh Institute	Clark University Worcester, MA	06/30/15
Dana Loomis, PhD Professor and Chair Department of Epidemiology	University of Nebraska Medical Center Omaha, NE	12/27/12
Stephen W. Looney, PhD Professor Department of Biostatistics Department of Oral Health and Diagnostic Science	Georgia Health Sciences University Augusta, GA	06/30/12

Name and Title	Affiliation	Term Ends
Melissa A. McDiarmid, MD, MPH Professor of Epidemiology and Preventive Medicine Director, Occupational Health Program	University of Maryland School of Medicine Baltimore, MD	06/30/13
Lisa Minor, PhD Consultant	In Vitro Strategies, LLC Flemington, NJ	6/30/13
Richard Miller, DVM, PhD Vice President Safety Assessment	GlaxoSmithKline Research Triangle Park, NC	06/30/13
Mitzi Nagarkatti, PhD Professor and Chair Department of Pathology, Microbiology and Immunology	University of South Carolina School of Medicine Columbia, SC	12/27/11
Ruthann A. Rudel, MS Senior Scientist Toxicology and Environmental Health Risk Assessment	Silent Spring Institute Newton, MA	12/27/11
Sonya Sobrian, Ph.D. Associate Professor Department of Pharmacology	Howard University Washington, DC	06/30/15
Gina M. Solomon, MD, MPH Senior Scientist	Natural Resources Defense Council San Francisco, CA	12/27/11
Justin G. Teeguarden, PhD Senior Scientist Fundamental and Computational Sciences Directorate	Pacific Northwest National Laboratory Richland, WA	12/27/11
Judith Zelikoff, PhD Professor of Environmental Medicine Director, Community Outreach	New York University School of Medicine Tuxedo, NY	12/27/12

iii. 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 Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Authorization Act of 2000 (42 U.S.C. 285-3(d)). SACATM advises ICCVAM, the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), and the Director of NIEHS regarding statutorily mandated duties of ICCVAM and activities of NICEATM (see page 74). 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. The SACATM charter and current roster are available at <http://ntp.niehs.nih.gov/go/167>. Table 3 provides the SACATM membership roster for FY 2012. SACATM typically meets once a year and members serve rotating terms of up to four years. Dr. Lori White, Designated Federal Officer, manages SACATM.

SACATM met once during FY 2012 at the NIEHS, on September 5–6, 2012 (<http://ntp.niehs.nih.gov/go/8202>). At that meeting, SACATM voted unanimously to support ICCVAM's high priority rating for the nomination of the Electrophilic Contact Allergen Identification Screening test and to use a contract mechanism for continuation of administrative and scientific support for NICEATM. SACATM voted to accept the report prepared by the Implementation Working Group with advice on implementation of ICCVAM-recommended methods. They were provided information on high-throughput adaptation and performance of



the BG1Luc ER TA agonist and antagonist assays and federal agency research, development, translation, and validation activities relevant to the NICEATM-ICCVAM Five-Year Plan. Additionally, they commented on a draft NICEATM-ICCVAM Five-Year Plan. They heard a report on the *International Workshop on Alternative Methods for Human and Veterinary Rabies Vaccine Testing: State of the Science and Planning the Way Forward* and about plans for an upcoming vaccine workshop. Liaisons from the European Union Reference Laboratory for Alternatives to Animal Testing /European Center for the Validation of Alternative Methods, the Korean Center for the Validation of Alternative Methods, the Japanese Center for the Validation of Alternative Methods, and Health Canada presented updates on the activities of their groups.

SACATM formed the Implementation Working Group to assess implementation of ICCVAM-recommended alternative methods. Dr. Joy Canvagnaro chaired the working group, which met eight times by teleconference during FY 2012. The working group prepared a report with recommendations for ICCVAM and NICEATM. Most of the recommendations concerned improvements in ICCVAM data collection regarding implementation of ICCVAM-recommended alternative methods by both industry and regulatory agencies. The group also recommended specific actions to enhance communication regarding implementation with the regulatory agencies, specifically the EPA and the FDA. SACATM reviewed and approved the report at the September 2012 meeting.



Members of SACATM, ICCVAM, and NIEHS/NTP staff at the September 2012 SACATM meeting.

Table 3. NTP SACATM Membership Roster FY 2012

Name and Title	Affiliation	Term Ends
Laura Andrews, PhD, DABT Vice President Pharmacology and Toxicology	Genzyme Corporation Framington, MA	06/30/12
Tracie E. Bunton, DVM, PhD Consultant	Eicarte LLC Gettysburg, PA	06/30/15
Joy Cavagnaro, PhD, DABT, RAC, ATS, RAPS President and Founder	Access BIO, L.C. Boyce, VA	11/30/14
Joan M. Chapdelaine, Ph.D. Consultant	Scott Township, PA	06/30/15
Eugene L. Elmore, PhD Senior Project Scientist Department of Radiation Oncology	University of California Irvine, CA	06/30/12
Mark G. Evans, DVM, PhD, ACVP Research Fellow La Jolla Laboratories	Pfizer San Diego, CA	06/30/15
Steven R. Hansen, DVM, MS, MBA, DABT, ABVT Senior Vice President Animal Health Services	ASPCA Animal Poison Control Center Urbana, IL	06/30/12
Gwendolyn Y. McCormick, DVM, MS, DACLAM Attending Veterinarian and Distinguished Research Fellow Animal Resources Department	Boehringer Ingelheim Pharmaceuticals, Inc Ridgefield, CT	06/30/12
Steven M. Niemi, DVM Director Center for Comparative Medicine	Massachusetts General Hospital Charlestown, MA	06/30/13
Ricardo Ochoa, DVM, PhD, ACVP President and Principal	Pre-Clinical Safety, Inc. Niantic, CT	11/30/14
Michael J. Olson, PhD, ATS Director Occupational Toxicology Corporate Environment, Health, Safety and Sustainability	GlaxoSmithKline Research Triangle Park, NC	06/30/13
Linda A. Toth, DVM, PhD Associate Dean for Research and Faculty Affairs Professor, Department of Pharmacology	Southern Illinois University School of Medicine Springfield, IL	06/30/13
Daniel M. Wilson, PhD, DABT Mammalian Toxicology Consultant Toxicology and Environmental Research and Consulting	The Dow Chemical Company Midland, MI	11/30/14
Marilyn Wind, PhD Consultant	Bethesda, MD	06/30/15

Interagency Coordinating Committee on the Validation of Alternative Methods

ICCVAM is a permanent interagency committee of the NIEHS under NICEATM. The committee was formally established by the ICCVAM Authorization Act of 2000 (42 U.S.C. 285I-3). The purpose of ICCVAM is to establish, wherever feasible, guidelines, recommendations, and regulations that promote the regulatory acceptance of new or revised scientifically valid toxicological tests that protect human and animal health and



the environment while reducing, refining, or replacing animal tests and ensuring human safety and product effectiveness (see http://iccvam.niehs.nih.gov/about/about_ICCVAM.htm). Members of this committee include representatives from the following Federal agencies:

- U.S. Consumer Product Safety Commission (CPSC)
- U.S. Department of Agriculture (USDA)
- U.S. Department of Defense (DOD)
- U.S. Department of Energy (DOE)
- U.S. Department of Health and Human Services
 - Centers for Disease Control and Prevention
 - Agency for Toxic Substances and Disease Registry (ATSDR)
 - National Institute for Occupational Safety and Health (NIOSH)
 - Food and Drug Administration (FDA)
 - National Institutes of Health (NIH)
 - National Cancer Institute (NCI)
 - National Institute of Environmental Health Sciences (NIEHS)
 - National Library of Medicine (NLM)
 - Office of the Director
- U.S. Department of the Interior (DOI)
- U.S. Department of Labor
 - Occupational Safety and Health Administration (OSHA)
- U.S. Department of Transportation
- U.S. Environmental Protection Agency (EPA)

iv. Special Emphasis Panels

The NTP uses ad hoc scientific experts, referred to as special emphasis panels (SEPs), as needed, to provide independent scientific peer review and advice on targeted issues such as on agents of public health concern, new/revised toxicological test methods, or other issues. These panels help ensure transparent, unbiased, and scientifically rigorous input to the program for its use in making credible decisions about human health hazards, setting research and testing priorities, and evaluating test methods for toxicity screening.

NTP Technical Reports Peer Review Panels

NTP Technical Reports (TRs) are publications of the results of long-term studies, generally two-year rodent toxicology and carcinogenesis studies. On February 8–9, 2012, the NTP convened an external, scientific panel to peer review seven draft NTP TRs at a public meeting at the NIEHS with opportunity for public comment. The panel was charged to (1) peer review the scientific and technical elements of the study and their presentation and (2) determine whether the study's experimental design and conduct supported the NTP's conclusions regarding the carcinogenic activity of the substance tested. The panel reviewed the draft TRs for NTP studies on *N,N*-dimethyl-*p*-toluidine, *Ginkgo biloba* extract, β -picoline, pyrogallol, trimethylolpropane triacrylate, 3'-azido-3'-deoxythymidine (AZT), and mixtures of 3'-azido-3'-deoxythymidine (AZT), lamivudine (3TC), and nevirapine (NVP). Ms. Danica Andrews served as the Designated Federal Official for the peer-review meeting.

Additional information about this past meeting and other TR review panel meetings is available at <http://ntp.niehs.nih.gov/go/36051>.

NTP Monographs Peer Review Panels

Monographs are publications of a single, detailed specific topic. On November 17-18, 2011, the NTP convened an external, scientific panel to peer review the Draft NTP Monograph on Health Effects of Low-level Lead at the NIEHS. The panel was charged (1) to determine whether the scientific information cited in the draft monograph is technically correct, clearly stated, and objectively presented and (2) to determine whether the scientific evidence presented in the draft monograph supports the NTP's conclusions regarding health effects of low-level lead. The meeting was open to the public with time scheduled for oral public comment. The panel consisted of experts to review the topics of exposure and the major health effect areas of immune, kidney, cardiovascular, neurological, and reproductive and developmental, for both of the life stages children and adults. Ms. Danica Andrews served as the Designated Federal Official for the peer-review meeting. After the meeting, the input from the panel was considered in finalizing the monograph. Additional information about this past meeting and other NTP Monograph review panel meetings is available at <http://ntp.niehs.nih.gov/go/36639>.

The final monograph on low-level lead was released in June 2012 and can be found at <http://ntp.niehs.nih.gov/go/36443>.



2. Funding

Current and Projected Research Capacity

The NTP relies on voluntary allocations from the program's three core agencies (NIEHS, FDA (NCTR), and NIOSH) to support its activities. These allocations are specified after annual appropriations have been determined. As shown in Figure 2, the total NTP budget for FY 2012 was \$126.8 million.

The NTP conducts its research studies through contract laboratories, in-house at the core agencies, or through Interagency Agreements with other agencies (see page 16). In FY 2012, the NIEHS funded 40 contracts (see Table 4), held two workshops (see page 74), two special emphasis expert panel peer-review meetings (see page 12), and three scientific advisory meetings (see pages 7 and 9) for the NTP.

Figure 2: Past, Current and Projected Budget

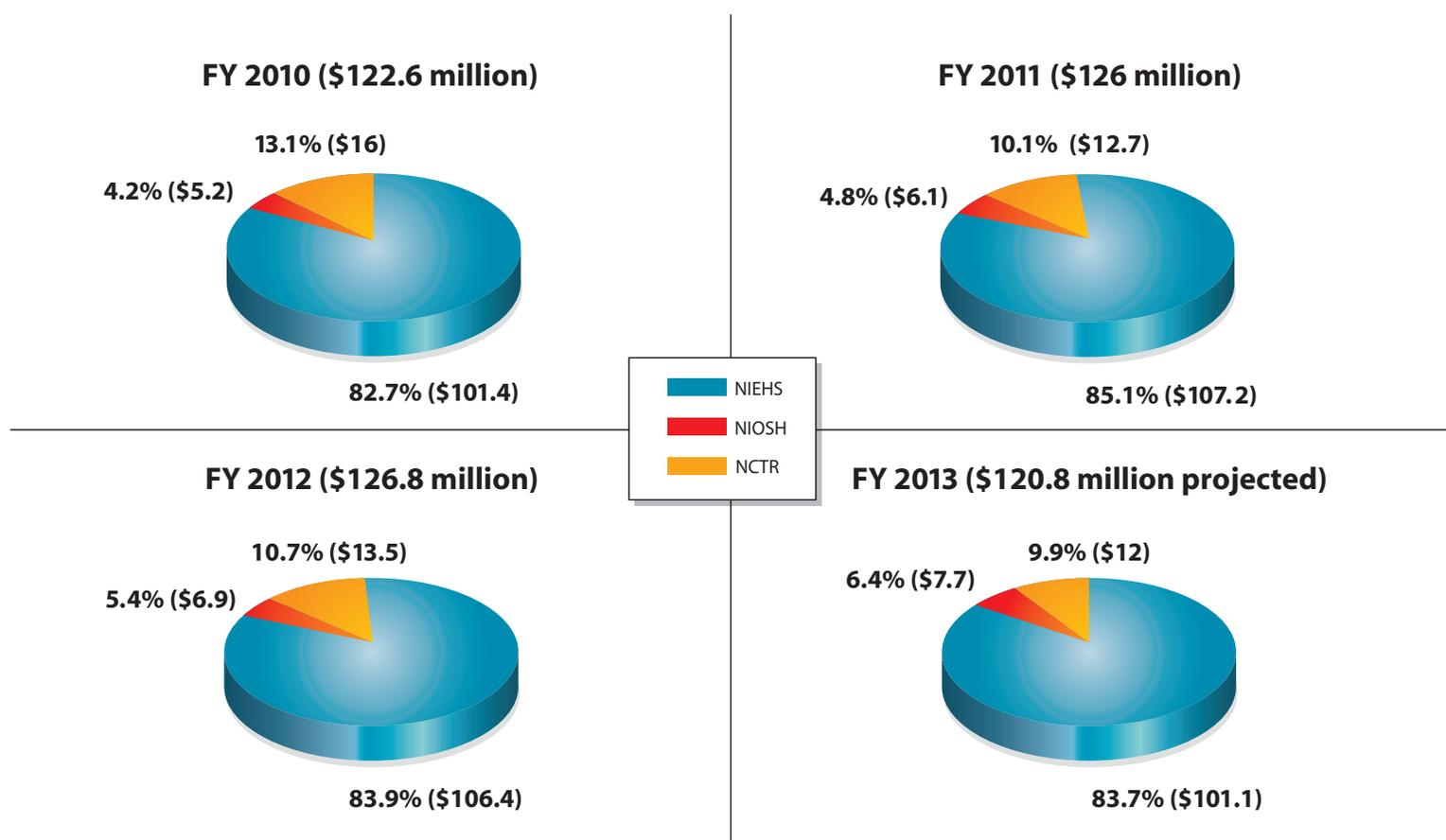


Table 4. NTP Contracts that Supported NTP Testing Activities in FY 2012

Description	Contractor
ADME chemical disposition in mammals	Lovelace Biomedical Research Triangle Institute
Analytical chemistry support services	Battelle Memorial Midwest Research Institute Research Triangle Institute
Archives and specimen repository	Experimental Pathology Labs
Bioinformatics methylation project	Murdock Research Institute
Bioinformatics support	Kelly Scientific
Chemistry support	Research Triangle Institute
Evaluate the toxicological potential for selected agents	Battelle Memorial
Evaluation of alternative toxicological methods	Integrated Laboratory Systems
Genetic toxicity in bacteria and rodents	Integrated Laboratory Systems
High throughput sequencing	Lieber Institute
Inhalation toxicology of environmental chemicals	Alion Science and Technology
Investigative research support	Integrated Laboratory Systems
NTP computer and user support	Vistrionix, Inc.
NTP information systems support	Scimetrika
Pathology support	Charles River Experimental Pathology Labs Integrated Laboratory Systems Ramazzini
Pathology support for quality assessment	Experimental Pathology Labs
Potential for environmental & therapeutic agents	Virginia Commonwealth
Production of B6C3F1 mice	Taconic Farms
Provantis software	INSTEM
Provision for animals and specialized services	Charles River Harlan Laboratories Jackson Laboratories Taconic Farms
QA and auditing	Labscience
Quality assessment support for conducts of audits	Dynamac
Reproductive assessments by continuous breeding	Research Triangle Institute
Scientific software	Leadscope, Inc.
Scientific software support	DrugMatrix Thomson Reuters Scientific
Statistical support	SRA International
Studies to evaluate effects of chemicals	Research Triangle Institute
Technical reports preparation support services	Biotechnical Sciences
Toxicological & carcinogenic potential of chemicals	Battelle Memorial
Toxicological & carcinogenic potential of lab animals	Battelle Memorial



Interagency Agreements

In FY 2012, the NIEHS provided support for NTP activities through interagency agreements with NIOSH and NCTR. Beginning in 1992, the NIEHS established an interagency agreement with FDA to support collaborative toxicology studies on FDA-regulated agents that were nominated to the NTP. This support has been primarily to study chemicals where the FDA has no legal authority to require the regulated community to provide toxicological data for a product. This agreement has led to assessments of toxicity for many classes of chemicals, including cosmetics, endocrine-disrupting compounds, food contaminants, food cooking by-products, dietary supplements, drugs, and anesthetics and investigations of mechanisms of action. The studies are conducted at the NCTR. In addition, the interagency agreement partially supports the NCTR/Office of Regulatory Affairs Phototoxicity Research and Testing Laboratory.

In 1997, the NIEHS began an interagency agreement with NIOSH for NTP studies to characterize and evaluate adverse effects of complex occupational exposures. For a comprehensive assessment of occupationally relevant exposures, the NTP and NIOSH are coordinating efforts to increase knowledge, identification, and education of occupational health research. NIOSH and NTP are also working together to support immunotoxicology projects, evaluating adverse health effect to the immune system from environmental exposure to chemical or physical agents.

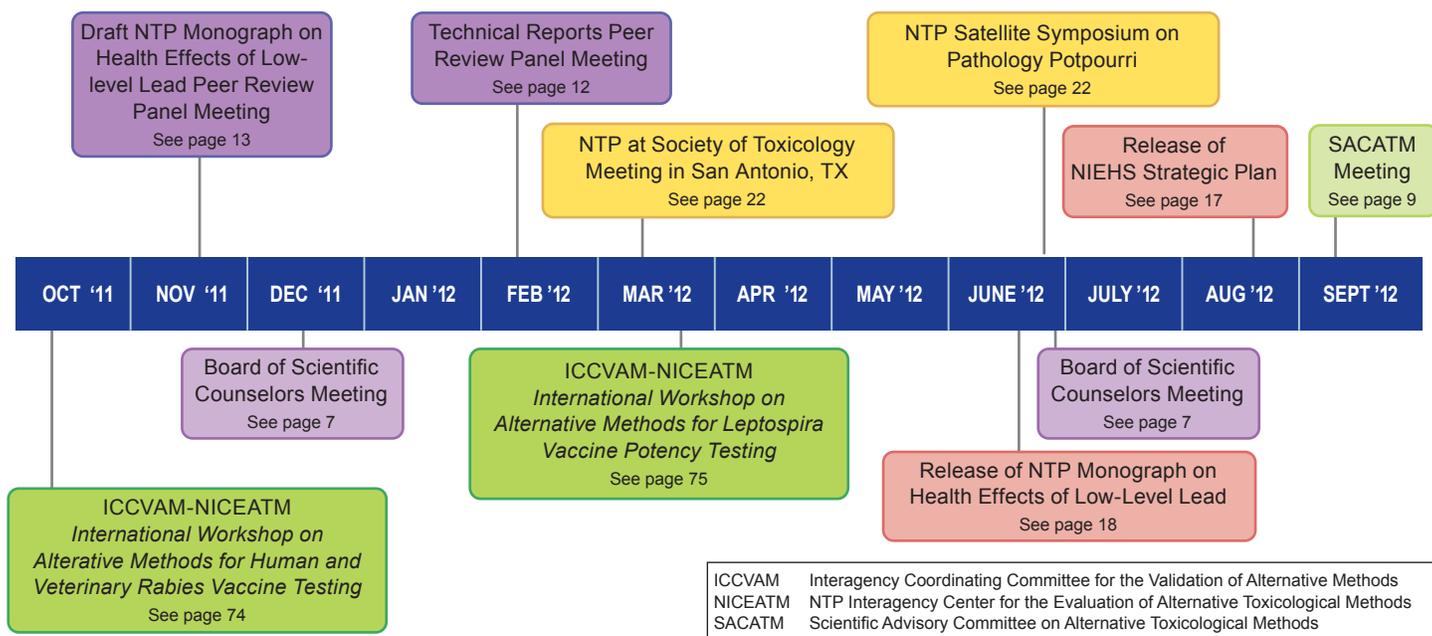
In 2008, the NTP entered into a partnership with the National Human Genome Research Institute's NIH Chemical Genomics Center (NCGC, now the NIH National Center for Advancing Translational Sciences) and the EPA's National Center for Computational Toxicology (NCCT), through a five-year memorandum of understanding (see <http://ntp.niehs.nih.gov/go/28213> for information about the memorandum). This interagency partnership is the basis for the United States Tox21 program (see page 70) and supports the NCGC BioPlanet (see page 79).

Also in 2008, the NIEHS and EPA signed the *Phthalate Initiative* interagency agreement to address nominations of bis(2-ethylhexyl) phthalate and other phthalates to the NTP for testing. Some of the study findings from this interagency agreement, which came to an end in FY 2011, were published in FY 2012.

3. NTP Highlighted Activities

Figure 3 displays the major events for the NTP from FY 2012. Below are additional activities of importance from FY 2012.

Figure 3: FY 2012 Highlights



A. NIEHS Strategic Plan

In FY 2012, the NIEHS released its Strategic Plan that set the Institute’s scientific and governance direction for the next five years (2012–2017). The NIEHS initiated the strategic planning process in 2011 and solicited stakeholder input before completion. The strategic plan includes the institute’s mission, vision, major themes, crosscutting themes, and strategic goals. As a division of NIEHS, the NTP’s toxicology research will continue to be integrated into the basic and translation programs at NIEHS to protect public health and solve health problems. The NIEHS strategic plan can be found at <http://www.niehs.nih.gov/about/strategicplan/>.



B. Systematic Review Process

In FY 2012, the NIEHS’ Office of Health Assessment and Translation (OHAT) and Office of Liaison, Policy and Review initiated an effort to incorporate systematic review methodology into NTP literature-based evaluations. Systematic reviews use a standardized methodology to identify relevant research and to report and critically appraise data from the studies that are included in a review. The systematic review format helps provide a structure to guide identification and determination of literature for inclusion, as well as extraction of data from studies, assessment of study quality and reporting, and synthesis of data toward reaching a conclusion. Currently, systematic reviews are most utilized in clinical epidemiology for health care interventions; however, there is increasing interest in adopting this format in the environmental health sciences and risk assessment.

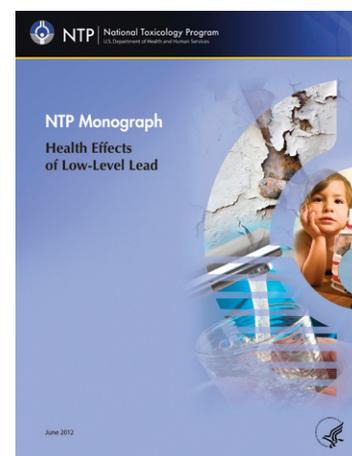


OHAT's goal is to provide a framework for carrying out literature-based assessments and enhance the transparency in reaching and communicating NTP conclusions. The systematic review format includes seven steps: (1) prepare the topic, (2) search for and select studies for inclusion, (3) extract data from studies, (4) assess the quality of individual studies, (5) rate the confidence in the body of evidence, (6) translate confidence ratings into level of evidence for health effect, and (7) integrate evidence to reach hazard identification conclusions. OHAT held two public webinars in FY 2012 on March 20 and April 23 to discuss issues relating to systematic review with a focus on approaches for assessing the quality of individual studies and risk of bias for individual studies and across studies. With an initial introduction to the BSC at its meeting in June 2012, the NTP convened a BSC working group (see page 8) to provide input regarding a draft approach in August 2012, with plans to present their report to the BSC and request public input in December 2012. In FY 2013, the goal is to obtain additional public input on a revised draft approach prior to OHAT moving forward with its implementation and evaluation. (<http://ntp.niehs.nih.gov/go/38673>).



C. Health Effects of Low-Level Lead

In FY 2012, the NTP released the *NTP Monograph on Health Effects of Low-Level Lead*. Prior to publication, an *ad hoc*, scientific panel peer reviewed the draft NTP monograph at a public meeting held November 17–18, 2011, at NIEHS (<http://ntp.niehs.nih.gov/go/37090>, see page 13). The NTP selected low-level lead for evaluation because of (1) the availability of a large number of epidemiological studies of lead, (2) a nomination by NIOSH for an assessment of lead at lower levels of exposure, and (3) public concern for effects of lead in children and adults. OHAT carried out the evaluation and produced the monograph. The monograph summarizes the evidence in humans and presents conclusions on health effects in children and adults associated with low-level lead exposure (less than 10 micrograms of lead per deciliter of blood). The assessment focused on epidemiological evidence at low blood lead levels because health effects at higher blood lead levels are well established. Overall, the NTP concluded that there is sufficient evidence that low blood lead levels are associated with adverse health effects in children and adults. The monograph can be found at <http://ntp.niehs.nih.gov/go/36443>.



D. Studies of Botanical Dietary Supplements

Ginkgo biloba extract

Ginkgo biloba extract has been used for centuries in traditional Chinese medicine and today as a botanical supplement with the potential to improve brain function and for its antioxidant and anticancer effects. However, this botanical supplement has the potential for consumption over extended periods of time, with a general lack of sufficient data on long-term carcinogenicity risk. The NIEHS supported NTP studies that looked at the long-term effects of *Ginkgo* extract in male and female F344/N rats and B6C3F1/N mice. *Ginkgo biloba* extract was given orally to the animals for up to two years. At the end of the two-year studies,



the NTP found an increase in liver cancer in male and female mice, and in cancer of the thyroid gland in male and female rats and male mice. The *NTP Technical Report on the Toxicology and Carcinogenesis Studies of Ginkgo Biloba Extract* was peer reviewed on February 8–9, 2012 (<http://ntp.niehs.nih.gov/go/36144>) and will be published in 2013 (http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/TR578_508.pdf).

In a companion study, the NTP examined the genetic profile of liver tumors in mice treated with *Ginkgo biloba* extract for two years. Exposure of B6C3F1/N mice to the extract in the two-year NTP carcinogenicity bioassay resulted in a dose-dependent increase in liver tumors, including development of cancerous tumors. This NTP study provides a molecular context for the genetic changes associated with the development of liver tumors in mice exposed to the *Ginkgo biloba* extract, and it illustrates the marked differences between those tumors and tumors that developed spontaneously in the mice. Reports in the scientific literature tout health benefits of *Ginkgo biloba* extract, although the NTP's findings in this companion study suggest that long-term use of high doses of the extract may pose potential health risks. The publication in *Toxicologic Pathology* is available at <http://dx.doi.org/10.1177/0192623312467520>.

Black cohosh extract

Black cohosh extract is used as a remedy for pain and gynecological ailments; modern preparations are commonly sold as ethanolic extracts available as dietary supplements. The NIEHS supported NTP studies in rodents (female B6C3F1/N mice and Wistar Han rats) to characterize the general toxicity of black cohosh extract and to address suspected estrogenic/anti-estrogenic activity.

Increasing doses of black cohosh extract caused increasing severity of a specific type of anemia along with increasing biomarkers of chromosomal damage in red blood cells. Effects were more severe in mice (seen at all exposure dose levels) than rats. Dose-dependent thymus and liver toxicity was also observed in rats. Apparent effects on puberty were observed, but were not associated with alteration in estrogenic/anti-estrogenic activity. These are the first studies to observe adverse effects of black cohosh extract in rodents. Further studies are underway to determine the reproductive toxicity, immune toxicity, and carcinogenicity of black cohosh extract. The publication in *Toxicology and Applied Pharmacology* is available at <http://dx.doi.org/10.1016/j.taap.2012.05.022>.



E. Diversity-Outbred Mice and Population Based Models for Toxicology and Disease

While there is great genetic diversity in human populations, many toxicology studies utilize mouse models that are genetically homogenous. Using genetically diverse mouse populations for studies can better indicate how human populations will respond to a substance. Such population-based models can be useful for quantifying how both genetic and epigenetic diversity impact the way animals react to potential toxins. Epigenetic diversity refers to differences in the expression of the genome that do not involve alterations in the actual DNA sequence. For example, previous NTP studies suggest that there are significant, population-based differences for benzene-induced genotoxicity (direct or indirect damage to genes) and hematotoxicity (damage to blood) among mice. Benzene is a known toxicant that harms humans and mice.

To obtain a genetically diverse mouse population, NIEHS/NTP researchers crossed different mouse breeds to create the diversity-outbred mice. The resulting mouse population has greater genetic diversity than what exists in human populations. The diversity-outbred mice should allow the NTP to perform rodent epidemiology



studies in a controlled environment. Scientists will be able to link adverse effects (e.g., cancer or toxicity to different organ systems) of exposure to a substance with particular genetic or epigenetic differences in the mouse population.

Research to determine the utility of diversity-outbred mice for the NTP research and testing program continued in FY 2012. This work involved 28-day-old diversity-outbred male mice exposed to inhaled benzene (0, 1, 10, or 100 ppm; 75 mice/group) for five days per week for four weeks, in two independent studies. NTP staff scientists evaluated the resulting data throughout FY 2012 and expect to complete the evaluation in FY 2013. Preliminary results indicate one specific gene is responsible for both increased resistance and susceptibility to genotoxicity and hematotoxicity from benzene exposure.

F. Mouse Methylome Project

Susceptibility to toxicity or disease and how that is inherited depends on more than DNA sequence variations. The methylome, a component of the epigenome, is one of the other factors that may affect susceptibility to cancer and other chemical exposure-related diseases. The methylome is an individual's genome-wide pattern of cytosine methylation, which is the addition of a methyl group to cytosine, one of the four major bases of DNA. DNA methylation is an important epigenetic modification of the genome that plays a major role in development, toxicity, and disease. Presently, there is no mouse reference database for the methylome, which significantly handicaps an understanding of the mouse model in toxicology and environmentally related diseases and in designing and conducting research to understand the associated mechanisms.

The Mouse Methylome project, which is being carried out by NIEHS/NTP, will use Next Generation sequencing technologies to create a high-resolution map of the mouse liver methylome from three different mouse strains (two parental strains C57BL/6N and C3H/HeN and their first generation hybrid offspring B6C3F1/N). These strains show dramatically different incidences of spontaneous liver tumors, which often confound two-year toxicology and carcinogenesis studies. This variable incidence of liver cancer may be due in part to differences in the epigenetic machinery and also to the sites and amounts of cytosine methylation in critical tumor suppressor genes and other regulatory regions of the genome that affect liver cancer susceptibility and its heritability across generations.

Scientists collected liver samples, along with samples of four other tissues (brain, cardiac and skeletal muscle, brown and white fat, epididymal sperm), from all mice in this project at the same age to minimize age as a confounding factor for gene expression and epigenetics. They prepared sequencing libraries of the liver samples and banked samples of the other four tissue types for future use. In FY 2012, scientists completed characterization of the liver transcriptome (the collection of RNA in the liver) and genomic sequence. Efforts will continue in FY 2013 to measure site-specific methylation of DNA.

G. NTP Impact on Regulatory Agencies

Federal and state regulatory agencies use NTP study data and recommendations in considering the need to regulate and test specific chemicals to protect human health. Table 5 lists NTP data and recommendations used by other agencies in FY 2012.

Table 5. Use of NTP Study Data or Recommendations by Federal and State Regulatory Agencies in 2012

Notice	NTP Information Cited	Summary of Notice
California Office of Environmental Health		
Changes to the Proposition 65: added to list of chemicals known to the State to cause cancer: isopyrazam and 3,3',4,4'-tetrachloroazobenzene	NTP <i>Toxicology and Carcinogenesis Studies of 3,3',4,4'-Tetrachloroazobenzene (TCAB)</i> (CAS No. 14047-09-7) Technical Report Series No. 558. NIH Publication No. 11-5899. http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/TR558.pdf	Effective July 24, 2012, the Office of Environmental Health Hazard Assessment is adding two chemicals, isopyrazam (CAS No. 881685-58-1) and 3,3',4,4'-tetrachloroazobenzene (CAS No. 14047-09-7), to the list of chemicals known to the State to cause cancer for purposes of the Safe Drinking Water and Toxic Enforcement Act of 1986 (commonly known as Proposition 65). http://oehha.ca.gov/prop65/prop65_list/072012listR.html
Centers for Disease Control and Prevention		
Final Rule: World Trade Center Health (WTC) Program; addition of certain types of cancer to the list of WTC-related health conditions	Five main sources, including the NTP 12th Edition of the <i>Report on Carcinogens</i> , were used to evaluate whether to add cancers to the WTC-Related Health Conditions list. http://ntp.niehs.nih.gov/?objectid=035E57E7-BDD9-2D9B-AFB9D1CADC8D09C1	In accordance with WTC Health Program regulations, which establish procedures for adding a new condition to the list of covered health conditions, this final rule adds to the List of WTC-Related Health Conditions the types of cancer proposed for inclusion by the notice of proposed rulemaking. September 12, 2012 – 77 FR 567138 http://www.gpo.gov/fdsys/pkg/FR-2012-09-12/pdf/2012-22304.pdf
U.S. Environmental Protection Agency		
Final Rule: national emission standards for hazardous air pollutants from coal- and oil-fired electric utility steam generating units and standards of performance for fossil-fuel-fired electric utility, industrial-commercial-institutional, and small industrial-commercial-institutional steam generating units	NTP <i>Toxicology and Carcinogenesis Studies of Nickel Sulfate Hexahydrate (Cas No. 10101-97-0) in F344/N Rats and B6C3F1 Mice (Inhalation Studies)</i> http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr454.pdf NTP <i>Toxicology and Carcinogenesis Studies of Nickel Sub sulfide (CAS NO. 12035-72-2) in F344/N RATS and B6C3F1 Mice (Inhalation Studies)</i> http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr453.pdf	On May 3, 2011, under authority of Clean Air Act (CAA) sections 111 and 112, the EPA proposed both national emission standards for hazardous air pollutants (NESHAP) from coal- and oil-fired electric utility steam generating units (EGUs) and standards of performance for fossil-fuel-fired electric utility, industrial-commercial-institutional, and small industrial-commercial-institutional steam generating units (76 FR 24976). After consideration of public comments, the EPA is finalizing these rules in this action. February 16, 2012 – 77 FR 9304 http://www.gpo.gov/fdsys/pkg/FR-2012-02-16/pdf/2012-806.pdf
Final Rule: 2017 and later model year light-duty vehicle greenhouse gas emissions and corporate average fuel economy standards	11th Edition of the <i>Report on Carcinogens</i> : acetaldehyde and naphthalene are listed as reasonably anticipated to be human carcinogens; benzene, 1,3-butadiene, and formaldehyde are listed as known human carcinogens. http://ntp.niehs.nih.gov/ntp/roc/toc11.htm	EPA and NHTSA, on behalf of the U.S. Department of Transportation, are issuing final rules to further reduce greenhouse gas emissions and improve fuel economy for light-duty vehicles for model years 2017 and beyond. On May 21, 2010, President Obama issued a Presidential Memorandum requesting that NHTSA and EPA develop through notice and comment rulemaking a coordinated National Program to improve fuel economy and reduce greenhouse gas emissions of light-duty vehicles for model years 2017-2025, building on the success of the first phase of the National Program for these vehicles for model years 2012-2016. This final rule, consistent with the President's request, responds to the country's critical need to address global climate change and to reduce oil consumption. October 15, 2012 – 77 FR 62624 http://www.gpo.gov/fdsys/pkg/FR-2012-10-15/pdf/2012-21972.pdf



Notice	NTP Information Cited	Summary of Notice
Occupational Safety and Health Administration		
Final Rule: Hazard Communication	Utilized the classification listing that NTP uses on Safety Data Sheets; based classification to determine carcinogenicity on the 12th Edition of the <i>Report on Carcinogens</i> . http://ntp.niehs.nih.gov/?objectid=03C9CE38-E5CD-EE56-D21B94351DBC8FC3	In this final rule, OSHA is modifying its Hazard Communication Standard (HCS) to conform to the United Nations' Globally Harmonized System of Classification and Labelling of Chemicals (GHS). OSHA has determined that the modifications will significantly reduce costs and burdens while also improving the quality and consistency of information provided to employers and employees regarding chemical hazards and associated protective measures. March 26, 2012 – 77 FR 17574 http://www.gpo.gov/fdsys/pkg/FR-2012-03-26/pdf/2012-4826.pdf

A complete listing of NTP studies used by Federal and state regulatory agencies is at: <http://ntp.niehs.nih.gov/go/regact>.

H. Additional Activities

The NTP participates in a number of meetings with stakeholders and the scientific community. At the 2012 Society of Toxicology (SOT) meeting in San Antonio, TX, NIEHS' Division of the NTP and other NIEHS staff participated in approximately 100 workshop/symposium/platform sessions, education/information sessions, and posters. A full listing of the NTP and NIEHS activities at SOT can be found at <http://ntp.niehs.nih.gov/go/35370>. Several posters were presented by ICCVAM on alternative methods development. Information about NICEATM and ICCVAM activities at the 2012 SOT Meeting can be found at <http://iccvam.niehs.nih.gov/meetings/SOT12/sotablst.htm>.

The NTP also hosts symposiums and workshops to discuss the state of the science and advance the field. For example, the NTP hosted the 2012 annual NTP Satellite Symposium, entitled "Pathology Potpourri," at the Society of Toxicologic Pathology on June 23. The goal of the NTP Symposium is to present current diagnostic pathology or nomenclature issues to the toxicological pathology community in a fun and interactive manner. The NTP also hosted two workshops related to alternative methods development (see page 74).

4. Literature Analysis Activities

NTP conducts literature analysis and review to examine the state of the science and assess if a substance has adverse health effects or is specifically carcinogenic.

A. Non-Cancer Health Effects

The NTP has made a commitment to studying non-cancer health effects. To accomplish this, the NIEHS established the Office of Health Assessment and Translation (OHAT) within the Division of NTP to serve as an environmental health resource to the public, and to regulatory and health agencies. This office conducts evaluations to assess the evidence that environmental chemicals, physical substances, or mixtures (collectively referred to as “substances”) cause adverse health effects and provides opinions on whether these substances may be of concern given what is known about current human exposure levels. Assessments of potential adverse effects of environmental substances on reproduction or development carried out by the Center for the Evaluation of Risks to Human Reproduction from 1998–2010 are now carried out by OHAT. OHAT also organizes workshops or state-of-the-science evaluations to address issues of importance in environmental health sciences. OHAT assessments are published as NTP Monographs. The OHAT evaluation process can be found at <http://ntp.niehs.nih.gov/go/38138>. Kristina Thayer, PhD, is the director of OHAT.

As highlighted on page 18, in FY 2012, OHAT published the final *NTP Monograph on Health Effects of Low-level Lead* and focused on incorporating systematic review methodologies into its evaluation. OHAT will ask for public comment on the framework document called the “Draft OHAT Approach for Systematic Review and Evidence Integration for Literature-based Health Assessments” (<http://ntp.niehs.nih.gov/go/38673>) in FY 2013. Table 6 lists literature analysis projects that were completed, ongoing, or initiated in FY 2012.

Table 6. NTP Non-Cancer Health Effects Projects in FY 2012

NTP Project [Study Scientist]	Objective and/or Summary
Completed Project	
NTP Monograph on Health Effects of Low-level Lead (http://ntp.niehs.nih.gov/go/36443) [Rooney]	This evaluation summarizes the evidence in humans and presents conclusions on health effects in children and adults associated with low-level lead exposure as indicated by less than 10 micrograms of lead per deciliter of blood (<10 µg/dL). The assessment focuses on epidemiological evidence at blood lead levels <10 µg/dL and <5 µg/dL because health effects at higher blood lead levels are well established.
Ongoing Projects	
Identifying Research Needs for Assessing Safe Use of High Intakes of Folic Acid – State of the Science Evaluation (http://ntp.niehs.nih.gov/go/38144) [Boyles]	The NTP in conjunction with the NIH Office of Dietary Supplements is planning a workshop to identify research needs based on consideration of the state of the science related to the safe use of high intakes of folic acid. The benefit of supplemental folic acid for pregnant women to prevent neural tube defects in their children is well established; at the same time, there is interest in understanding potential adverse health impacts from high intakes of folic acid. This project aims to identify research needs and inform the development of a research agenda for evaluating the safe use of high intakes of folic acid.



NTP Project [Study Scientist]	Objective and/or Summary
Draft NTP Monograph on Developmental Effects and Pregnancy Outcomes Associated with Cancer Chemotherapy Use During Pregnancy (http://ntp.niehs.nih.gov/go/36495) [Howdeshell]	The overall goal of this monograph is to summarize the reports of effects of gestational exposure to cancer chemotherapy on pregnancy outcomes to serve as a resource for the clinical and patient communities.
Initiated Project	
Air Pollution and Children's Health (http://ntp.niehs.nih.gov/go/37853) [Howdeshell]	This project focuses on exposures related to outdoor air pollution and their association with emerging children's health outcomes.

B. Report on Carcinogens

The Report on Carcinogens (RoC) is a congressionally mandated listing of substances (1) that either are known to be human carcinogens or may reasonably be anticipated to be human carcinogens and (2) to which a significant number of persons residing in the United States are exposed [Section 301(b)(4) of the Public Health Services Act, 42 U.S.C. 241(b)(4)].

Each substance listed in the RoC has a profile, which contains the listing status, a summary of the cancer studies supporting the listing status, information on human exposure, and Federal regulations to reduce exposure. The RoC is a cumulative report and consists of substances newly reviewed in addition to those listed in previous editions. The Secretary of Health and Human Services has delegated preparation of the RoC to the NTP, with assistance from other Federal health and regulatory agencies. Preparation of the RoC is managed by the Office of the RoC (ORoC) under the direction of Ruth Lunn, DrPH, within the NIEHS Division of the NTP. Integrated Laboratory Systems, Inc. (ILS), provided contract support for preparation of the RoC in FY 2012. The 12th RoC, the latest edition, was published on June 10, 2011.

Preparation of the RoC

During the early part of FY 2012, the NTP made revisions to the multi-step process used to prepare the RoC. The development of the process included opportunity for public input on the proposed process and NTP BSC review of the revised process (for more information see <http://ntp.niehs.nih.gov/go/37153>). The NTP published a *Federal Register* notice in October 2011 inviting written comments on the proposed process for preparing the RoC and convened a listening session in November 2011 to receive oral public comments. The revised process for the preparation of the RoC was presented to the NTP BSC on December 11, 2011 (<http://ntp.niehs.nih.gov/go/9741>), and the final process was released in January 2012 (available at <http://ntp.niehs.nih.gov/go/rocprocess>).

With the revised process, the NTP maintains critical elements of the previous process including external scientific and public involvement, scientific rigor, and external peer review. New elements of the revised process include the concept document and the monograph. Each substance proposed for review for the RoC will have a concept document prepared for public comment and comment from the NTP BSC. The concept document will outline the reason for a substance's review for the RoC and lay out the proposed approach for obtaining external scientific and public inputs in development of the cancer evaluation component of the draft RoC monograph. The monograph is an integrated document that will contain a cancer evaluation component

and substance profile. The monograph will undergo public peer review. This revised process should enhance transparency and enable the NTP to publish the RoC in a timelier manner.

In January 2012, the NTP invited public input on 15 nominations for the 13th and future editions of the RoC (<http://ntp.niehs.nih.gov/go/rocnom>). Based upon input by the public and NTP’s interagency partners, ORoC identified five substances for evaluation, hereafter referred to as “candidate substances”. A draft concept document was developed for each candidate substance to outline the rationale and proposed approach for its review. The NTP BSC reviewed the draft concepts at the June 21–22, 2012 public meeting (<http://ntp.niehs.nih.gov/go/9741>). Following the meeting, the NTP Director approved the five candidate substances for formal review for the RoC, these are listed in Table 7.

During the last part of FY 2012, ORoC initiated preparation of draft RoC monographs for the five candidate substances and established a website to share information regarding their reviews and to receive public input (accessed from <http://ntp.niehs.nih.gov/go/37893>). ORoC will complete the preparation of draft monographs for several candidate substances during FY 2013, after which they will be released for public comment and peer review by an external panel at a public meeting.

Candidate Substance CASRN [Study Scientist]	Primary Uses/Exposures
1-Bromopropane 106-94-5 [Spencer]	A brominated hydrocarbon used as a solvent cleaner to degrease electronics, precision optics, and metals, as a solvent vehicle in industries that use aerosolized adhesives (e.g., foam cushion manufacturing), as a spot remover in the textile industry, and as a solvent in the dry cleaning industry.
Cumene 98-82-8 [Jahnke]	An alkylated benzene found in fossil fuels and used primarily to produce phenol and acetone.
Pentachlorophenol 87-86-5 [Jahnke]	A chlorinated aromatic compound that is primarily used as wood preservatives in the United States. Its use as a wood preservative has been limited to non-residential and non-agricultural applications (such as the treatment of utility poles and cross arms) since 1984.
<i>ortho</i> -Toluidine* 95-53-4 [Lunn]	An arylamine used as an intermediate to manufacture herbicides, dyes, pigments and rubber chemicals.
Trichloroethylene* 79-01-6 [Lunn]	Halogenated alkene used primarily for degreasing metals; it is also used as a solvent for applications related to adhesives, painting, lacquering, and varnishes. It was commonly used in the dry cleaning industry from the 1930s to the 1950s, but is rarely used today.

* Currently listed as *reasonably anticipated to be a human carcinogen* in the RoC.



5. Testing and Research

The NTP maintains a balanced research and testing program that provides data addressing a wide variety of issues important to public health. The NTP actively seeks to identify and select study chemicals and other substances for which there is insufficient information to adequately evaluate potential human health hazards. The NTP nomination process is open to the public (nomination website: <http://ntp.niehs.nih.gov/go/nom>) and nominations can be submitted via the NTP website (<http://ntp.niehs.nih.gov/go/27911>). The agencies represented on the NTP Executive Committee also identify and forward nominations to the NTP. The review and selection of nominations for study is a multi-step process with input from NTP participating Federal agencies, the NTP BSC (see page 7), and the public (see <http://ntp.niehs.nih.gov/go/156> for details). Table 8 lists the substances whose draft research concepts were reviewed in FY 2012 by the NTP BSC. Research concepts are developed to outline the general elements of a program of study that would address the specific issues that prompted the nomination of a chemical or substance for testing. The full research concepts for the substances in Table 8 can be found at <http://ntp.niehs.nih.gov/go/37038>. Questions about the nomination, review, and selection process can be sent to Dr. Scott Masten (masten@niehs.nih.gov).

Table 8. Research Concepts Reviewed by the BSC in FY 2012

Substance CASRN [Nominator]	Nomination Rationale	Proposed Studies [Study Scientist]
Octrizole and related phenolic benzotriazoles 3147-75-9 [NIEHS]	High production volume and use as UV stabilizers in a wide variety of industrial and consumer products; possess physico-chemical properties that suggest persistence in the environment and potential to bioaccumulate; limited toxicological data, and reproductive and developmental effects data for several class members suggest potential hazard	<ul style="list-style-type: none"> • Short-term in vivo and in vitro toxicity studies on multiple (10 or more) class members to prioritize individual compounds for further study • For one or more selected class members: <ul style="list-style-type: none"> ◦ ADME and toxicokinetics studies by oral and dermal routes of administration ◦ Reproductive and developmental toxicity studies ◦ Subchronic toxicity studies ◦ Chronic toxicity and carcinogenicity studies, if warranted based on above [Blystone]
Sulfolane 126-33-0 [Alaska Department of Environmental Conservation, Fairbanks North Star Borough Mayor, Alaska Department of Health and Social Services, Alaska State Senator John Coghill, National Center for Environmental Health / Agency for Toxic Substances and Disease Registry]	High production volume and use in oil and gas refining; public concern related to groundwater contamination in Alaska; inadequate data to evaluate potential adverse health effects from long-term exposures	<ul style="list-style-type: none"> • Short-term oral toxicity studies to evaluate species sensitivity • ADME and toxicokinetics studies by multiple routes of administration • Perinatal exposure studies to evaluate reproductive and developmental toxicity, immune toxicity, and developmental neurotoxicity • Chronic toxicity and carcinogenicity studies [Blystone]

Substance CASRN [Nominator]	Nomination Rationale	Proposed Studies [Study Scientist]
Trimethylsilyldiazomethane 18107-18-1 [Occupational Safety and Health Administration]	Low volume production and use as a reagent in synthetic and analytical chemistry; developed and promoted as a safer substitute for diazomethane; inadequate toxicological data; case reports of severe lung injury and death in exposed laboratory personnel	<ul style="list-style-type: none"> • Chemistry studies to evaluate stability and reactivity • Acute inhalation toxicity studies [Gwinn]

A. Technical Reports

The results of toxicology and carcinogenesis studies undergo rigorous peer review and are published in several NTP report series: Technical Reports (TR), NTP Toxicity Reports (TOX), and Genetically Modified Models Reports (GMM). TRs present the results of NTP's long-term, generally 2-year, toxicology and carcinogenicity studies. TOX reports are prepared for studies when the substance exposure period is short term, generally up to 13 weeks. GMM reports present the results of substances evaluated by the NTP in transgenic mouse strains (e.g., p53+/- heterozygous and Tg.AC mice). Draft NTP reports undergo peer review by *ad hoc* scientific panels or by letter review. All peer reviewers are screened for conflict of interest prior to confirming their service.

Abstracts and completed reports of the TR, TOX, and GMM series are available on the NTP website (<http://ntp.niehs.nih.gov/go/reports>) and are catalogued in PubMed. Study summaries for other types of studies, such as immunotoxicity, developmental toxicity, and reproductive toxicity studies, are also available on the "NTP Study Reports" page on the website.

The following tables (Tables 9–10) list Technical Reports completed or published in FY 2012. The NTP held a peer-review meeting on February 8-9, 2012, to review the seven reports listed in Table 9, see page 12 for more details. The NTP used established criteria to evaluate the findings (<http://ntp.niehs.nih.gov/go/bareresults>) and determine the strength of the evidence for conclusions regarding the carcinogenic activity of the substance. The conclusions for strength of the evidence for carcinogenic activity are included in the tables. The reports are available at <http://ntp.niehs.nih.gov/>. The NTP anticipates seven draft NTP Technical Reports will undergo peer review in FY 2013, as shown in Table 11.



Table 9. Technical Reports Peer Reviewed during FY 2012

Chemical/ Exposure – Study Type	Technical Report Number/ CASRN	Use	Levels of Evidence of Carcinogenic Activity			
			Male Rats	Female Rats	Male Mice	Female Mice
3'-Azido-3'- deoxythymidine (AIDS)*	GMM-14 30516-87-1	Pyrimidine nucleoside analog with antiviral activity used in the treatment of AIDS (Merck 1989)	N/A	N/A	N/A	N/A
3'-Azido-3'- deoxythymidine (AIDS)* in combination with Lamivudine and Nevirapine	GMM-16 30516-87-1	Pyrimidine nucleoside analog with antiviral activity used in the treatment of AIDS (Merck 1989), special combination to study AIDS therapeutics including Lamivudine and Nevirapine	N/A	N/A	N/A	N/A
<i>N,N</i> -Dimethyl- <i>p</i> - toluidine	TR-579 99-97-8	Used as a polymerization accelerator for the manufacture of bone cements & dental materials. Found in industrial glues & artificial fingernail preps. Intermediate in dye & pesticide synthesis.	■ Clear Evidence	■ Clear Evidence	■ Clear Evidence	■ Clear Evidence
<i>Ginkgo biloba</i> extract	TR-578 90045-36-6	Herbal supplement	■ Some Evidence	■ Some Evidence	■ Clear Evidence	■ Clear Evidence
β -Picoline	TR-580 108-99-6	Used as a solvent in the synthesis of pharmaceuticals, resins, dyes & rubber accelerators and as a lab reagent. Also used as an intermediate in the manufacture of insecticides, waterproofing agents, niacin & niacinamide.	■ No Evidence	■ Some Evidence	■ Equivocal Evidence	■ Clear Evidence



Chemical/ Exposure – Study Type	Technical Report Number/ CASRN	Use	Levels of Evidence of Carcinogenic Activity			
			Male Rats	Female Rats	Male Mice	Female Mice
Pyrogallol	TR-574 87-66-1	Naturally occurring in food. Used as a modifier in oxidation dyes including hair dyes & colors. Also used as developer in photography; a mordant for dyeing wool; a reagent for antimony & bismuth; and as a reducer for gold, silver & mercury salts. Used for process engraving & for making colloidal solutions of metals. Used in the manufacture of pharmaceuticals & pesticides. Associated with tobacco: reported either as a natural component of tobacco, pyrolysis product (in tobacco smoke), or additive for one or more types of tobacco products.	No Evidence	No Evidence	Equivocal Evidence	Some Evidence
Trimethylolpropane triacrylate	TR-576 15625-89-5	Used in the production of ultraviolet-curable inks, electron beam irradiation-curable coatings, & polymers & resins; as a component of photopolymer & flexographic printing plates & photoresists; & as an ingredient in acrylic glues & anaerobic sealants. Also used in paper & wood impregnates, wire & cable extrusion, polymer-impregnated concrete, & polymer concrete structural composites.	Some Evidence	No Evidence	No Evidence	Some Evidence

* Indicates study conducted using genetically-modified model.





Table 10. Technical Reports Published During FY 2012

Chemical/ Exposure – Study Type	Technical Report Number/ CASRN	Use	Levels of Evidence of Carcinogenic Activity			
			Male Rats	Female Rats	Male Mice	Female Mice
Acrylamide	TR-575 79-06-1	Polyacrylamides and dye intermediate Flocculants. Waste and water treatment. Paper and pulp industry. Associated with tobacco: reported either as a natural component of tobacco, pyrolysis product (in tobacco smoke), or additive for one or more types of tobacco products.	■ Clear Evidence	■ Clear Evidence	■ Clear Evidence	■ Clear Evidence
alpha/beta Thujone mixture	TR-570 76231-76-0	The essential oils derived from natural oil of cedar leaves in which thujone occurs are used in herbal medicine and as flavorings, fragrances, and rodent and mite repellents. Thujone is banned as a direct food additive in the United States Thujone-containing plant oils are used as flavoring substances in the alcoholic drink industry.	■ Some Evidence	■ No Evidence	■ No Evidence	■ No Evidence
Diethylamine	TR-566 109-89-7	Used in the production of the corrosion inhibitor n,n-diethylethanolamine, and in the production of some pesticides and insect repellents, pharmaceuticals and rubber processing chemicals (Executive Summary). Associated with tobacco: reported either as a natural component of tobacco, pyrolysis product (in tobacco smoke), or additive for one or more types of tobacco products.	■ No Evidence	■ No Evidence	■ No Evidence	■ No Evidence

Chemical/ Exposure – Study Type	Technical Report Number/ CASRN	Use	Levels of Evidence of Carcinogenic Activity			
			Male Rats	Female Rats	Male Mice	Female Mice
<i>N,N</i> -Dimethyl- <i>p</i> -toluidine	TR-579 99-97-8	Used as a polymerization accelerator for the manufacture of bone cements & dental materials. Found in industrial glues & artificial fingernail preps. Intermediate in dye & pesticide synthesis.	■ Clear Evidence	■ Clear Evidence	■ Clear Evidence	■ Clear Evidence
Kava kava extract	TR-571 9000-38-8	Herbal supplement alternative to anti-anxiety drugs, used to help children with hyperactivity and as a skin-conditioning agent in cosmetics.	■ Equivocal Evidence	■ No Evidence	■ Clear Evidence	■ Clear Evidence
Methyl trans-styryl ketone	TR-572 1896-62-4	Reactive carbonyl compound used in organic synthetic reactions such as intermediate in organic synthesis, electroplating chemical; pharmaceutical intermediate, biochemical reagent, agricultural chemical intermediate, proposed sunscreen intermediate. Used as flavoring and fragrance additive. Associated with tobacco: reported either as a natural component of tobacco, pyrolysis product (in tobacco smoke), or additive for one or more types of tobacco products.	■ No Evidence	■ No Evidence	■ No Evidence	■ No Evidence
Retinoic acid and retinyl palmitate	TR-568 79-81-2	Retinol compound (vitamin A) used in skin products.	N/A	N/A	N/A	N/A
Senna*	GMM-15 8013-11-4	Herbal product, extract of senna fruit, used in laxative preparations.	N/A	N/A	N/A	N/A
Styrene-acrylonitrile trimer	TR-573	SAN Trimer is a by-product of the production of acrylonitrile styrene plastics and is created in specific manufacturing processes for polymers of acrylonitrile and styrene.	■ No Evidence	■ No Evidence	N/A	N/A

* Indicates study conducted using genetically-modified model.





Table 11. Technical Reports Expected to Undergo Peer Review in FY 2013

Chemical	Technical Report Number/ CASRN	Use
Bromodichloroacetic acid (water disinfection byproducts)	TR-583 71133-14-7	Bromodichloroacetic acid is a water disinfectant byproduct. Naturally occurring bromides in the water participate in the formation of this compound. This chemical is formed after disinfection of water with halogenated oxidants, usually chlorine.
Cimstar 3800 (metal working fluids)	TR-586	Semisynthetic; metalworking fluid.
Cobalt	TR-581 7440-48-4	Nuclear medicine and research, industry, paints, water treatment, metallurgy. Associated with tobacco: reported either as a natural component of tobacco, pyrolysis product (in tobacco smoke), or additive for one or more types of tobacco products.
Glycidamide	TR-588 5694-00-8	Metabolite of acrylamide. Associated with tobacco: reported either as a natural component of tobacco, pyrolysis product (in tobacco smoke), or additive for one or more types of tobacco products.
Green Tea extract	TR-585	Extract of green tea used as dietary supplement.
Indole-3-carbinol	TR-584 700-06-1	Natural component of brassica vegetables; marketed as a dietary supplement and cancer preventative agent.
Tetrabromobisphenol A	TR-587 79-94-7	Flame retardant for plastics, paper, and textiles.
Vinylidene chloride	TR-582 75-35-4	Copolymerized with vinylchloride or acrylonitrile for saran and saran fibers. A widely used chemical intermediate and monomer.

B. NTP Testing

The NTP testing program evaluates substances for a variety of health-related effects, generally using rodent models for study. NTP staff designs protocols specifically to fully characterize a substance's toxic potential. For each agent studied, a project leader designs a comprehensive testing strategy to address the identified research and testing needs. A project review committee evaluates the testing strategy and proposes an appropriate mechanism for performing the study (e.g., grant, contract). The following NIEHS DNTP branches are involved in the testing program: Biomolecular Screening Branch (led by Raymond Tice, PhD), Cellular and Molecular Pathology Branch (led by Robert Sills, DVM, PhD), NTP Laboratory (led by Mike Waalkes, PhD), Program Operations Branch (led by Michelle Hooth, PhD, DABT), and Toxicology Branch (led by Paul Foster, PhD).

i. Disposition, Metabolism, and Toxicokinetic Studies

Complete dosimetry of a chemical or physical agent describes its absorption, distribution, metabolism and excretion (ADME) in the body at differing levels of exposure, over all ages, via several routes of exposure, and under varying genetic backgrounds in humans and test animals. Data from NTP chemical disposition and toxicokinetic studies are used in these studies. Substances evaluated during FY 2012 are listed in Table 12, and studies planned for FY 2013 are listed in Table 13. More information can be found at <http://ntp.niehs.nih.gov/go/sp>.

Table 12. Ongoing and Completed Disposition, Metabolism and Toxicokinetic Studies During FY 2012

Chemical	CASRN	Species/Strain	Route	Study Scientist
Anatase (TiO ₂)	1317-70-0	Mice: Tg.AC (FVB/N) Mice: FVB/N	Topical Application	Howard
Bisphenol A	80-05-7	Rats: Sprague Dawley (NCTR)	<i>In-vitro</i>	Doerge
Bisphenol AF	1478-61-1	Mice: B6C3F1 Rats: Harlan Sprague Dawley	Intravenous	Mercado-Feliciano
2-Butene-1,4-diol	110-64-5	N/A	<i>In-vitro</i>	Doerge
Butyl paraben (n-Butyl- <i>p</i> -hydroxybenzoate)	94-26-8	Rats: Harlan Sprague Dawley	Gavage	Blystone
1,3-Dichloro-2-propanol	96-23-1	Mice: B6C3F1 Rats: Harlan Sprague Dawley	Gavage	Waidyanatha
Di(2-ethylhexyl) phthalate	117-81-7	Monkey: Rhesus	Gavage	Delclos
Dimethylamine borane	74-94-2	Rats: Harlan Sprague Dawley Human	Gavage	Germolec
Dimethylethanolamine	108-01-0	Mice: B6C3F1 Rats: Wistar Han	Gavage	Waidyanatha
2,2'-Dimorpholinodiethyl ether	6425-39-4	Rats: Harlan Sprague Dawley Mice: B6C3F1/N	Intravenous	Waidyanatha
2',2'''-Dithiobisbenzanilide	135-57-9	Rats: Sprague Dawley Mice: B6C3F1/N	<i>In-vitro</i>	DeVito
2-Ethylhexyl- <i>p</i> -methoxycinnamate	5466-77-3	Rats: Harlan Sprague Dawley Mice: B6C3F1	Dermal	McIntyre
Fullerene C60 (nanoscale material)	99685-96-8	Rats: F344/N	Insufflation	Waidyanatha
Furan	110-00-9	Rats: Tg.Lac1/C57BL/6 (Big Blue) Rats: F344 (NCTR)	Gavage	Walker
2-Hydroxy-4-methoxybenzophenone	131-57-7	Mice: B6C3F1 Rats: Sprague Dawley	Gavage	Auerbach



Chemical	CASRN	Species/Strain	Route	Study Scientist
2-Methoxy-4-nitroaniline	97-52-9	Mice: B6C3F1 Rats: Harlan Sprague Dawley	Topical application	Auerbach
L-beta-Methylaminoalanine	15920-93-1	Mice: B6C3F1/N Rats: Harlan Sprague Dawley	Gavage	Ryan
Rutile titanium dioxide (nanoscale material)	1317-80-2	Mice: SKH-1 hairless	Topical Application	Howard
tris(2-Chloroisopropyl) phosphate	13674-84-5	Rats: Harlan Sprague Dawley Mice: B6C3F1/N	Intravenous	Stout
Tris(4-chlorophenyl)methane	27575-78-6	Rats: Harlan Sprague Dawley Mice: B6C3F1	Gavage	Surh
Tris(4-chlorophenyl)methanol	3010-80-8	Rats: Harlan Sprague Dawley	Gavage	Surh

Table 13: Disposition, Metabolism, and Toxicokinetic Studies Planned for FY 2013

Chemical	CASRN	Species/Strain	Route
Bisphenol AF	1478-61-1	Rats: Harlan Sprague Dawley Mice: B6C3F1	Intravenous

* Known test articles as of 10/1/2012. Others may be scheduled as protocols are finalized.

ii. Genetic Toxicity

Genetic toxicity test results are used to help interpret toxicity, carcinogenicity, or other in vivo test results and to provide a database for use in structure-activity analyses. Substances tested for genetic toxicity during FY 2012 are listed in Table 14. More information can be found at <http://ntp.niehs.nih.gov/go/gt>.

Table 14. Ongoing and Completed Genetic Toxicity Studies during FY 2012

Chemical	CASRN	Testing Battery
3'-Azido-3'-deoxythymidine	30516-87-1	<i>Salmonella</i>
Black cohosh	84776-26-1	Micronucleus
Bromodichloroacetic acid	71133-14-7	<i>Salmonella</i>
N-Butylbenzenesulfonamide	3622-84-2	<i>Salmonella</i>
Chlorhexidine	55-56-1	<i>Salmonella</i>
Furan	110-00-9	Micronucleus
<i>Garcinia cambogia</i> extract	90045-23-1	<i>Salmonella</i>
2-methyl-6-ethylaniline	24549-06-2	<i>Salmonella</i>
Nelfinavir	159989-64-7	<i>Salmonella</i>

Chemical	CASRN	Testing Battery
2-Nitro-2-ethyl-1,3-propanediol	597-09-1	<i>Salmonella</i>
2-Nitro-2-methyl-1,3-propanediol	77-49-6	<i>Salmonella</i>
2-nitro-1-propanol	2902-96-7	<i>Salmonella</i>
2,3-Pentanedione	600-14-6	Micronucleus
Perfluorobutane sulfonate	375-73-5	Micronucleus
Perfluorodecanoic acid	335-76-2	Micronucleus
Perfluorohexane sulfonate potassium salt	3871-99-6	Micronucleus
Perfluorohexanoic acid	307-24-4	Micronucleus
Perfluorononanoic acid	375-95-1	Micronucleus
Perfluorooctane sulfonate (PFOS)	1763-23-1	Micronucleus
Perfluorooctanoic acid (PFOA)	335-67-1	Micronucleus
Potassium hydroxycitrate tribasic monohydrate	232281-44-6	<i>Salmonella</i>
Valerian (root extract, root oil)		<i>Salmonella</i>
Wyeth 14,643	50892-23-4	Micronucleus
Zinc carbonate, basic	5263-02-5	Micronucleus

iii. Organ System Toxicity

The NTP studies toxicity of environmental substances on organ systems, such as it relates to the immune system, development, and reproduction. Table 15 lists ongoing and completed organ systems toxicity studies during FY 2012. More information can be found at <http://ntp.niehs.nih.gov/go/type>.

Table 15. Ongoing and Completed Neurotoxicity, Developmental Toxicity and Reproductive Toxicity Studies During FY 2012

Chemical	CASRN	Species/Strain	Route	Study Scientist	Testing Battery
Acrylamide	79-06-1	Rats: F344 (NCTR)	Gavage	Beland	Neurotoxicity assessment
Black cohosh	84776-26-1	Rats: Harlan Sprague Dawley	Gavage	Mercado-Feliciano	Continuous breeding
Butyl paraben (n-Butyl-p-hydroxybenzoate)	94-26-8	Rats: Harlan Sprague Dawley	Feed	Blystone	Continuous breeding
Dimethylethanolamine	108-01-0	Rats: Harlan Sprague Dawley	Gavage		Teratology pilot study
2-Hydroxy-4-methoxybenzophenone	131-57-7	Rats: Harlan Sprague Dawley	Feed	Hansen, Gwinn	Teratology pilot study, Developmental toxicity
4-Methylimidazole	822-36-6	Rats: Harlan Sprague Dawley	Feed	Behl	Continuous breeding: Range-finding



Chemical	CASRN	Species/Strain	Route	Study Scientist	Testing Battery
Nonylphenol	84852-15-3	Rats: Sprague Dawley (NCTR)	Feed	Newbold, Delclos	Multigeneration
3,3',4,4'-Tetrachloroazobenzene	14047-09-7	Rats: CrI: CD (Sprague Dawley)	Gavage	Hooth	Developmental–pre-implantation, Postnatal developmental toxicity
Tris (2-Chloroisopropyl) phosphate	13674-84-5	Rats: Harlan Sprague Dawley	Gavage	Stout	Developmental toxicity

Immunotoxicity Testing

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. Table 16 lists ongoing and completed immunotoxicity studies during FY 2012. More information can be found at <http://ntp.niehs.nih.gov/go/9399>.

Table 16. Ongoing and Completed Immunotoxicity Studies During FY 2012

Chemical	CASRN	Species/Strain	Route	Study Scientist	Testing Battery
Autumn sunset true color concentrate		Mice: CBA/ Ca Jackson	Subcutaneous injection	Howard	Hypersensitivity
3'-Azido-3'-deoxythymidine	30516-87-1	Mice: B6C3F1	Gavage	Irwin	Immunosuppression–Range Finding*; Developmental
Black cohosh	84776-26-1	Mice: B6C3F1	Gavage	Mercado-Feliciano	Immunosuppression
		Rats: Harlan Sprague Dawley	Gavage	Mercado-Feliciano	Range-finding*
Blasting sand (abrasive blasting agents)		Rats: Harlan Sprague Dawley	Inhalation	Gwinn	Immunosuppression
2,3-Butanedione (Diacetyl)	431-03-8	Mice: BALB/c	Topical application	Morgan	Hypersensitivity
		Mice: BALB/c	Inhalation	Morgan	Immunosuppression–Range-finding*
Dermal lotion vehicle development		Mice: BALB/c	Topical application	Germolec	Hypersensitivity
2,3-Dibromo-7,8-dichlorodibenzo- <i>p</i> -dioxin	50585-40-5	Mice: B6C3F1	Gavage	DeVito	Immunosuppression

Chemical	CASRN	Species/ Strain	Route	Study Scientist	Testing Battery
Dibenz(a,h)anthracene	53-70-3	Mice: B6C3F1	Gavage	Germolec	Immunosuppression– Range finding*; Developmental; Immunosuppression– Full protocol**
Dibromoacetic acid (water disinfection byproducts)	631-64-1	Rats: Harlan Sprague Dawley	Dosed-Water	Germolec	Immunosuppression– Range finding*
1,3-Dichloropropene (Telone II)	542-75-6	Mice: B6C3F1	Dosed-Water	Germolec	Immunosuppression– Full protocol**
Dimethylamine borane	74-94-2	Mice: BALB/c	Topical application	Germolec	Hypersensitivity
Double dark fudge true color concentrate		Mice: CBA/ Ca Jackson	Subcutaneous injection	Howard	Hypersensitivity
Double fudge concentrate		Mice: CBA/ Ca Jackson	Subcutaneous injection	Howard	Hypersensitivity
<i>Echinacea purpurea</i> extract	90028-20-9	Mice: B6C3F1	Gavage	Ryan	Immunosuppression– Full protocol**
Elmiron (sodium pentosanpolysulfate)	37319-17-8	Mice: B6C3F1	Gavage	Germolec	Immunosuppression– Range finding; Immunosuppression– Full protocol**
2-Ethylhexyl <i>p</i> -methoxycinnamate	5466-77-3	Mice: BALB/c	Topical Application	McIntyre	Hypersensitivity
Fullerene-C60 (1 micron) (nanoscale material)	99685-96-8	Rats: Wistar Han Mice: B6C3F1	Inhalation	Walker	Immunosuppression– Range finding*
Fullerene-C60 (50 nanometers) (nanoscale material)	99685-96-8	Rats: Wistar Han Mice: B6C3F1	Inhalation	Walker	Immunosuppression– Range finding*
Genistein	446-72-0	Mice: NOD/ MrKTac	Gavage	Germolec	Autoimmunity
Lovastatin	75330-75-5	Mice: B6C3F1	Gavage	Germolec	Immunosuppression– Range finding*
2-Methoxy-4-nitroaniline	97-52-9	Mice: BALB/c	Dermal	Surh	Hypersensitivity
Monoclonal antibody protein therapeutics (CD-4)		Mice: B6C3F1	Intraperitoneal injection	Germolec	Immunosuppression– Full protocol**
Monoclonal antibody protein therapeutics (CD-8)		Mice: B6C3F1	Intraperitoneal injection	Germolec	Immunosuppression– Full protocol**
Nelfinavir mesylate	159989-65-8	Mice: B6C3F1	Gavage	Germolec	Immunosuppression – Range finding*; Developmental



Chemical	CASRN	Species/ Strain	Route	Study Scientist	Testing Battery
Nevirapine	129618-40-2	Mice: B6C3F1	Gavage	Germolec	Developmental; Immunosuppression– Full protocol**
1,2,3,7,8- Pentabromodibenzofuran	107555-93-1	Mice: B6C3F1	Gavage	DeVito	Immunosuppression
2,3,4,7,8- Pentabromodibenzofuran	13116-92-2	Mice: B6C3F1	Gavage	DeVito	Immunosuppression
1,2,3,7,8- Pentachlorodibenzofuran	57117-41-6	Mice: B6C3F1	Gavage	DeVito	Immunosuppression
2,3,4,7,8- Pentachlorodibenzofuran	57117-31-4	Mice: B6C3F1	Gavage	DeVito	Immunosuppression
2,3-Pentanedione	600-14-6	Mice: BALB/c	Topical application	Germolec	Hypersensitivity
Perfluorodecanoic acid	335-76-2	Rats: Harlan Sprague Dawley	Gavage	Blystone	Immunosuppression
Phenol	108-95-2	Mice: B6C3F1	Dosed-Water	Germolec	Immunosuppression– Full protocol**
Resveratrol	501-36-0	Mice: NOD/ MrKTac	Gavage	Germolec	Autoimmunity
Rosewood true color concentrate		Mice: CBA/ Ca Jackson	Subcutaneous Injection	Howard	Hypersensitivity
Sodium tungstate, dihydrate	10213-10-2	Mice: B6C3F1	Dosed-Water	Hooth	Immunosuppression– Full protocol**
Specular hematite (abrasive blasting agents)		Rats: Harlan Sprague Dawley	Inhalation	Gwinn	Immunosuppression
3,3',4,4'- Tetrachloroazobenzene	14047-09-7	Rats: Sprague Dawley	Gavage	Behl	Immunosuppression– Range finding*
		Rats: CrI: CD (Sprague Dawley)	Gavage	Behl	Developmental
2,3,7,8- Tetrabromodibenzofuran	67733-57-7	Mice: B6C3F1	Gavage	DeVito	Immunosuppression
2,3,7,8- Tetrachlorodibenzo- <i>p</i> -dioxin	1746-01-6	Mice: B6C3F1	Gavage	DeVito	Immunosuppression
2,3,7,8- Tetrachlorodibenzofuran	51207-31-9	Mice: B6C3F1	Gavage	DeVito	Immunosuppression
2,3,7- Tribromodibenzo- <i>p</i> - dioxin	51974-40-4	Mice: B6C3F1	Gavage	DeVito	Immunosuppression

* Range finding studies are performed in order to establish the potential effects of a substance on the immune system and to determine doses that could be used in a full immunotoxicology study.

** Full protocols are more comprehensive studies that establish potential adverse effects of a substance on the immune system.

Modified One-generation Reproduction Studies

Classical studies used to evaluate reproductive toxicity are a multigenerational reproduction experimental design. The NTP has modified this classical study design to better utilize the animals produced and to reduce animal use by improved experimental design and statistical power. Table 17 lists planned or ongoing modified one-generation studies. More information can be found at <http://ntp.niehs.nih.gov/go/MG>.

Table 17. Planned or Ongoing Modified One-generation Studies					
Chemical	CASRN	Species/ Strain	Study Route	Planned Cohorts	Study Scientist
Bisphenol AF	1478-61-1	Rats: Harlan Sprague Dawley	Feed	Dose range finding ¹ Maternal transfer ² Developmental toxicity ³ Fertility assessment ⁴ Neurotoxicity assessment ⁵	Mercado- Felliciano
N-Butylbenzennsulfonamide	3622-84-2	Rats: Harlan Sprague Dawley	Feed	Dose range finding ¹ Maternal transfer ² Developmental toxicity ³ Fertility assessment ⁴ Neurotoxicity assessment ⁵ Subchronic toxicity ⁶	Rider
Butyl paraben	94-26-8	Rats: Harlan Sprague Dawley	Feed	Dose range finding ¹	Blystone
Dong quai (<i>Angelica sinensis</i>) root extract	299184- 76-2	Rats: Harlan Sprague Dawley	Gavage	Dose range finding ¹ Developmental toxicity ³ Fertility assessment ⁴ Neurotoxicity assessment ⁵ Subchronic toxicity ⁶	McIntyre
2-Ethylhexyl <i>p</i> -methoxycinnamate	5466-77-3	Rats: Harlan Sprague Dawley	Feed	Dose range finding ¹ Developmental toxicity ³ Fertility assessment ⁴ Subchronic toxicity ⁶	McIntyre
<i>Garcinia cambogia</i> extract	90045-23-1	Rats: Harlan Sprague Dawley	Feed	Dose range finding ¹ Maternal transfer ² Developmental toxicity ³ Fertility assessment ⁴ Subchronic toxicity ⁶	Rider
Hydroquinone	123-31-9	Rats: Harlan Sprague Dawley	Gavage	Dose range finding ¹ Developmental toxicity ³ Fertility assessment ⁴ Neurotoxicity assessment ⁵	DeVito



Chemical	CASRN	Species/ Strain	Study Route	Planned Cohorts	Study Scientist
2-Hydroxy-4-methoxybenzophenone	131-57-7	Rats: Harlan Sprague Dawley	Feed	Dose range finding ¹ Developmental toxicity ³ Fertility assessment ⁴ Neurotoxicity assessment ⁵	McIntyre
Hydroxyurea	127-07-1	Rats: Harlan Sprague Dawley	Gavage	Dose range finding ¹ Developmental toxicity ³ Fertility assessment ⁴ Neurotoxicity assessment ⁵ Subchronic toxicity ⁶	McIntyre
Isopropylphenyl phosphate	68937-41-7	Rats: Harlan Sprague Dawley	Feed	Dose range finding ¹ Neurotoxicity assessment ⁵	Behl
Perfluorooctane sulfonate (PFOS)	1763-23-1	Rats: Harlan Sprague Dawley	Gavage	Dose range finding ¹	Blystone
Perfluorooctanoic acid (PFOA)	335-67-1	Rats: Harlan Sprague Dawley Mice: CD-1 Reg. [CrI: CD1(ICR)]	Gavage	Dose range finding ¹	Blystone
Sulfolane	126-33-0	Rats: Harlan Sprague Dawley	Dosed water	Dose range finding ¹ Developmental toxicity ³ Fertility assessment ⁴ Neurotoxicity assessment ⁵ Subchronic toxicity ⁶	Blystone
Triphenyl phosphate	115-86-6	Rats: Harlan Sprague Dawley	Feed	Dose range finding ¹ Neurotoxicity assessment ⁵	Behl
Valerian (<i>Valeriana officinalis L.</i>) root extract (0.8%)	8057-49-6	Rats: Harlan Sprague Dawley	Gavage	Dose range finding ¹	DeVito
Wyeth 14,643 (WY)	50892-23-4	Rats: Harlan Sprague Dawley Mice: CD-1 Reg. [CrI: CD1(ICR)]	Gavage	Dose range finding ¹	Blystone

¹ Dose range finding: to find the ideal dose for toxicological studies.

² Maternal transfer: to study the transfer of chemical from mother to offspring.

³ Developmental toxicity: to study adverse developmental outcomes such as birth defects.

⁴ Fertility assessment: to study adverse effects on fertility in males and females.

⁵ Neurotoxicity assessment: to study adverse effects in the structure or function of the central and/or peripheral nervous system.

⁶ Subchronic toxicity: 90-day study of adverse effects in the exposed rodent.

iv. Toxicology/Carcinogenicity Studies

The NTP performs appropriate toxicity studies in part to provide dose-setting information for chronic studies and to address specific deficiencies in the toxicology database for the chemical. Toxicology/Carcinogenicity studies generally fall into two categories: prechronic toxicity studies and two-year toxicology and carcinogenicity studies; studies are generally conducted in rats and mice. Each of these study types is performed according to the *Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological, and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP) January 2011*. Additional information can be found at <http://ntp.niehs.nih.gov/go/ba>.

Tables 18, 19, and 20 list the toxicity studies that were ongoing, initiated, and completed, respectively, during FY 2012. Table 21 lists toxicity studies planned for FY 2013. Chronic toxicology/carcinogenicity studies ongoing and initiated in FY 2012 are listed in Tables 22 and 23, respectively.

Table 18. Prechronic Ongoing Toxicology/Carcinogenicity Studies during FY 2012

Study	CASRN	Species/Strain	Study Route	Length	Study Scientist
Bisphenol A	80-05-7	Rats: Harlan Sprague Dawley	Gavage	90 days	Delclos
Black cohosh	84776-26-1	Rats: Harlan Sprague Dawley Mice: B6C3F1	Gavage	14 days	Mercado-Feliciano
Cell phone radiation (CDMA)		Rats: Harlan Sprague Dawley Mice: B6C3F1	Whole body exposure	5 days 49 days 28 days	Wyde
Cell phone radiation (GSM)		Rats: Harlan Sprague Dawley Mice: B6C3F1	Whole body exposure	5 days 49 days 28 days	Wyde
bis(2-Chloroethoxy) methane	111-91-1	Mice: C57BL/6J (Jackson) Mice: C3H/HeJ Mice: B6C3F1 (Jackson)	Gavage	3 days 10 days	Dunnick
Diet evaluation study		Mice: CD-1 Reg.[CrI: CD1(ICR)]	Feed	90 days	Delclos
Ephedrine + caffeine combination		Mice: C57BL/6J (Jackson) Mice: C3H/HeJ Mice: B6C3F1 (Jackson)	Gavage	3 days 10 days	Dunnick
Formaldehyde*	50-00-0	Mice: C57BL/6 Mice: C3B6F1-+/TRP53<TM1BRD> (NCTR) Mice: B6C3F1	Inhalation	2 weeks 8 weeks	Morgan
Melamine + Cyanuric acid combination		Rats: F344 (NCTR) Rats: Sprague Dawley (NCTR)	Gavage	90 days	Gamboa de Costa
Nanoscale silver	7440-22-4	Rats: Harlan Sprague Dawley	Gavage	13 weeks	Walker
Perfluorobutane sulfonate	375-73-5	Rats: Harlan Sprague Dawley	Gavage	28 days	Blystone
Perfluorodecanoic acid	335-76-2	Rats: Harlan Sprague Dawley	Gavage	28 days	Blystone



Study	CASRN	Species/Strain	Study Route	Length	Study Scientist
Perfluorohexane sulfonate potassium salt	3871-99-6	Rats: Harlan Sprague Dawley	Gavage	28 days	Blystone
Perfluorohexanoic acid	307-24-4	Rats: Harlan Sprague Dawley	Gavage	28 days	Blystone
Perfluorononanoic acid	375-95-1	Rats: Harlan Sprague Dawley	Gavage	28 days	Blystone
Perfluorooctane Sulfonate (PFOS)	1763-23-1	Rats: Harlan Sprague Dawley	Gavage	28 days	Blystone
Perfluorooctanoic acid (PFOA)	335-67-1	Rats: Harlan Sprague Dawley	Gavage	28 days	Blystone
Triclosan	3380-34-5	Mice: B6C3F1/N	Dermal	90 days	Fang
Usnea lichen		Rats: F344 (NCTR) Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Feed	2 weeks 90 days	Leakey
(+)-Usnic Acid	7562-61-0	Rats: F344 (NCTR) Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Feed	2 weeks 90 days	Leakey
Wyeth 14,643 (WY)	50892-23-4	Rats: Harlan Sprague Dawley	Gavage	28 days	Blystone

* Indicates study conducted using genetically-modified model

Table 19. Prechronic Toxicology/Carcinogenicity Studies Initiated during FY 2012

Study	CASRN	Species/Strain	Study Route	Length	Study Scientist
Black cohosh	84776-26-1	Rats: Harlan Sprague Dawley	Gavage	14 days	Mercado-Feliciano
Diet evaluation study		Mice: CD-1 Reg. [CrI: CD1 (ICR)]	Dosed-feed	90-days	Delclos
Formaldehyde*	50-00-0	Mice: C57BL/6 Mice: C3B6F1-+/TRP53<TM1BRD> (NCTR) Mice: B6C3F1	Inhalation	2 weeks 8 weeks	Morgan
Melamine + Cyanuric Acid combination		Rats: F344 (NCTR)	Gavage	90 days	Gamboa de Costa
Perfluorobutane sulfonate	375-73-5	Rats: Harlan Sprague Dawley	Gavage	28 days	Blystone

Study	CASRN	Species/Strain	Study Route	Length	Study Scientist
Perfluorodecanoic acid	335-76-2	Rats:Harlan Sprague Dawley	Gavage	28 days	Blystone
Perfluorohexane sulfonate potassium salt	3871-99-6	Rats:Harlan Sprague Dawley	Gavage	28 days	Blystone
Perfluorohexanoic acid	307-24-4	Rats:Harlan Sprague Dawley	Gavage	28 days	Blystone
Perfluorononanoic acid	375-95-1	Rats:Harlan Sprague Dawley	Gavage	28 days	Blystone
Perfluorooctane Sulfonate (PFOS)	1763-23-1	Rats:Harlan Sprague Dawley	Gavage	28 days	Blystone
Perfluorooctanoic acid (PFOA)	335-67-1	Rats:Harlan Sprague Dawley	Gavage	28 days	Blystone
Wyeth 14,643 (WY)	50892-23-4	Rats:Harlan Sprague Dawley	Gavage	28 days	Blystone

* Indicates study conducted using genetically-modified model

Table 20. Completed Prechronic Toxicology/Carcinogenicity Studies during FY 2012

Study	CASRN	Species/Strain	Study Route	Length	Study Scientist
2-Aminopyridine	504-29-0	Rats:F344/NTac Mice:B6C3F1	Gavage	14 days	Dunnick
3-Aminopyridine	462-08-8	Rats:F344/NTac Mice:B6C3F1	Gavage	14 days	Dunnick
4-Aminopyridine	504-24-5	Rats:F344/NTac Mice:B6C3F1	Gavage	14 days	Dunnick
Comparison study of aminopyridines/troponin levels		Rats:F344/NTac Mice:B6C3F1	Gavage	1 and 4 hours	Dunnick
Glucosamine hydrochloride + Chondroitin sulfate		Rats:Zucker - Obese (HsdHlr:ZUCKER-Leprfa) Rats:Zucker - Lean (HsdHlr:ZUCKER-Lepr+)	Gavage	13 weeks	Leakey
1020 Long multiwalled carbon nanotube		Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Inhalation	30 days	Walker
Pyridine	110-86-1	Mice:B6C3F1	Gavage	14 days	Dunnick
Serotype 2 adeno-associated viral vector hAQP1 (rAAV2hAQP1)		Mice:BALB/c	Intraductal cannulation	13 weeks	Germolec
Usnea lichen		Rats:F344 (NCTR) Mice:B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Dosed-feed	2 weeks 90 days	Leakey



Study	CASRN	Species/Strain	Study Route	Length	Study Scientist
(+)-Usnic Acid	7562-61-0	Rats:F344 (NCTR) Mice:B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Dosed-feed	2 weeks 90 days	Leakey
Vincamine	1617-90-9	Rats:Harlan Sprague Dawley Mice:B6C3F1	Gavage	2 weeks range finding; 2 weeks	McIntyre

Table 21. Prechronic Toxicology/Carcinogenicity Studies Planned for FY 2013*

Study	CASRN	Species/Strain	Study Route	Length	Study Scientist
Formaldehyde	50-00-0	Mice:C57BL/6 Mice:C3B6F1-+/TRP53<TM1BRD> (NCTR) Mice:B6C3F1	Inhalation	2 weeks 8 weeks	Morgan

* Known test articles as of 10/1/2012. Others may be scheduled as protocols are finalized.

Table 22. Chronic Toxicity/Carcinogenicity Studies Ongoing During FY 2012

Study	CASRN	Species/Strain	Study Route	Length	Study Scientist
Aging cohort study		Mice:129S1/SvImJ Mice:B6C3F1 (Jackson) Mice:C3H/HeJ Mice:C57BL/6J (Jackson) Mice:CAST/EiJ (<i>M. m. castaneus</i>) Mice:NZO/HiLtJ Mice:PWK/PhJ Mice:WSB/EiJ (<i>M. m. domesticus</i>) Mice:A/J Mice:NOD. B10Sn-H2(b)/J	N/A	2 years	French
Antimony trioxide	1309-64-4	Rats:Wistar Han Mice:B6C3F1/N	Inhalation	2 years	Stout
3'-Azido-3'-deoxythymidine	30516-87-1	Mice:P53 +/- (FVB/N)	Gavage	45 weeks	Leakey
Bisphenol A	80-05-7	Rats:Sprague Dawley (NCTR)	Gavage	2 years	Delclos
Black cohosh	84776-26-1	Rats:Harlan Sprague Dawley, Mice:B6C3F1/N	Gavage	2 years	Mercado-Feliciano
Bromodichloroacetic acid (water disinfection byproducts)	71133-14-7	Rats:F344/NTac Mice:B6C3F1	Water	2 years	Hooth

Study	CASRN	Species/Strain	Study Route	Length	Study Scientist
2,3-Butanedione (Diacetyl)	431-03-8	Rats:Wistar Han Mice:B6C3F1/N	Inhalation	2 years	Morgan
Cell phone radiation (CDMA)		Rats:Harlan Sprague Dawley Mice:B6C3F1	Whole body exposure	2 years	Wyde
Cell phone radiation (GSM)		Rats:Harlan Sprague Dawley Mice:B6C3F1	Whole body exposure	2 years	Wyde
<i>p</i> -Chloro- <i>a,a,a</i> -trifluorotoluene	98-56-6	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Inhalation	2 years	Stout
CIMSTAR 3800 (metal working fluids)		Rats:Wistar Han Mice:B6C3F1/N	Inhalation	2 years	Morgan
Cobalt	7440-48-4	Rats:F344/NTac Mice:B6C3F1	Inhalation	2 years	Hooth
Dibutyl phthalate	84-74-2	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Feed	2 years	Blystone
Di(2-ethylhexyl) phthalate	117-81-7	Rats:Harlan Sprague Dawley	Feed	Perinatal and 2 years	Foster
Furan	110-00-9	Rats:F344 (NCTR)	Gavage	2 years	Beland
Glycidamide	5694-00-8	Rats:F344 (NCTR) Mice:B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Water	2 years	Beland
Green tea extract		Rats:Wistar Han Mice:B6C3F1	Gavage	2 years	Thakur
2-Hydroxy-4-methoxybenzophenone	131-57-7	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Feed	2 years	McIntyre
Indole-3-carbinol	700-06-1	Rats:Harlan Sprague Dawley Mice:B6C3F1	Gavage	2 years	Wyde
Insertional mutagenesis - definitive vector study		Mice:C57BL/6	Intravenous	14 months	Germolec
Pentabromodiphenyl oxide (technical) (DE 71)	32534-81-9	Rats:Wistar Han Mice:B6C3F1	Gavage	2 years	Dunnick
Perfluorooctanoic acid (PFOA)	335-67-1	Rats:Harlan Sprague Dawley	Feed	2 years	Blystone
Resveratrol	501-36-0	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Gavage	2 years	Germolec
Sodium tungstate, dihydrate	10213-10-2	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Water	2 years	Hooth
Tetrabromobisphenol A	79-94-7	Rats:Wistar Han Mice:B6C3F1/N	Gavage	2 years	Dunnick
Trim VX (metal working fluids)		Rats:Wistar Han Mice:B6C3F1/N	Inhalation	2 years	Morgan
Tripelennamine hydrochloride	154-69-8	Rats:F344/N Mice:B6C3F1	Feed	11 months	Jackson
tris(2-Chloroisopropyl) phosphate	13674-84-5	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Feed	2 years	Stout



Study	CASRN	Species/Strain	Study Route	Length	Study Scientist
Vinylidene chloride	75-35-4	Rats:F344/N Mice:B6C3F1	Inhalation	2 years	Wyde
Zinc carbonate, basic	5263-02-5	Rats:Harlan Sprague Dawley	Feed	2 years	Wyde

* Indicates study conducted using genetically-modified model

Table 23. Chronic Toxicity/Carcinogenicity Studies Initiated during FY 2012

Study	CASRN	Species/Strain	Study Route	Length	Study Scientist
Bisphenol A	80-05-7	Rats:Sprague Dawley (NCTR)	Gavage	2 years	Delclos
Black cohosh	84776-26-1	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Gavage	2 years	Mercado-Feliciano
Cell phone radiation (CDMA)		Rats:Harlan Sprague Dawley Mice:B6C3F1	Whole body exposure	2 years	Wyde
Cell phone radiation (GSM)		Rats:Harlan Sprague Dawley Mice:B6C3F1	Whole body exposure	2 years	Wyde
Resveratrol	501-36-0	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Gavage	2 years	Germolec
Sodium tungstate, dihydrate	10213-10-2	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Dosed-water	2 years	Hooth
tris(2-Chloroisopropyl) phosphate	13674-84-5	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Dosed-feed	2 years	Stout

v. Toxicogenomic Studies

The NTP is working to bring the latest toxicogenomics technology into its testing program to help revolutionize the way the program conducts its studies. Toxicogenomics examines how the entire genetic structure, or genome, is involved in an organism's response to environmental toxicants. Microarray, NextGen sequencing, proteomics, and metabolomics are among the advanced technologies that the NTP is using to study the way chemical exposures change the expression of genes, proteins, and metabolites in critical cells and tissues. Measuring genome-wide changes in affected tissues might be useful for identifying biomarkers of disease and exposure to toxic substances and for understanding individual genetic susceptibilities. Biomarkers that can be found in easily obtainable samples (blood and urine) could then be monitored in clinical studies. When biomarkers are validated, they can be repeatedly sampled during long-term NTP studies to determine whether chemical exposures can be detected or whether developing cancers will provide a genetic signature.

The NTP is interested in determining if analyzing the patterns of gene expression can provide indicators of toxicity at earlier time points and at lower doses than possible with traditional toxicology parameters. Evaluating patterns of gene expression may provide more than a link between genetics and morphology, because it is expected to provide insights into the pathogenesis of the disease and how different rodent models respond to toxicants. Some of the FY 2012 toxicogenomic studies have involved NextGen sequencing technologies that bring gene expression to a base-pair resolution of accuracy and increased sensitivity. In addition, metabolomics represents a promising area of study, as it can elucidate how chemicals affect metabolism within cells relative to changes in gene expression.

The NTP is currently evaluating study conditions that may contribute to gene expression (e.g., animal and tissue variability), best methods of tissue sampling, and establishing standards for conducting toxicogenomic studies under laboratory conditions. Planned or ongoing NTP toxicogenomic studies are listed in Table 24. More information can be found at <http://ntp.niehs.nih.gov/go/20358>.

Table 24. Toxicogenomic Studies (Planned or Ongoing)

Chemical	CASRN	Species/ Strain	Study Route	Study Length	Study Scientist
Aflatoxin B1	1162-65-8	Rats: F344/N	Feed	90 days	Merrick
Acetachlor	34256-82-1	Rats: Harlan Sprague Dawley	Gavage	4 days	DeVito
Toxicogenomic study of allylbenzene & propenylbenzene class flavor constituents Anethole Estragole Eugenol Isoeugenol Isosafrole Methyleugenol Myristicin Safrole	104-46-1 140-67-0 97-53-0 97-54-1 120-58-1 93-15-2 607-91-0 94-59-7	Rats: F344/N Tac	Gavage	90 days	Vallant
tert-Butylphenyl diphenyl phosphate	56803-37-3	Rats: Harlan Sprague Dawley	Gavage	4 days	Auerbach
N,N-Dimethyl- <i>p</i> -toluidine	99-97-8	Rats: F344/N	Gavage	5 and 90 days	Dunnick
Toxicogenomic estrous cycle study		Rats: Wistar Han	Not applicable	90 days	Auerbach
2-Ethylhexyl diphenyl phosphate	1241-94-7	Rats: Harlan Sprague Dawley	Gavage	4 days	Auerbach
Fusilazole	85509-19-9	Rats: Harlan Sprague Dawley	Gavage	4 days	DeVito
Isodecyl diphenyl phosphate	29761-21-5	Rats: Harlan Sprague Dawley	Gavage	4 days	Auerbach
Isopropylated phenol phosphate	68937-41-7	Rats: Harlan Sprague Dawley	Gavage	4 days	Auerbach



Chemical	CASRN	Species/ Strain	Study Route	Study Length	Study Scientist
Pentabromodiphenyl oxide (technical) (DE 71)	32534-81-9	Rats: Wistar Han	Gavage	Dams gestation day 6 through postnatal day 21 Pups postnatal day 12–90	Dunnick
Polybrominated diphenyl ether (PBDE) toxicogenomic study: BDE 153 BDE 99 BDE 47 DE 71 BDE Mixture	68631-49-2 60348-60-9 5436-43-1 32534-81-9 Mixtures	Rats: Wistar Han Mice: B6C3F1/N	Gavage	Dams gestation day 6 through postnatal day 21 Pups postnatal day 12–90	Dunnick
Simazine	122-34-9	Rats: Harlan Sprague Dawley	Gavage	4 days	DeVito
Tetrabromobisphenol A	79-94-7	Rats: Wistar Han	Gavage	90 days	Dunnick
<i>p</i> -Toluidine	106-49-0	Rats: F344/NTac	Gavage	5 days	Dunnick
Tricresyl phosphate	1330-78-5	Rats: Harlan Sprague Dawley	Gavage	4 days	Auerbach
Triphenyl phosphate	115-86-6	Rats: Harlan Sprague Dawley	Gavage	4 days	Auerbach
Microarray analysis studies: 2,3,7-Tribromodibenzo- <i>p</i> -dioxin 2,3,4,7,8-Pentabromodibenzofuran 1,2,3,7,8-Pentabromodibenzofuran 2,3,7,8-Tetrabromodibenzofuran 2,3-Dibromo-7,8-dichlorodibenzo- <i>p</i> -dioxin 2,3,4,7,8-Pentachlorodibenzofuran 1,2,3,7,8-Pentachlorodibenzofuran (PCDF)	51974-40-4 13116-92-2 107555-93-1 67733-57-7 50585-40-5 57117-31-4 57117-41-6	B6C3F1 mouse	Gavage	Single dose–3 days	DeVito

C. NTP Research

In addition to the testing activities, a variety of research projects within the NTP are underway at NIEHS, NCTR, and NIOSH. The following NIEHS/Division of the NTP (DNTP) branches are actively involved with NTP research activities: Biomolecular Screening Branch (led by Raymond Tice, PhD), Cellular and Molecular Pathology Branch (led by Robert Sills, DVM, PhD), NTP Laboratory (led by Mike Waalkes, PhD), Program Operations Branch (led by Michelle Hooth, PhD, DABT), and Toxicology Branch (led by Paul Foster, PhD).

The NTP Laboratory within the NIEHS/DNTP conducts in-house, agent-specific, targeted research related to the development and application of modern toxicology and molecular biology tools. These tools are used in the evaluation of specific substances of concern to NTP, issues of central importance to NTP programs, or methods development to advance the NTP mission. The NTP Laboratory also focuses on the study of the developmental origins of adult diseases. Table 25 includes projects in the NTP laboratory in FY 2012.

Table 25. NIEHS/NTP Laboratory Projects in FY 2012

NIEHS/NTP Project [Study Scientist]	Objective and/or Project Summary
Development of in vitro models of metal carcinogenesis [Waalkes]	To develop in vitro cell transformation models with target relevant cells using arsenic and cadmium.
Epigenetics in malignant transformation [Waalkes, Thayer]	To assess the epigenome of a series of isogenic cell lines transformed by genotoxic or epigenetic carcinogens and perform gene specific methylation analyses.
Formaldehyde in p53 knockout mice [Morgan]	To define the role of formaldehyde inhalation and hematopoietic tumor induction.
Formaldehyde-induced transformation of human myeloid progenitor cells [Waalkes]	To perform a proof of concept study, in vitro formaldehyde induced malignant transformation in hematopoietic stem cells. Companion study to the p53 study mentioned above.
Indium-tin-oxide and indium compounds [Morgan]	To perform various in vivo inhalation or in vitro toxicity studies.
Isoflavones and soy formula as estrogens [Fenton, Howdeshell]	To define estrogenicity of soy formula isoflavones in mice.
Japan arsenic poisoning human study; Developmental basis of human disease [Waalkes]	To determine the genomics of response to early life arsenic exposure in survivors of a baby food poisoning event in Japan in the mid-1950s from a population now getting excess cancer typical for arsenic exposure. Human proof of the developmental basis of adult disease.
"Metalloestrogens" and uterine/breast response [Dixon, Waalkes, Fenton]	To re-test the ability of reported "metalloestrogens" like cadmium and arsenic to cause ER stimulation in the uterus as a mode of action towards cancer development.
Method for assessing biological impact of metal particle dissolution [Morgan, Waalkes]	(1) To develop in vitro trans-well method with metal particles and macrophages in one well and cells of interest (eg., lung epithelium) in the other; and (2) to define various types of macrophages ability to release different metals from different particles.
Methods in histopathology of mammary gland development [Fenton]	To develop standardized methods to quantitatively assess chemical insult to mammary gland development.
Refinement of developmental neurotoxicology methods [Harry]	To improve methods for various efforts including genetic signatures, stem cells, inflammation, behavior, conditioning.
Role of MicroRNAs in malignant transformation [Waalkes]	To study genes of interest involved with the epigenetics of malignant transformation using in vitro human model systems of carcinogenesis. MicroRNAs (miRNAs) are thought to be a key epigenetic or post-transcriptional gene express control mechanism.
Role of stem cells in cancer associated with formaldehyde exposure [Waalkes]	To define the potential role of stem cells in relocating in hematopoietic cancers in mice.
Stem cells in toxicology and carcinogenesis [Waalkes]	To perform various in vitro studies on the role of stem cells and cancer stem cells in carcinogenesis and the developmental basis of adult disease.



NIEHS/NTP Project [Study Scientist]	Objective and/or Project Summary
Studies on estrogen receptor in vitro [Waalkes]	To study mammary cells and so called “metalloestrogens”.
Toxicants and mammary gland development [Fenton]	To determine the effects of different toxicants including atrazine on mammary gland development in rats and mice

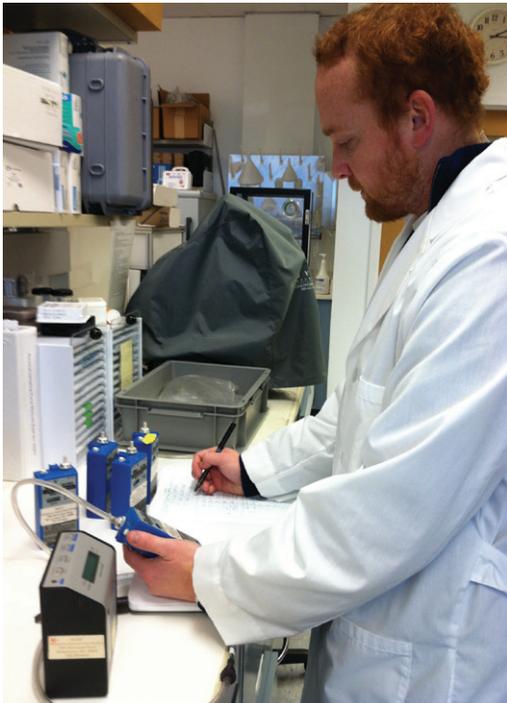
Genetic and epigenetic differences between individuals within the human population are believed to be the basis for individual susceptibility to environmental stressors. Environmental and drug safety assessments are currently conducted with a small number of commonly used animal models that have limited genetic diversity and are insufficient to evaluate the influence of individual genetic differences on chemical and drug toxicity. These models are of limited value in extrapolating results to human toxicity and disease, and this program works toward developing models that are more appropriate. The NIEHS/DNTP Biomolecular Screening Branch is conducting several in-house projects aimed at understanding individual susceptibility.

Table 26. NIEHS/NTP Host Susceptibility Projects in FY 2012

NIEHS/NTP Project [Study Scientist]	Objective and/or Project Summary
Aging cohort [French]	Reference data is being collected on 10 inbred strains of mice including classical and wild-derived inbred strains representing the greatest degree of genetic diversity in the mouse genome that is known at the present. This data includes survival rates, spontaneous disease incidence, histopathology, hematology, clinical chemistry, quantitative trait loci, and behavioral observations, as well as tissue/fluids collection for future genetic/genomic/metabolomic analysis. See Table 22 for more details.
Diversity outbred mice and population based models for toxicology and disease [French]	Research to determine the utility of diversity outbred mice for the NTP research and testing program using 28-day old diversity outbred male mice exposed to inhaled benzene (0, 1, 10, or 100 ppm; 75 mice/group) for 5 days per week for 4 weeks in two independent studies. Differences in the clearance of the chemical and its metabolites suggest significant population differences for toxicity.
Ionizing radiation [French]	Development of tumor suppressor gene deficient mice for predicting carcinogenicity, determining the mode of action, the presumptive risk of environmental exposures to humans, and the identification of causally related genes and the specific functional allelic and copy number variants within inbred strains of mice that modify carcinogen potency. Ongoing studies are to define system level differences in toxicogenomics associated with differences in strain susceptibilities and to better define a short-term cancer bioassay for research and testing.
Mouse methylome project [Merrick, Wade]	Male and female C57BL/6N mice were crossed with C3H/HeN mice, and five tissues (brain, liver, cardiac and skeletal muscle, brown and white fat, epididymal sperm) from the first generation offspring were collected at the average age mice would start an NTP subchronic toxicity study and flash-frozen for DNA/RNA isolation and liver sequencing. Progress in FY 2012 involves completion of transcript expression levels of both parental strains and the resulting first generation offspring by RNA high-throughput sequencing technologies and DNA sequencing data analyses.

i. Assessing Exposure to Substances in the Workplace

In following its mandate to protect workers' health and safety, NIOSH is carrying out research projects for the NTP to assess the effects of exposure to substances through an interagency agreement with NIEHS (see page 16). Setting priorities in occupational toxicological research is based upon several sources of information that are developed and maintained by NIOSH. These include health hazard evaluations, industry-wide studies, gaps in knowledge identified while developing criteria for recommended standards or criteria documents, current intelligence bulletins, hazard reviews or alerts, other technical reports, and information profiles on chemical hazards. Table 27 lists NIOSH/NTP projects in FY 2012.



Calibration of air sampling pumps after field sample collection at Health Effects Laboratory Division of NIOSH.



NIOSH Industrial hygienist conducting a nanomaterial exposure assessment.



Table 27. NIOSH/NTP Research Projects FY 2012

NIOSH/NTP Projects [Project Officer]	Objective and/or Summary
Biomonitoring, Biomarker Development and Health Assessment	
Reproductive health assessment of male workers [Schrader]	To evaluate reproductive health hazards using a health profile consisting of biomarkers for assessing male fecundity. Current efforts will focus on completing the Longitudinal Investigation of Fertility and the Environment (LIFE) project, a collaborative effort between NIOSH and the NICHD/NIH. This work includes development of new biomarkers to include in the male reproductive health profile.
Immunochemical biological monitoring for occupational exposure and disease [Striley]	To evaluate industrial chemicals with known acute and chronic toxicities, which present a significant exposure risk for workers. Biological monitoring can assess exposure by analyzing acute and latent metabolites in various biological media. The goal of this project is to develop low-cost, rapid immunochemical and analytical chemistry biomonitoring methods that will be used to identify exposures and evaluate potential interventions. Concurrent with development of exposure assessment methods, this project will identify and develop new multiplex immunochemical methods to evaluate biomarkers of occupational illness or subclinical signs of occupational illness. Biological monitoring, through the validation and development of new methods, is a powerful tool for reducing risk and creating safer work practices.
UV native fluorescence-based monitor for workplace exposures [Snawder]	To develop and evaluate a readily adaptable, next generation, direct reading, personal monitors for use in measuring worker exposure to a wide variety of chemicals including naphthalene and components of asphalt fume. The development of personal monitors for volatile and semi-volatile workplace chemicals will be helpful in rapidly assessing chemical exposure and will result in more realistic occupational exposure assessments and allow for rapid interventions leading to reduced worker exposures and thus preventing occupational illness and disease.
Workplace exposure, inflammation, and cardiovascular toxicity [Erdely]	To investigate the role of ultrafine/nanoparticle-induced cardiopulmonary inflammation and to identify specific markers of lung inflammation that directly correlate to systemic effects. This laboratory-based research will evaluate novel molecular mechanisms involved in the link between occupational exposures to ultrafine/nanosize particulates and the development of cardiovascular diseases. Planned studies will help to identify potential risk factors, biomarkers, and specific targets for prevention and therapeutic intervention of occupational-related cardiovascular diseases.
Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS)-induced oxidative stress [Qian]	To investigate whether exposure to PFOA and PFOS induces an oxidative stress response in a mouse model and in human cells. PFOA and PFOS are widely known man-made fluorocarbon-based acids, which have been used in various industrial processes in the aircraft, automotive, chemical, building material, and personal care products industries. They are non-biodegradable and persistent in the human body and environment. Surveillance data suggests that PFOA and PFOS may cause adverse health effects, but no consistent association between exposure and health effects has been proven.
Industry-wide studies of workers exposed to carbon nanotubes and nanofibers [Dahm]	To collect exposure data from participating pilot-scale or full-scale manufacturers or users of single-walled or multi-walled carbon nanotubes and carbon nanofibers. A study of biomarkers of early pulmonary, cardiovascular, and carcinogenic effect will be carried out among workers at these facilities.
Environmental Monitoring	
Analytical research and development infrastructure [Streicher]	To provide for the administrative needs and analytical instrumentation repair and maintenance in support of Chemical Exposure and Monitoring Branch chemists conducting research on sampling and analytical methods development for workplace chemicals. New methods needed to assess chemicals being investigated as part of the NIOSH/NTP exposure assessment interagency agreement are developed in this project.

NIOSH/NTP Projects [Project Officer]	Objective and/or Summary
Diacetyl exposure assessment [Streicher]	To develop and evaluate sampling and analytical methods for diacetyl and other flavoring compounds to enable accurate exposure assessment and evaluation of the effectiveness of control technology. Two sampling and analytical methods are being investigated for measurement of specific flavoring compounds, most notably diacetyl and 2, 3-pentanedione in airborne particles and bulk powders. Finally, broader gas chromatography-mass spectrometry method(s) will be developed for a range of compounds present in flavorings.
Chemical exposure monitoring with indoor positioning [Brown]	To investigate a direct reading exposure method that uses a personal photo ionization detector chemical monitor with telemetry and an indoor positioning system to provide remote monitoring of a worker's exposure to volatile organic chemical (VOC)s with position and time. The personal monitor continuously samples and analyzes the workers breathing zone air for VOCs while recording their position and time of exposure. Indoor positioning is accomplished using a radio transmitter attached to the personal monitor and receivers place in the ceiling corners of the room. The positioning receivers communicate with each other and a remote laptop using wireless local area network technology. The remote laptop calculates and visualizes the worker position and exposure level. Once developed, this technology will be applied to analyze workplace exposures to diacetyl.
Exposure Assessment	
Exposure assessment for toxicologically-important chemicals [Curwin]	To characterize workplace exposures to (1) welding fumes with emphasis on manganese, (2) indium and indium compounds, (3) diacetyl, (4) 2-methoxy-4-nitroaniline, and (5) 2', 2'''-Dithiobisbenzanilide. A new study will investigate worker exposures to Bisphenol A (BPA). These chemicals have been nominated by various groups to the National Toxicology Program. We will identify possible candidate industries, labor unions, workplaces, and uses and users; determine if there is relevance for occupational health; estimate number of workers exposed; and perform limited workplace exposure sampling.
Industry-wide Studies Branch research, development, and planning [Whelan]	To support strategic planning and feasibility studies of high priority/emerging problems in occupational health.
Nanotechnology field evaluations [Geraci]	To obtain information from as many different facilities as possible, in the field, on the nature of engineered nanomaterials; the processes involved in their manufacture and use; potential worker exposures; and work practices and control procedures used where nanomaterials are produced or used. As toxicology studies identify the biologic hazards of nanomaterial, it is important to gain a better understanding of actual workplace exposures.
Immunotoxicity and Immunology	
Immunotoxicological evaluation of occupational chemicals [Anderson]	To identify occupational and environmental chemical hazards and evaluate immune function and mechanism associated with exposure. The Immunotoxicology and Hazard Identification Lab will achieve this goal through both individual projects and collaborations. This research will contribute to increased identification of immunological hazards encountered in the workplace. Further evaluation of these compounds will allow for better risk assessment which will ultimately establish occupational exposure limits.
Evaluation of perfluoralkyl acids immunotoxicity [Franko]	To investigate the immunotoxicity of PFOA, no longer used in manufacturing, but still persistent in the environment, which has been shown in a murine model to be both immunosuppressive and to have a potential role in asthma and allergy. Due to the potential health effects linked to PFOA exposure, replacement perfluoralkyl acids are now being used in the manufacturing process but little is known about what effects of these compounds will have on immune function. This project will evaluate the immunotoxic effects associated with individual perfluoralkyl acids that are still in use, and to investigate the mechanism mediating the identified immunological alterations associated with PFOA exposure.



NIOSH/NTP Projects [Project Officer]	Objective and/or Summary
Airway fungal exposure and allergic sensitization in mice [Templeton]	To compare the immunological health effects of lung exposure to fungal spores or to hyphal fragment preparations. Agriculture as well as construction and remediation workers are exposed to elevated levels of fungi and can experience rhinitis, respiratory allergic symptoms and/or asthma as a result of their exposure. This project will have two major areas of study; (1) determination of the health effects following aspiration of hyphal fragments from <i>Stachybotrys chartarum</i> and <i>Alternaria alternata</i> in the absence of intact spores in mice, and (2) comparison of the ability of aspirated spores or hyphal suspensions from <i>Aspergillus</i> spp, <i>S. chartarum</i> , and <i>A. alternata</i> to exacerbate respiratory allergy to ovalbumin.
Immune and inflammatory aspects of occupational rhinitis [Johnson]	To investigate occupational asthma in workers who often exhibit concurrent occupational rhinitis with the likelihood that rhinitis developed first. Thus, understanding the mechanisms of occupational rhinitis is an important area of research in occupational safety, health and medicine. A combined study design utilizing human and animal research will be employed to identify the orthologously conserved pathways and gene networks that characterize the pathobiology of occupational rhinitis induced by diisocyanates. The outcomes of this research will benefit occupational safety and health through improved diagnosis and prevention of allergic airways disease caused by diisocyanates.
Cutaneous bioactivation of xenobiotics: hapten vs. prohaptent [Siegel]	To develop an in vivo model of allergic skin sensitization that can discriminate between chemicals requiring metabolic activation for sensitization (prohaptens) and those that can sensitize without biological activation (haptens). The model will involve the dermal application of various pharmacological inhibitors of the cytochrome P450 pathway prior to performing either the local lymph node assay (LLNA) or/and mouse ear swelling test. Selective inhibition of the cytochrome P450 pathway should distinguish between direct acting haptens and metabolically activated pro-haptens. Validation of the models will be done using known direct acting haptens and pro-haptens. Successful development of these models will produce data that strengthens <i>in silico</i> hazard predictive models and allows for substitution or modification of allergenic chemicals and drugs.
Identification of occupational allergens [Beezhold]	To identify exposures to substances that can cause inflammatory or immune reactions in certain work environments. These exposures are important causes of occupational lung diseases such as asthma and allergic alveolitis. This project is intended to address these concerns through the development of improved techniques for the detection of such immune reactions before adverse clinical outcomes occur, and through the development of improved techniques for the detection and identification of inciting occupational agents. The project will involve the analyses of clinical samples, environmental bulk samples, and environmental aerosol samples. Successful completion of these investigations should lead to the development of effective prevention strategies for occupational allergies and asthma.
Genetics	
Genetics in occupational diseases [Yucesoy]	To investigate susceptibility gene variants that contribute to the development and severity of occupational irritant contact dermatitis and asthma using high-density and high-throughput genotyping platforms. Previous and on-going studies in our laboratory showed that cytokine polymorphisms have a major influence on silicosis, dementia, and accelerated decline in lung function and vaccine efficacy. Understanding the genetic contribution to the development, progression and outcomes of complex occupational diseases will help improve the accuracy of risk assessment and improve safe exposure levels for genetically susceptible groups in the workforce.
Genetic fingerprint of mouse lung cancer [Reynolds]	To determine if there are different carcinogen-specific chromosomal (genetic) markers in spontaneously-occurring and chemically-induced mouse lung adenocarcinomas using in vitro and in vivo animal models. Mice were exposed by inhalation to vanadium pentoxide, nickel oxide or cumene (a benzene derivative). Workers in the construction and manufacturing sectors are exposed to these compounds. We are also planning to analyze mouse lung tumors induced by single-wall carbon nanotubes. If these experiments are successful we plan to extend these findings to tumors from occupationally-exposed human populations. Results from these studies will be used to establish biomarkers for early detection and therapeutic intervention of lung cancer in worker populations.

ii. Comprehensive Assessment of Occupationally-Relevant Exposures

The NIEHS is coordinating an NTP effort with NIOSH to better understand worker exposures, identify occupational health research gaps, and educate workers. The NIEHS/NIOSH interagency agreement supports these projects. Current efforts listed in Table 28 address worker exposures to welding fumes, nano-sized materials, food flavorings, bisphenol A, indium compounds, and other industrial chemicals.

Table 28. NIEHS/NIOSH Interagency Agreement on Occupationally Relevant Exposures in FY 2012

NIEHS/NIOSH Study [Study Scientist]	Objective and/or Rationale
Administrative support [Whelan]	To enable NIOSH scientists to (1) participate in review and oversight of NTP activities and (2) attend NTP-related meetings in Research Triangle Park, NC and Washington, DC.
Assess the feasibility of an occupational exposure assessment of welding fume with emphasis on manganese compounds [Hanley]	(1) To identify industries (e.g., construction, shipbuilding, railroad, and manufacturing), companies, and/or unions involved in welding operations where the potential for substantial manganese exposure exists, for exposure assessments; (2) to develop methods to identify specific manganese compounds, different valence states, and potential solubility contained within various welding fumes matrices; and (3) to characterize welding fume exposures based on welding-associated jobs, tasks, and processes.
Exposure assessment of diacetyl and other flavorings in food production industries [Curwin]	(1) To characterize workplace inhalation exposures to diacetyl in food production industries that use food flavorings; (2) to document high-exposure activities and processes in the flavored food production industries; (3) to identify work practices and procedures that affect exposure; (4) to document engineering controls; and (5) to field test novel techniques for both gravimetric and volatile sampling.
Exposure assessment of dithiobisbenzanilide in a manufacturing setting [Wurzelbacher]	(1) To identify worker populations at increased risk of inhalation and surface exposure to dithiobisbenzanilide during a manufacturing process; (2) to develop a NIOSH analytical method for quantitatively assessing dithiobisbenzanilide airborne particulate and surface exposures; and (3) to characterize industry-wide occupational exposures, including total number of workers, and evaluate patterns of exposure to dithiobisbenzanilide.
A pilot exposure assessment for 2-methoxy-4-nitroaniline in a manufacturing setting [Wurzelbacher]	(1) To identify worker populations at increased risk of inhalation and surface exposure to 2-methoxy-4-nitroaniline during a manufacturing process; (2) to develop a NIOSH analytical method for quantitatively assessing 2-methoxy-4-nitroaniline airborne particulate and surface exposures; and (3) to characterize industry-wide occupational exposures, including total number of workers, and evaluate patterns of exposure to 2-methoxy-4-nitroaniline.
Assessment of use of indium and indium compounds in the workplace [Hines]	(1) To contact and visit companies to determine indium materials being used, jobs and processes with potential indium exposure, exposure controls, and indium use trends and (2) to conduct preliminary sampling for indium, if possible.
Exposure assessment of engineered nanoparticles [Geraci]	(1) To identify workplaces engaged in the synthesis, manufacture, and use of engineered nanomaterials and (2) to characterize workplace exposure to selected engineered nanoparticles.
Exposure assessment of 1-chloro-4-(trifluoromethyl) benzene (PCBTF) [Harper]	(1) To identify worker populations at elevated risk of inhalation and surface exposure to PCBTF during manufacturing processes; (2) to update a previously published analytical method for quantitatively assessing PCBTF airborne vapors and surface exposures to allow the use of capillary column chromatography; and (3) to characterize industry-wide occupational exposures, including total number of workers, and evaluate patterns of exposure to PCBTF.



NIEHS/NIOSH Study [Study Scientist]	Objective and/or Rationale
A pilot exposure assessment for ethylene glycol 2-ethylhexyl ether (EGEHE) in a manufacturing setting [Harper]	(1) To identify worker populations at elevated risk of inhalation and surface exposure to EGEHE during manufacturing processes; (2) to develop an analytical method for quantitatively assessing EGEHE airborne aerosols, vapors, and surface contamination; and (3) to characterize industry-wide occupational exposures, including total number of workers, and evaluate patterns of exposure to EGEHE.
Durability of nanoscale cellulose fibers in artificial human lung fluids [Stefaniak]	To investigate the in vitro durability of nanocellulose materials in artificial lung fluids. Data generated from this study will be used to inform larger and more costly in vivo inhalation studies.
Exposure characterization and reproductive health of men working with bisphenol A in the United States [Hines]	(1) To determine bisphenol A (BPA) usage in industry, e.g., which industries and jobs use BPA and which tasks are associated with exposure; (2) to develop air and wipe sampling methods for BPA using liquid chromatography mass spectrometry and liquid chromatography with UV detection; (3) to assess exposure to BPA among workers in these industries through air, wipe, and urine sample collection. If worker exposures are confirmed (4) to assess the reproductive health of men exposed to BPA in the workplace and (5) to determine if there is a relationship between occupational exposure to BPA and reproductive health.
Industry-wide exposure assessment study of workers exposed to carbon nanotubes and nanofibers [Dahm]	(1) To establish sampling and analysis protocols for detection and quantification of carbon nanotubes and nanofibers; (2) Recruit companies and conduct exposure assessments for carbon nanotubes and nanofibers in a representative sample of United States workplaces; (3) Document high exposure tasks and processes as well as collect full work shift, personal breathing zone samples; (4) Refine exposure assessment methods which include lowering the detection limit for elemental carbon (NMAM 5040), and evaluating higher-flow, respirable cyclones to assess health-relevant exposures.

iii. Immunotoxicology Research

The NIEHS/NIOSH interagency agreement provides support of NTP hazard identification activities aimed at preventing diseases or adverse effects caused by environmental exposure to chemical or physical agents. These cooperative studies continue to improve risk assessment by measuring what constitutes an adverse health effect on the immune system in humans. The studies, listed in Table 29, evaluate unique cohorts of individuals from professions associated with immune-mediated occupational diseases.

Table 29. NIEHS/NIOSH Interagency Agreement on Immunotoxicology Studies, FY 2012

NIEHS/NIOSH Study [Study Scientist]	Objective and/or Rationale
NIEHS agricultural pesticide study [Beezhold]	In support of the NIEHS Agricultural Health Study, our laboratory has completed screening 1454 farmers serum for total immunoglobulin E (IgE) and mold mix specific IgE using the Phadia Immunocap assay. Those farmers who were mold mix positive have recently been tested against a 10 mold specific IgE panel (n = 126). Our laboratory has completed this component of the study and the compiled data has been forwarded to NIEHS. In further support of the NIEHS Agricultural Health Study, our laboratory has been requested to screen an additional 640 farmers' sera samples for total and specific IgEs. Total IgE and mold mix specific IgE will be determined using Phadia ImmunoCap assays as previously described. The data derived from this analysis will be sent to the NIEHS and prepared for publication in an allergy journal.
A marker for <i>Aspergillus terreus</i> exposure [Beezhold]	To develop new and improved methods for detecting fungal exposure. In this project the emerging opportunistic fungal pathogen, <i>Aspergillus terreus</i> , has been used as a model fungal species. Terrelysin, a cytolyisin and potential biomarker of fungal infection, was characterized and a recombinant protein produced. The recombinant terrelysin was then used to immunize mice to produce terrelysin specific monoclonal antibodies. Seven specific monoclonal antibodies were produced and used to characterize the production of terrelysin. Monoclonal antibodies binding sites are currently being determined in epitope mapping experiments. Several manuscripts have been recently published that report these findings. The development of a sensitive immunoassay that can be used in the serological detection of this biomarker is anticipated.
Animal model for airway exposure to dry fungal aerosols [Green]	To develop a murine model of dry fungal exposure to better mimic natural human exposures to fungi. In collaboration with aerosol scientists at NIOSH, an acoustical generation system has been developed. In preliminary experiments, histopathology and bronchoalveolar lavage fluid analysis demonstrated pulmonary deposition of conidia following dry fungal bioaerosol exposure. The system has been optimized for the generation of fungal spores. Once the system has been fully characterized, experiments are planned to further characterize the immune responses associated with various fungal species that frequently colonize water-damaged buildings or are occupationally relevant.
Characterization of fungal diversity in the indoor built environment [Green]	To investigate and characterize the diversity of fungal bioaerosols in the indoor built environment using large-scale ribosomal (rRNA) sequencing in collaboration with the Kansas City Safe and Healthy Homes Partnership Project. In preliminary studies, various methods of extraction were compared and tested on occupational dust samples. A standardized extraction method was then used on 30 air and dust samples derived from homes participating in the project. Results from this analysis have been compiled and provide detailed insight into the diversity of previously overlooked fungal bioaerosol sources in the Kansas City Environment. Future studies in collaboration with Assured Bio Inc. are planned for 2013. These studies aim to further evaluate indoor environments using large scale rRNA approaches from samples collected in contaminated and non-contaminated Atlanta, Georgia homes. In addition, fungal species richness identified in this analysis will be directly compared to commercially available methods of fungal analysis including the Environmental Relative Mold Index.
The role of genetic variation in environmental and occupational diseases - irritant contact dermatitis [Yucesoy]	(1) To investigate whether 24-hour irritant patch test is predictive of occupational hand dermatitis caused by high exposure to hand washing in health care workers; and (2) to investigate association between genetic variations in specific candidate genes (with emphasis on variants of cytokines, major histocompatibility complex region, antioxidant enzyme genes and genes related to skin barrier integrity) and irritation threshold levels of the subjects with development of irritant contact dermatitis. This study is in collaboration with Case Western Reserve and West Virginia Universities. Subject recruitment and genotyping have been completed. Data analyses have been initiated.



NIEHS/NIOSH Study [Study Scientist]	Objective and/or Rationale
The role of genetic variation in environmental and occupational diseases - allergic contact dermatitis [Yucesoy]	(1) To investigate genetic factors in individuals predisposed to develop allergic contact dermatitis, specifically induced by nickel; and (2) to investigate genetic factors involved in the development of allergic contact dermatitis in individuals sensitized to weak allergens, individuals sensitized to allergens that require metabolism in the skin, and individuals who react to more than three allergens of the standard screening series. This study is in collaboration with Case Western Reserve University and Dartmouth-Hitchcock Medical Center. Subject enrollment and sample processing are currently underway.
The role of genetic variation in environmental and occupational diseases – occupational asthma [Yucesoy]	(1) To investigate whether genetic variations in specific candidate genes (e.g., cytokine, major histocompatibility complex region, antioxidant enzyme genes) are associated with asthma induced by diisocyanates; and (2) to investigate potential associations between genetic variations in candidate genes and occupational asthma caused by low molecular weight agents. This project is in collaboration with the Universities of Montreal and Cincinnati.
The role of genetic variation in environmental and occupational diseases – chronic beryllium disease [Yucesoy]	To investigate the contribution of genetic variations in the major histocompatibility complex region to the development of beryllium sensitization and chronic beryllium disease. This study is in collaboration with National Jewish Medical and Research Center.
Investigations into health effects caused by exposure to indoor air reaction products (supportive animal studies) [Wells, Anderson]	(1) To identify and measure the reaction products of gas-phase compounds present in the indoor environment, especially oxygenated organics; (2) further develop and validate a novel in vitro exposure methods utilizing realistic indoor chemistry scenarios to expose cells and tissues to these indoor air reaction products; (3) complete both in vitro and in vivo assays to assess adverse health effects caused by indoor air reaction products; and (4) further investigate the role of structurally similar indoor air chemicals present in mixtures in the indoor environment.
Diisocyanate monoclonal antibody production and characterization (improved methods) [Siegel]	(1) To develop monoclonal antibodies that recognize methylene diphenyldiisocyanate conjugated protein as a potential biomonitoring and research tool; (2) to test the specificity of the methylene diphenyldiisocyanate monoclonal antibodies; and (3) to evaluate the monoclonal antibodies for potential use in immunoassay-based biomonitoring.
Alternative methods for chemical allergen identification and assessment [Siegel]	(1) To develop an amine based probe for kinetic assessment of chemical binding (haptentation) that will complement the thiol based probe previously reported by our laboratory; (2) to assess potential for inclusion of a metabolic activation step in our kinetic based assays for identification of prohaptens; and (3) to expand the compilation of chemical allergens assessed by kinetic electrophilic reactivity analyses for comparison to reported allergenic potencies (murine local lymph node assay exposure concentration values).
Analysis of mycotoxins in dust samples from a water-damaged building [Park]	To apply and modify newer, chemical-based methods, including the use of gas chromatography-tandem mass spectrometry (GC-MSMS) and ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MSMS), for measuring microbial cell-wall components and toxins, the methods of which are still being developed and are not readily available. This will quantify fungal toxins in environmental samples from water damaged buildings for which we have existing data on other fungal and bacterial components as well as health questionnaire data on building occupants. Especially, the UPLC-MSMS technology does not require significant sample preparation, and thus the technology enables us to develop rapid and robust methods to screen multiple mycotoxins in samples. Specific aims of the study are: (1) develop robust, rapid, and cost-effective methods for simultaneous determination of multiple mycotoxins in environmental samples in a single analysis using UPLC-MSMS; and (2) apply the developed UPLC-MSMS methods to analyze archived dust samples from water-damaged buildings collected in previous projects for characterizing exposure profiles to multiple mycotoxins.

iv. NTP Research in Partnership with NCTR

The National Center for Toxicological Research (NCTR), in partnership with researchers from elsewhere in FDA, other government agencies, academia, and industry, provides innovative technology, methods development, vital scientific training, and technical expertise. The unique scientific expertise of NCTR is critical in supporting FDA product centers and their regulatory roles. These NCTR/NTP studies, funded by NCTR voluntary allocations, are listed in Table 30. Table 31 lists projects that are funded through FDA and NTP interagency agreements.

Table 30. NCTR/NTP Projects in FY 2012	
NCTR/NTP Project [Study Scientist]	Objective and/or Project Summary
Global and locus-specific DNA hypomethylation: a common mechanism involved in genotoxic and non-genotoxic rat hepatocarcinogenesis [Pogribny]	(1) To determine if the temporal alterations in genomic methylation profile in preneoplastic liver tissue observed in the folate/methyl-deficient model of rat endogenous hepatocarcinogenesis also occur in other carcinogenesis models, (2) to identify genes that are consistently up-regulated or down-regulated in target tissue during the promotion stage of carcinogenesis, and (3) to evaluate whether or not the global and locus-specific DNA hypomethylation, along with aberrant expression of related genes and changes in chromatin conformation, is specific only to target tissues and may be used for early detection of chemicals with carcinogenic potential.
Relationship between liver epigenetic phenotype and susceptibility to nonalcoholic steatohepatitis (NASH)-induced hepatocarcinogenesis in mice [Pogribny]	(1) To determine the role of epigenetic dysregulation in the etiology and pathogenesis of dietary NASH-induced hepatocarcinogenesis in mice, (2) to determine whether or not interstrain-specific susceptibility of mice to NASH-induced hepatocarcinogenesis is associated with differences in individual hepatic epigenetic phenotypes, (3) to determine the role of epigenetic dysregulation in the etiology and pathogenesis of NASH-induced hepatocarcinogenesis in mice induced by tamoxifen administration, and (4) to determine whether or not aberrant epigenetic markers can be used as targets for prevention of NASH-induced hepatocarcinogenesis in mice.
Biologically-based, dose-response (BBDR) modeling for the thyroid axis in the fetus and neonate [Fisher]	(1) To develop biologically-based, dose-response models for the hypothalamic-pituitary-thyroid axis in the developing rat and human as a function of iodide status; (2) to interface the BBDR hypothalamic-pituitary-thyroid models with physiologically-based pharmacokinetic or toxicokinetic models for thyroid active chemicals to predicted conditions (iodide status and chemical exposure) for which brain thyroid hormone homeostasis cannot be maintained in the fetus and neonate; and (3) to use the models to evaluate the possible influence of population exposures to thyroid active chemicals on fetal and neonatal thyroid status as a function of iodide intake.
Development of methods for evaluating DNA damage using single cell gel electrophoresis (comet assay) in rodents [Manjanatha]	To evaluate and establish methods and conditions that enhances the sensitivity and reproducibility of the in vivo alkaline-comet assay for use in preclinical-hazard identification and genotoxicity testing of food ingredients and chemicals for regulatory purposes.
Biomarkers of liver toxicity [Mendrick]	(1) To discover biomarkers of hepatotoxicity in preclinical studies that are predictive of adverse effects in humans, for eventual evaluation of predictivity in rodent assays (preclinical studies); and (2) qualification of the discovered biomarkers.
Development of predictive mitochondrial biomarkers for drug-induced cardiotoxicity using a system biology approach [Desai]	(1) To determine doxorubicin-induced changes in plasma troponin T, creatinine kinase MB, and cardioplipin levels in rats, and to correlate with non-invasive measurements of heart rate, heart rate variability, and electrocardiogram; (2) to determine morphological changes in cardiac mitochondria in left ventricular region by electron microscopy; (3) to quantify analyte profiling in the heart using transcriptional profiling of approximately 906 mitochondria-related genes using MitoChip (genomics); (4) to conduct protein profiling by 2D-high performance liquid chromatography/tandem mass spectrometry (proteomics); and (5) to measure endogenous metabolites (creatinine, creatine, lactate, Krebs cycle intermediates, small ketone bodies in plasma) by nuclear magnetic resonance imaging and mass spectrometry (metabolomics).



NCTR/NTP Project [Study Scientist]	Objective and/or Project Summary
<p>Development and application of a mitochondria-specific gene array (Mitochip) for the investigation of pre-clinical and clinical predictive biomarkers of toxicity.</p> <p>[Desai]</p>	<p>(1) To develop MitoChip for various mammalian species, including rat, non-human primate, and human; (2) to investigate the mechanisms of drug toxicities and degenerative diseases associated with mitochondrial dysfunction in different mammalian species by conducting transcriptional profiling of mitochondria-related genes; and (3) to characterize species-specific transcriptional profiles to predict risk of drug toxicity or disease onset in different mammalian species.</p>
<p>Validation of recently established gpt-delta mice at NCTR</p> <p>[Manjanatha]</p>	<p>(1) To dose gpt-delta transgenic mice with low, intermediate, or high doses of cyclophosphamide and bleomycin and 100 mg/kg ethylnitrosourea (cumulative dose) as a positive controls for induction of mutations in the transgenes gpt, red and gam genes (spi-selection), and (2) characterize recovered mutants from target tissues for generation of gpt and spi mutational spectra, and (3) to analyze red blood cells for phosphatidylinositol glycan complementation group A (Pig-A) mutant frequencies and erythrocytes for micronucleus frequencies.</p>
<p>Physiologically-based pharmacokinetic models for BPA</p> <p>[Fisher]</p>	<p>1) To create physiologically-based pharmacokinetic models for BPA in three species of adult, neonatal, and pregnant (mother and fetus) and lactating (mother and neonate) laboratory animals (mouse, rat, and rhesus monkey); (2) to use physiologically-based pharmacokinetic models to calculate internal measures of dose for both aglycone (i.e. active) and conjugated (i.e. inactive) forms of BPA; (3) to create physiologically-based pharmacokinetic models for BPA exposure in humans (adult, child, and pregnant mother and fetus, and lactating mother and infant); (4) to extrapolate the internal doses of BPA associated with toxicity in laboratory animals to humans using the human suite of physiologically-based pharmacokinetic models; and (5) to extrapolate dosimetry from regions of observation to low levels of exposure to BPA for which no experimental data exist.</p>
<p>Evaluate the impact of Deepwater Horizon oil contaminated gulf seafood residues in edible tissues on the human intestinal microbiota of the consumer</p> <p>[Cerniglia]</p>	<p>(1) To determine whether polycyclic aromatic hydrocarbon residues in edible tissues of Deepwater Horizon oil-contaminated seafood adversely affect the human intestinal microbiota, (2) to determine if the human intestinal microbiota metabolize polycyclic aromatic hydrocarbons that are toxic components of Deepwater Horizon oil, and (3) to identify, characterize, and determine the toxicity of polycyclic aromatic hydrocarbon metabolites generated from degradation by human intestinal microbiota.</p>
<p>Human biomonitoring for BPA</p> <p>[Doerge]</p>	<p>(1) To develop and implement sensitive and selective analytical methodology to measure BPA from blood and urine samples collected under controlled conditions from children and adults with known exposures, reducing the current level of uncertainty about exposure of affected individuals and populations to BPA for use in risk assessment; and (2) to integrate human biomonitoring data with pharmacokinetic data from animals and humans to produce a physiologically-based pharmacokinetic model for BPA.</p>
<p>Evaluation of the types of genetic events detected by the mouse lymphoma assay and the role of the assay in mechanistically based risk assessment</p> <p>[Moore]</p>	<p>(1) To determine if the L5178Y TK[±] mouse lymphoma assay adequately detects both aneuploidy and mitotic recombination; (2) to determine if L5178Y mouse lymphoma cells have active recombinase functions that lead to a large proportion of mutants that result from recombinase-mediated rearrangements; and (3) to determine the fundamental genetic mechanism(s) causing the small and large colony thymidine kinase mutant phenotypes.</p>

NCTR/NTP Project [Study Scientist]	Objective and/or Project Summary
Phosphatidylinositol glycan complementation group A (Pig-A) mutagenesis: an international validation study comparing Pig-A mutation in rats with other biomarkers of genetic toxicity [Heflich]	(1) To generate data using a standardized protocol that, in combination with results from other investigators, will be used to determine the sensitivity, specificity, and portability of the rat red blood cell/reticulocyte Pig-A gene mutation assay and (2) to compare the Pig-A assay results with the in vivo Comet and micronucleus formation assays, and hypoxanthine-guanine phosphoribosyltransferase lymphocyte gene mutation assays.
Detection of DNA adducts in mice treated with benzo[a]pyrene at low-exposure levels [Fu]	To determine the dose-response curves for benzo[a]pyrene DNA adducts in the A/J mouse lung utilizing application of high performance liquid chromatography electrospray ionisation with tandem mass spectrometry methodologies developed at NCTR.
Development of methods for determining nanoparticle penetration/permeation into vaginal mucosal tissue [Zhang]	(1) To develop/adapt methods to deliver nanoscale material into rat vaginal tract and (2) to develop the analytical methods to quantify vaginal mucosal penetration of select nanomaterials following intravaginal lavage.
Methods development for high-resolution dedicated positron emission tomography (microPET) to rodent neuroplasticity and toxicity during development [Wang]	To use microPET to screen and evaluate in vitro and in vivo measurements from a broad range of pathophysiological or pharmacological parameters using specific tracers in the developing rat, using three different age groups of developing rats (gestational day 18 female rats, post-natal day 7 rat pups, and post-natal day 35 rats).
Cancer mutations as biomarkers of cancer risk: human studies with implications for personalized medicine [Parsons]	(1) To develop the information necessary for the rational use of oncogene mutations as quantitative biomarkers of cancer risk; specifically allele-specific competitive blocker polymerase chain reaction will be used to determine normal and pathological levels of relevant oncogene mutations in multiple human tissues and tumors; (2) to compare the information derived from human tissues with data generated in a parallel rodent protocol as an approach for incorporating carcinogenesis-relevant data into the rodent for human extrapolation necessary in cancer risk assessment; (3) to validate a streamlined allele-specific competitive blocker polymerase chain reaction methodology and develop the methodology necessary to measure oncogene mutation frequency in cell-free DNA isolated from plasma; and (4) to communicate to the regulatory risk-assessment community the regulatory significance of data on tumor-associated mutations in rodents and humans.
Development of a new safety evaluation method using microRNA (miRNA) expression analysis as a biomarker for detecting carcinogens [Chen]	(1) To determine miRNA expression profiles of the tumor target tissues of rats and mice treated with the genotoxic carcinogens: aristolochic acid, riddelliine and comfrey, and the non-genotoxic carcinogens: propiconazole and triadimefon, and the non-carcinogen myclobutanil using microarray technologies; (2) to develop a polymerase chain reaction array containing the primers, which are specifically used to amplify carcinogenesis-related miRNAs, and to use the polymerase chain reaction array to conduct time-course and dose-response studies for miRNA expression alterations in tissues of rats treated with carcinogens; and (3) to define the miRNA biomarker genes that are associated with carcinogen exposure by predicting their target genes and determining their biological functions.



NCTR/NTP Project [Study Scientist]	Objective and/or Project Summary
Neurotoxicity assessment of silver nanoparticles in PC-12 cells and in rats [Ali]	(1) To evaluate the neurotoxicity of different sizes of silver nanoparticles using cultured PC-12 cells; (2) to determine if in vitro exposure to silver nanoparticles selectively induces specific genomic changes in cultured PC-12 cells using microarrays; (3) to determine if single or multiple doses of silver nanoparticles produce reactive oxygen species, alterations in lipid peroxidation, or changes in antioxidant enzymes (catalase, superoxide dismutase, glutathione peroxidase) or glutathione levels in the rat brain; (4) to determine if single or multiple doses of silver nanoparticles induce specific genomic changes (microarrays), neurotransmitter concentrations, or 3-nitrotyrosine formation in the rat brain; and (5) to determine if multiple doses of silver nanoparticles produce morphological alterations in blood-brain barrier, brain, or other visceral organs of the rat.
Assessment of gaseous anesthetics in the developing nonhuman primate [Wang]	(1) To evaluate whether prolonged exposure to gaseous anesthetics nitrous oxide or isoflurane results in increased neuronal cell death, and to determine if combinations of nitrous oxide and isoflurane have additive effects in the developing nonhuman primate; (2) to determine if a relatively high dose or prolonged exposure of the developing nonhuman primates to nitrous oxide or isoflurane alone, or their combination will induce long-term behavioral deficits or pathological changes; (3) to determine the effectiveness of using noninvasive imaging techniques [high resolution dedicated positron emission tomography (microPET) and magnetic resonance imaging to monitor pathological changes in this model; and (4) to identify potential, underlying mechanisms that could link alteration of mitochondrial function and elevation of reactive oxygen species to gaseous anesthetic-induced neuronal cell death.
Method development for study of antioxidant properties in dietary supplements [Fu]	(1) To determine whether or not herbal dietary supplements can enhance or inhibit free radical formation or lipid peroxidation, mediated by microsomal metabolism, in a dose-dependent manner; (2) to determine the toxic effects, including mitochondrial dehydrogenase activity, intracellular reactive oxygen species concentration, and mitochondrial membrane potential; and (3) to use of the electron spin resonance oximetry technique to determine the inhibition/induction of lipid peroxidation of selected herbal dietary supplements in cells, including A549 human lung carcinoma cells and rabbit brain rBCECs cells.
Use of electron spin resonance spectroscopy to characterize the interactions between nanoscale materials and model biological systems [Fu]	(1) To determine whether nanomaterials can catalyze Fenton reaction to initiate hydroxyl radical formation in a nanoparticle-size- dependent manner, or reduction by natural reducing agents, such as ascorbic acid and glutathione, leading to the formation of reactive oxygen species; (2) to determine whether nanomaterials enhance or inhibit free radical formation mediated by microsomal metabolism or inhibit microsomal metabolism mediated lipid peroxidation, in a nanoparticle size dependent manner; (3) to determine the toxic effects, including mitochondrial dehydrogenase activity, intracellular reactive oxygen species concentration, and mitochondrial membrane potential; and (4) to use electron spin resonance oximetry technique to determine the inhibition/induction of lipid peroxidation by nanomaterials of different particle size in cells (A549 human lung carcinoma cells and rabbit brain rBCECs cells).
Development of an FDA resource and knowledge base for sex difference in drug-induced liver injury [Tong]	(1) To develop a knowledge base for the sex differences in drug-induced liver injury through analysis and modeling molecular data in the public domain, through development and fostering of the collection of genomic data from public resources, and through development of a standard data curation model for the sex-biased drug-induced liver injury in ArrayTrack to manage the collected data and (2) to conduct meta-analysis, text mining, and network analysis to develop a relationship between drugs, molecular signatures, liver-specific biomarkers, genes/proteins functions, pathways and sex-biased liver toxicity.
QT interval correction via mixed-effects modeling [George]	To develop an appropriate non-linear mixed effects pharmacokinetic model in order to examine the effects of bitter orange/synephrine extract on electrocardiogram data from a rodent study. QT interval is a measure of time in the heart's electrical cycle.

NCTR/NTP Project [Study Scientist]	Objective and/or Project Summary
Establishment of embryonic stem cells as an in vitro model to explore developmental toxicity [Inselman]	(1) To develop an in vitro culture system utilizing mouse mesodermal embryonic stem cells and human pluripotent stem cells and (2) to examine the mechanisms(s) responsible for embryotoxicity associated with selected known or suspect embryotoxins that affect differentiation into osteoblasts.
Methods development for toxicity assays using the zebrafish embryo as a model system: whole animal high-throughput assays for chemical testing [Kanungo]	(1) To use the established high-throughput assay system using zebrafish embryos for morphological and behavioral endpoints of toxicity and subtle organ-specific toxicities to study the effect of methamphetamine on zebrafish embryos, especially relating to sensory and motor neuron development; (2) to determine if carbon nanotubes pass through the blood brain barrier in zebrafish embryos, and if so, do these nanomaterials generate reactive oxygen species, deplete dopamine and its metabolites (dihydroxyphenylacetic acid and homovanillic acid), and alter markers of oxidative stress; and (3) to determine the effect of nicotine on zebrafish embryos, especially relating to sensory and motor neuron development and the mechanism of action.
Effect of pediatric anesthetics on zebrafish embryos: neurotoxicity versus gene expression changes and neuronal kinase cyclin-dependant kinase 5 as a mediator of toxicity [Kanungo]	(1) To determine whether ketamine has neurotoxic effects (on neurogenesis and axonogenesis) in zebrafish and (2) to determine if the window of such effects varies between early and late differentiating neurons (sensory and motor neurons, respectively).
Long-term consequences of neonatal ketamine anesthesia in rhesus monkeys: extended cognitive assessments [Paule]	(1) To continue monitoring the cognitive capabilities of rhesus monkey subjects that were exposed to a single, 24-hour duration of ketamine-induced anesthesia during the first week postpartum; and (2) to extend the functional domains that are being assessed beyond learning, the ability to perform simple visual discriminations, motivation, and speed of psychomotor processing, to include performance of a temporal discrimination task (timing task), a counting task, and reversal learning tasks (cognitive flexibility).
Assessing acetaminophen-induced liver injury and the influence of dietary supplements: potential synergistic interactions [Shi]	Using a battery of dietary supplements: (1) to determine the dose-response toxicological effect in vivo in mice following repeated dosing with each dietary supplement in the absence and presence of acetaminophen; and (2) where dietary supplements and acetaminophen administration resulted in greater hepatotoxicity, to examine the mechanism of action using genomics, proteomics, and metabolomics approaches for in vivo samples from mice and in vitro samples from primary hepatocyte cultures.
In vitro assay to predict developmental neurotoxicity of pediatric anesthetics [Wang]	To use rodent in vitro organotypic and primary culture models: (1) to examine the toxicity of anesthetics including propofol (gamma-amino butyric acid (GABA)-A agonist), baclofen (GABA-B agonist), diazepam (GABA-A agonist), pentobarbital (GABA-A agonist and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist), etomidate (GABA-A agonist), sevoflurane (N-methyl-D-aspartate antagonist and GABA agonist), fentanyl (opiate agonist) and anesthetic combinations commonly used in pediatric surgical procedures; (2) to determine the utility of in vitro culture systems to predict in vivo outcomes in subsequent studies; (3) to determine the dose and time-course over which the potential neurotoxic effects of anesthetics are expressed in the developing brain; (4) determine effective ways to protect against anesthetic-induced developmental neurotoxicity that have potential clinical utility; (5) to identify mechanisms that link altered N-methyl-D-aspartate receptor function and/or elevation of reactive oxygen species to anesthetic-induced neuro-apoptosis; and (6) to identify biomarkers such as genomic pathway signatures and determine their validity for predicting in vitro outcomes of pediatric anesthetic exposure.



NCTR/NTP Project [Study Scientist]	Objective and/or Project Summary
Interaction of nanoparticles with the gastrointestinal tract [Khare]	To investigate the role of various cellular components of the intestine involved in the uptake of nanoparticles and their accumulation in various cell types and potential effects on biodistribution by: (1) determining the effect of nanomaterials on the permeability of epithelial cells and establish immune correlates; (2) delineating the interaction of nanomaterials with gastro-intestinal tract and gut-associated microbiota using <i>ex vivo</i> models (intestinal explants); and (3) establishing the effect of nanoparticles on the developmental stage of intestine and assess biodistribution of nanoparticles using a zebrafish model.
Assessment of size and shape dependent-toxicity of silver nanoparticles as measured by changes in the permeability at the gastrointestinal surface [Khare]	To investigate various cellular components involved in the uptake of nanoparticles in intestine, their accumulation in various cell types and the effect of nanoparticles on the intestinal microbiome, by: (1) determining the effect of nanomaterials on the permeability of intestinal epithelial cells <i>in vitro</i> and ileal mucosa <i>ex vivo</i> ; and (2) measuring the toxicity of silver nanoparticles as measured by changes in the expression of genes involved in the epithelial integrity of polarized epithelial cells and ileal mucosa.
Effect of fetal exposure to oxybenzone on reproductive organs of postnatal day 21 rats [Nakamura]	To determine if fetal exposure to oxybenzone influences the male (testes, steroid biosynthesis) and female (ovary) reproductive organs of Harlan Sprague Dawley rats on postnatal day (PND) 21 by examining morphology of the reproductive organs and mRNA expression of genes related to the endocrine system.
Effect of fetal or postnatal exposure to oxybenzone on reproduction in male rats [Nakamura]	(1) To evaluate the expression of genes involved in testosterone synthesis in testes and prostate of adult males treated with oxybenzone perinatally and as young adults; (2) to evaluate the expression of androgen-receptor genes in prostate and testes of rats treated with oxybenzone both perinatally and as young adults; and (3) to evaluate expression of DNA methyltransferase genes in the testes and prostate of rats treated with oxybenzone both perinatally and as young adults.
Development and evaluation of exposure dosimetry methods to optimize the standard <i>in vitro</i> mammalian genotoxicity assays for assessing engineered nanomaterials [Chen]	(1) To evaluate whether the <i>in vitro</i> mammalian genotoxicity assay is suitable for assessing the genotoxicity of nanomaterials; (2) to explore the possible mechanisms underlying genotoxicity of engineered nanomaterials by conducting genomic analysis; (3) to identify potential improvements to the assay and general strategies for evaluating nanomaterials; and (4) to examine whether the suitable methods and other experiences learned from the micronucleus assay are applicable to other genotoxicity tests, such as mouse lymphoma assay and <i>in vivo</i> micronucleus assay.
Do engineered silver nanomaterials varying by size and coatings behave differently than bulk silver in their ability to induce genetic damage? [Chen]	To evaluate the genotoxicity of various sizes of engineered silver nanoparticles and bulk silver in the Ames test, mouse lymphoma assay, and <i>in vitro</i> micronucleus assay.
Evaluation of growth, pubertal development and cardiovascular function in male rhesus monkeys (<i>Macaca mulatta</i>) chronically exposed to methylphenidate hydrochloride [Salminen]	(1) To determine whether cardiac biomarker levels are associated with echocardiographic measures of abnormal cardiac structure and function in non-human primates exposed to methylphenidate hydrochloride and (2) to determine whether panels of cardiac biomarker levels will more accurately predict echocardiographic and clinical status than do individual biomarkers.

NCTR/NTP Project [Study Scientist]	Objective and/or Project Summary
Assessment of ketamine toxicity in the developing non-human primate [Wang]	(1) To determine, using neurohistochemical approaches, if, and at what developmental stages, ketamine exposure increases neuronal apoptosis/proliferation; (2) to determine, using neurohistochemical approaches, the dose-response for ketamine to produce apoptosis at the most sensitive developmental stage; (3) to determine the reversibility or permanence of the response using behavioral, imaging, and neurohistochemical approaches; and (4) to determine, at the most sensitive stage and dose, genomic and proteomic responses to ketamine treatment.
Effect of p53 genotype on gene-expression profiles in mice exposed to the model mutagen, N-ethyl-N'-nitrosourea [Morris]	(1) To determine the effect of mutation in the p53 tumor suppressor gene on gene-expression profiles in young and aged mice and (2) to determine the effect of mutation in p53 tumor-suppressor gene on gene-expression profiles in young and aged mice exposed to the model mutagen N-ethyl-N'-nitrosourea.
Quality control for focused and unfocused liquid chromatography-mass spectrometry based metabolomic profiling of blood samples [Beger]	To develop and test a quality control protocol for liquid chromatography-mass spectrometry based metabolomic profiling of blood samples on NCTR preclinical hepatotoxicity protocols.
Assessment of iron oxide nanoparticle-induced neurotoxicity in cell cultures and whole animal models [Binienda]	To determine if acute or chronic exposure of different sizes of iron oxide nanoparticles produce: (1) specific changes in the mitochondrial function, cell death and generation of reactive oxygen species in different regions of rat and mice brain using in vivo microdialysis; (2) significant changes in neurotransmitter concentrations in different regions of mice/rat brains using microdialysis; (3) alterations in the brain free fatty acid levels; (4) alterations in lipid peroxidation and/or changes in antioxidant enzyme activity (catalase, superoxide dismutase, glutathione peroxidase) and glutathione levels in mice and rat brains; and (5) selective pattern of deposition and damage produces in different regions of rat and mice brain using in vivo magnetic resonance imaging.
Study of nanoparticles migration from food-contact nanomaterials. characterization and quantification of silver nanoparticles in stimulants [Trbojevich]	(1) To quantify the migration of nanoparticles from nanocomposites used in food-contact material and (2) to characterize and quantify silver nanoparticles in food simulants.
3D- and 4D- quantitative spectrometric data-activity relationship (QSDAR) modeling applied to various toxicological endpoints [Beger]	(1) To develop 3D- and 4D- QSDAR models for endocrine disruptors, lowest-observed-adverse-effects level and no observed-adverse-effects level, and other relevant toxicological endpoints and (2) to determine how the technique used to predict ¹³ C or ¹⁵ N nuclear magnetic resonance spectra affects 3D-QSDAR modeling.
Methylphenidate (Ritalin) exposure during pregnancy: assessment of neurotoxicity in offspring [Ferguson]	To determine the neurobehavioral toxicity associated with pre- and early postnatal treatment with methylphenidate in rats using a range of behaviors at preweaning, adolescent, and adult ages.



NCTR/NTP Project [Study Scientist]	Objective and/or Project Summary
Evaluation of the applicability of in vivo micronucleus assays for assessing genotoxicity of engineered nanomaterials [Chen]	(1) To assess the genotoxicity of four types of nanoscale materials (carbon nanotubes, nanoscale titanium dioxide, nanoscale gold, and nanoscale silver) in three standard tests used for genotoxicity assessment by the FDA (Salmonella Ames test, mouse lymphoma assay, and in vivo mouse micronucleus assay) and (2) to evaluate the possible mechanisms of nanomaterial-induced genotoxicity using a transgenic mutation system, comet assay and genomic analysis.
Characterizing the amphetamine-induced changes in vascular tone, vasotrauma and alterations in angiogenesis in rodent brain [Bowler]	To use acute and repeated dose models in the rat: (1) to evaluate the effects of both acute and chronic amphetamine exposure on the vasculature of the rat brain, examining the vasculature within the parenchyma of three brain regions (striatum, parietal cortex, and combined piriform and amygdaloid nuclear cortices) and (2) to determine the effects of amphetamine on the vasculature associated with meninges pial and arachnoid membranes and vasculature of the choroid plexus.

Table 31. NIEHS/NCTR Interagency Agreement Studies in FY 2012

Study CASRN [Study Scientist]	Objective and/or Rationale
Assessment of molecular changes in male and female Sprague Dawley rats orally exposed to bisphenol A (BPA) from GD 6 through PND 90 80-05-7 [Camacho]	To determine BPA-induced molecular changes in gene expression, protein levels, and epigenetic modifications in tissues collected from Sprague Dawley rats orally exposed to BPA from GD 6 through PND 90.
Evaluation of toxicity of BPA in male and female Sprague Dawley (NCTR) Rats exposed orally from GD 6 through PND 90 80-05-7 [Delclos]	(1) To assess the toxicity of BPA in rats dosed perinatally via gavage and (2) to evaluate estrogenic endpoints from the first filial offspring generation.
Evaluation of various diets on endpoints critical to the evaluation of BPA and other endocrine-active agents [Delclos]	To evaluate reproductive and developmental endpoints in F0-F2 generation in CD-1 mice with various chows (e.g., Purina Mills 5K96, NIH-41, Purina Mills 5001), some of which have low isoflavone levels, in preparation of studies on BPA in CD-1 mice.
The role of perinatal development on pharmacokinetics of BPA 80-05-7 [Doerge]	To develop additional data from rat and monkey exposures that will provide data to be used in the creation and validation of a physiologically-based pharmacokinetic model to predict internal exposures to free BPA in the appropriate target tissues of fetuses and babies that are derived from food contact and medical device exposures.
Two year chronic toxicology study of BPA administered by gavage to Sprague Dawley (NCTR) Rats from GD 6 until birth and directly to pups from PND1; continuous and stop dose exposures 80-05-7 [Delclos]	To characterize the long-term toxicity of orally administered BPA, including developmental exposure, in the NCTR Sprague Dawley rat over a broad dose range. In addition, animals generated in this study will be assigned to separate protocols for assessment of a range of molecular, morphological, and functional endpoints to determine if these endpoints are predictive of long term toxic effects or reveal potential effects undetected by standard toxicological evaluations.

<p style="text-align: center;">Study CASRN [Study Scientist]</p>	<p style="text-align: center;">Objective and/or Rationale</p>
<p>Evaluation of molecular, morphological, and functional endpoints in Sprague Dawley (NCTR) rats treated with BPA administered by gavage from GD 6 until birth and directly to F1 pups from PND 1; continuous and stop dose (PND 21) exposures <i>80-05-7</i> [Delclos]</p>	<p>To evaluate a range of molecular, morphological, and functional endpoints in rats dosed orally with a wide range of BPA doses in a chronic toxicology study. These evaluations will be conducted by investigators funded by the NIEHS. The endpoints were selected based on reports from previous animal toxicology or human epidemiology studies suggesting that they are affected by BPA exposure. Assessments will be conducted at various ages (PND 1, 21, and 90 and 6 and 12 months) and it will be determined if any effects observed are predictive of long term effects evaluated in the companion chronic toxicology study or reveal potential effects undetected by standard toxicological evaluations.</p>
<p>Neurobehavioral effects of BPA across age and sex <i>80-05-7</i> [Ferguson]</p>	<p>(1) To characterize how orally administered BPA or ethinyl estradiol treatment during the perinatal period in Sprague Dawley rats affects anxiety, learning, and memory-related behaviors during juvenile and adult life across three human-relevant dose and one dose of the reference estrogen and (2) to identify the molecular and morphological changes induced by perinatal BPA treatment or ethinyl estradiol in the hypothalamus and hippocampus, which are critical brain regions governing these behavioral responses.</p>
<p>Thirteen-week studies to determine the pathogenesis of the whole leaf extract of the <i>Aloe vera</i> plant in the cecum and large intestine of the F344 rat <i>85507-69-3</i> [Boudreau]</p>	<p>To investigate the pathogenesis of <i>Aloe vera</i> extracts and gel, with and without added Aloin A, in the cecum and large intestine of the F344 rat. Senna, having similar components to those in <i>Aloe vera</i>, will also be studied to determine if it exerts comparable effects when administered in the drinking water of F344 rats.</p>
<p>Assessment of the nephrotoxicity from the 90-day combined exposure to melamine and cyanuric acid in F344 rats <i>108-78-1, 108-90-5</i> [Gamboa]</p>	<p>To investigate the nephrotoxic effects noted in F344 rats exposed in NTP Study number C10119 to melamine, cyanuric acid and melamine cyanurate. The initial toxicity was reported in the kidneys of the pets and children exposed to adulterated foods.</p>
<p>Assessment of nephrotoxicity from an exposure to melamine, cyanuric acid, and its combination in newborn F344 rats from PND 1 to weaning <i>108-78-1, 108-90-5</i> [Gamboa]</p>	<p>(1) To determine if a combined exposure to melamine and cyanuric acid in newborn F344 rats is more nephrotoxic than exposure to the individual compounds, (2) to establish the dose-response curve for the combined exposure, and (3) to investigate the longer-term effects of these lesions during a recovery period.</p>
<p>Thirteen-week study to evaluate the toxicology of silver nanoparticles in Dawley rats <i>744-22-4</i> [Boudreau]</p>	<p>To determine if exposure over a 13-week period to nanoscale (10, 70, and 107 nm) silver particles induces toxicity.</p>
<p>Thirteen-week dermal toxicity of triclosan in B6C3F1 mice <i>3380-34-5</i> [Fang]</p>	<p>(1) To determine the toxicity of dermally applied triclosan with ethanol as the vehicle and (2) to determine the possible toxicity and phototoxicity of triclosan under normal use conditions.</p>



Study CASRN [Study Scientist]	Objective and/or Rationale
Effect of oxybenzone on fertility and early embryonic development in Sprague Dawley rats (Segment I) 131-57-7 [Inselman]	(1) To examine the reproductive toxicity of oxybenzone in male and female rats and to focus specifically on fertility and early embryonic development to implantation and (2) to compare the results of a typical Segment I, II, and III study design with results from a modified one-generation study proposed by the NTP.
Effect of oxybenzone on embryo/fetal development in Sprague Dawley rats (Segment II) 131-57-7 [Inselman]	To determine the potential developmental toxicity of oxybenzone and to compare the results of a typical Segment I, II, and III study design with results from a modified one-generation study proposed by the NTP.
Effect of oxybenzone on pre and postnatal development in Sprague Dawley rats (Segment III) 131-57-7 [Inselman]	To determine the potential toxicity of oxybenzone on pre and early postnatal development in male and female rats and to compare the results of a typical Segment I, II, and III study design with results from a modified one-generation study proposed by the NTP.
Neurotoxicity assessment of cell phone radio frequency radiation using rat and bovine brain microvascular endothelial cells as model blood brain barrier systems, PC-12 cultured cells, and whole animal models [Ali]	(1) To determine whether power levels of radio frequency radiation that are emitted from mobile phones produce any changes in the central nervous system of mice and rats and (2) to determine if there are disruptions in the blood brain barrier after being subjected to radio frequency radiation.
Two-year carcinogenicity bioassay of furan in Fischer 344 rats 110-00-9 [Beland]	To determine the dose-response relationship for the carcinogenicity of furan in F344/N/NCTR male rats in a two-year bioassay.
Subchronic toxicity of <i>Usnea</i> lichen in male and female Fischer 344 rats and B6C3F1 mice 84696-53-7 [Leakey]	To evaluate the subchronic toxicity of <i>Usnea</i> lichen in a 90-day toxicology study with dose administered in chow.
Subchronic studies of usnic acid in Fischer 344 rats and B6C3F1 mice 125-56-2 [Leakey]	To evaluate the subchronic toxicity of usnic acid in male and female Fischer 344 rats and B6C3F1 mice using 90-day toxicology studies.
Toxicity studies of glucosamine and glucosamine/chondroitin sulfate combination in obese and lean Zucker rats 3416-24-8, 9007-28-7 [Leakey]	To investigate the potential toxicity of glucosamine and glucosamine/chondroitin sulfate combinations administered by oral gavage in male rats.
Perinatal carcinogenicity of drug combinations used to prevent mother-to-child transmission of HIV 30616-87-1, 134678-17-4 [Beland]	To determine the carcinogenicity, genotoxicity, and metabolism of antiretroviral drug combinations administered to mice transplacentally and perinatally. The studies include 14-day range-finding and two-year chronic in pregnant C57BL6N females and in B6C3F1 hybrid offspring.

Study CASRN [Study Scientist]	Objective and/or Rationale
Toxicity studies of combination of AIDS drugs in p53(+/-) transgenic mice 30616-87-1, 134678-17-4 [Leahey]	(1) To evaluate the potential toxicity and carcinogenicity of perinatal and chronic exposures to AIDS drugs, 3'-Azido-3'-Deoxythymidine (AZT) and lamivudine (3TC) in C3B6F1trp53(+/-) haplodeficient F1 transgenic mice in a range-finding and a 6-9 month chronic phase, and (2) to evaluate the potential toxicity and carcinogenicity of AZT/3TC/Nevirapine (NVP) combinations in C3B6F1trp53(+/-) in a 9-month exposure in mice.
Developmental neurotoxicity assessment of acrylamide in rats: long-term exposure 79-06-01 [Paule]	To determine the consequences of long-term exposure to acrylamide on a variety of developmental milestones and measures of nervous system integrity throughout life.
Genotoxicity and carcinogenicity of acrylamide and its metabolite, glycidamide, in rodents 79-06-1, 5694-00-8 [Beland]	To determine the genotoxicity and carcinogenicity of acrylamide and its metabolite, glycidamide, in male and female Fischer 344 rats and B6C3F1 mice using range-finding, subchronic, and two-year chronic carcinogenicity studies.



6. Alternative Methods Development

A. Tox 21

In FY 2008, the NTP established a high-throughput screening initiative, representing a new paradigm in toxicological testing. On February 14, 2008, a Memorandum of Understanding (MOU) was signed for High Throughput Screening, Toxicity Pathway Profiling and Biological Interpretation of Findings (See <http://ntp.niehs.nih.gov/go/28213> for information about the MOU). Through this MOU, the NIEHS/NTP formally entered into a partnership with the NIH Chemical Genomics Center at the National Human Genome Research Institute (now the NIH Center for Advancing Translational Sciences or NCATS) and the U.S. EPA's National Center for Computational Toxicology located within the Office of Research and Development. The MOU was amended in 2010 to include the FDA. FDA's active participation is in recognition of its commitment to developing new methods to evaluate the toxicity of the substances it regulates. This interagency partnership is the basis for the U.S. Tox21 Program and makes it possible to pool resources to overcome the resource limitations of a single agency, build on existing expertise, and avoid the need to create a new administrative and support structure



The Tox 21 Program was developed in response to the National Research Council's 2007 report *Toxicity Testing in the 21st Century: A Vision and a Strategy*. A central component of this MOU is exploration of quantitative high-throughput screening (qHTS) assays using phylogenetically lower animal species (e.g., fish, worms), as well as high-throughput, whole-genome, analytical methods to evaluate mechanisms of toxicity. The ultimate goal of Tox21 is to provide the data generated by these new tools to risk assessors for use to protect human health and the environment.

The goals of Tox21 and the NTP high-throughput screening program are the same, i.e., prioritization of chemicals for further in-depth toxicological evaluation, identification of mechanisms of action for individual chemicals as well as chemical classes and structures, and ultimately, predictive toxicology. The results of this collaborative effort should yield test methods for toxicity determination that are more scientifically and economically efficient, that inform adverse outcome pathway analyses, and that provide models for risk assessment that are more biologically and mechanistically based than current models. This approach should ultimately reduce or replace animals in regulatory testing and is anticipated to occur in parallel with an enhancement of the ability to evaluate the large numbers of chemicals that currently lack adequate toxicological evaluation.

Phase I

In Tox21 Phase I (FY 2006 through FY 2010), a library of approximately 2,800 compounds provided by the NIEHS/NTP and EPA to the NCGC was tested in approximately 100 qHTSs. These assays broadly evaluated the ability of compounds (1) to induce cytotoxicity, apoptosis, DNA damage, changes in methylation status, mitochondrial toxicity, and up-regulation of various stress response pathways (e.g., antioxidant, hypoxia, heat shock) in a variety of cell types or (2) to perturb nuclear receptor signaling in 12 different signaling pathways including those involving the critically important estrogen and androgen receptors.

Phase II

Based on the knowledge gained from Phase I, a screening approach for Tox21 Phase II was identified that would be used to evaluate the biological effects of a 12,000 substance library (8307 unique; informally known as the "10K" library), with approximately 1/3 of the total substances assembled by each partner (NTP, EPA, and

NCGC). The compounds cover a wide variety of classifications, and include consumer products, food additives, chemicals found in industrial processes, and human and veterinary drugs. A complete list of the compounds is publicly available at <http://www.epa.gov/ncct/dsstox/>. Chemical analyses to determine the identity, purity, and stability of all compounds in this library were initiated in FY 2012 and will continue through FY 2013.

Also in FY 2012, screening of the 10K library began as well as screening on a subset of these compounds (~700) in Phase II of EPA's ToxCast™ Program (<http://www.epa.gov/ncct/toxcast/>). The data from all these assays, along with full chemical characterizations and assay protocol details, are being deposited into publicly accessible, relational databases such as the National Library of Medicine's PubChem (<http://pubchem.ncbi.nlm.nih.gov/>), EPA's ACToR (<http://www.epa.gov/ACToR/>) and NTP's CEBS (<http://www.niehs.nih.gov/research/resources/databases/cebs/>).

The 10K library contains 88 duplicate compounds that are present on each compound plate as well as approximately 1,900 compounds that are present in the library in multiple copies and were obtained from different sources. This compound replication provides a means of evaluating inter- and intra-plate variability as well as cross-assay variability in compound activity as a monitor of the technical quality of a screen. The emphasis during the first 18–24 months of screening in Phase II is on assays measuring nuclear receptor signaling in agonist and antagonist mode (e.g., aryl hydrocarbon receptor, androgen receptor (partial, full), estrogen receptor alpha (partial, full), farnesoid x receptor, glucocorticoid receptor (full), liver x receptor, peroxisome proliferator-activated receptor delta and gamma, pregnane x receptor, retinoic acid receptor-related orphan receptor, retinoid x receptor, thyroid receptor, Vitamin D receptor), induction of stress response pathways (e.g., antioxidant, DNA damage, heat shock, hypoxia), and assays measuring specific toxicity endpoints such as mitochondrial membrane changes, caspase activation, aromatase inhibition, and upregulation of NFκB (nuclear factor kappa beta), a transcription factor that has an important role in the immune system.

By the end of FY 2012, 87 qHTS assays measuring 29 endpoints were completed and 12 assays were optimized for screening the 10K library. For the majority of assays, cell viability was assessed using a complementary readout in the same wells as the main readout. In addition to the nuclear receptor and stress response assays, compound biological stability was assessed by screening the 10K library at 0, 2, 4, and 6 months of being maintained in use at room temperature in an assay measuring upregulation of p53. Further, autofluorescence of compounds within the library was evaluated in two screens to identify potential confounding issues in data interpretation.

The Tox21 Phase II screening is being conducted in a new, high-speed robotics screening facility dedicated at the NCGC in mid FY2011; it was built with funds provided by the NIEHS/NTP. This robotics facility was used to screen the 10K compound library in triplicate (30K compounds per screen). In FY 2011 the differential cytotoxicity response of cells from humans was evaluated by screening 1089 densely sequenced lymphoblastoid cell lines representing nine racial groups against 179 toxic chemicals. This study was designed to measure inter-individual differences in sensitivity to environmental toxicants, based on genotype. Evaluation of the data generated by this study occurred throughout FY 2012, with completion scheduled for FY 2013.

Table 32 describes the NTP Tox 21 projects in FY 2012 that are being carried out by NIEHS/DNTP staff. This includes the projects in the NTP WormTox Facility, which develops toxicological assays using the nematode *Caenorhabditis elegans* (*C. elegans*) and evaluates their utility as medium-throughput screening tools. The use of *C. elegans* is consistent with NTP's strategy to reduce the number of mammals used in testing. In FY 2012, screening using the *C. elegans* growth assay was completed on the EPA's ToxCast Phase II chemical library of 700 compounds. The data from this screen are currently being analyzed and will be ready for publication in FY 2013.



Table 32: NTP Tox 21 Projects in FY 2012

NTP Project Title [Study Scientist]	Objective and/or Summary
Screening for aromatase inhibitors [Teng]	To screen aromatase inhibitors from the Tox21 10K library. In collaboration with Dr. Shiu-an Chen at Beckman Institute of City of Hope, CA, NTP developed an "AroER Tri-screen" to detect compounds that inhibits aromatase and estrogen receptor activities. The data are being analyzed.
Develop stable cell line to screen estrogen-related receptor/ peroxisome proliferator-activated receptor coactivator pathway [Teng]	To screen compounds which interfere with estrogen-related receptor/peroxisome proliferator-activated receptor gamma coactivator pathway, a critical pathway for metabolic homeostasis. Two steps are required to develop the stable cell line and the first step to produce stable cell lines expressing PGC has been accomplished.
Modeling mixtures of androgen receptor- and estrogen receptor-active compounds [Parham]	To determine (1) which mathematical models can describe the toxicity of the mixtures of these compounds and (2) whether the behavior of the mixtures can be predicted from the behavior of the individual components. (3) Collaborative work with University of NC involves providing data for their structure–activity relationship mixture model.
Analysis of Tox21 qHTS assay data [Hsieh]	To develop data analysis pipelines for Tox21 Phase II qHTS data to determine the activity of compounds in assays. The ranking/calling procedure takes into account compound potency, efficacy, and data reproducibility.
Prioritization of Tox21 compounds [Hsieh]	To prioritize compounds that show clear evidence of activity in qHTS genotoxic assays, some weakly active compounds could be prioritized based on chemical structure–activity relationship analysis.
Low-dose extrapolation [Parham]	To determine points of departure for low-dose extrapolation by using signal-to-noise ratios and a benchmark-dose method.
High content screening with HepaRG cells [Ferguson]	To establish metabolically functional human HepaRG liver cells in 384-well format to multiplex high content screening assays in collaboration with the NCGC.
Polycyclic aromatic hydrocarbon mixture project [Ferguson]	To evaluate ~20 poly-aromatic hydrocarbons (Gulf Oil Spill) in metabolism-competent HepaRG cells (derived from a human hepatic progenitor cell line) using multiplexed high content screening assays. Multiple measures of cellular health, damage, and gene expression will be used in collaboration with the NCGC.
Stem cells [Ferguson]	To screen for chemical toxicity in stem cell lines by qHTS at the NCGC. Initially, the project is focused on fostering collaborations with stem cell technology providers and assessing control compounds and subsets of NTP chemicals using various assay approaches. Stem cell technology platforms and model systems shown to be useful for in vitro toxicology screening would be employed with larger sets of chemicals for hazard identification and chemical prioritization for toxicity testing.
<i>In silico</i> prediction of metabolism [Ferguson]	To evaluate various <i>in silico</i> methods of predicting the extent of xenobiotic metabolism, identity metabolites, and prioritize chemical in the Tox21 10K library. Computational methods will be used to 'bin' the 10K library and develop sub-sets of chemicals likely to be appreciably metabolized in humans.
Sequencing quality control toxicogenomics project [Auerbach]	To compare transcriptomic technologies (technologies that examine the RNA molecules in a cell population by microarray, high throughput screening, etc.) within the context of toxicogenomics.
Genomic signatures forecasting chemical carcinogenicity [Auerbach]	To develop transcriptomic signatures related to carcinogen treatment using DrugMatrix data in combination with a machine learning approach. Signatures are being validated using an independent set of data from the Japanese Toxicogenomics Project.

NTP Project Title [Study Scientist]	Objective and/or Summary
Unsupervised, data-driven analysis of Tox21 assay data [Auerbach]	To employ unsupervised data analysis (data organization based on patterns and performed by software) methods to identify chemicals that exhibit similar biological properties to well characterized toxicants.
NextGen sequencing in toxicology [Merrick]	To develop pipelines for genomic and transcriptomic gene expression and mutational analysis on a genome-wide level using NextGen sequencing technologies.
Epigenetic changes in chemical toxicity [Merrick]	To determine methylation on a genome-wide basis and validation of selected CpG sites (regions of DNA where a cytosine nucleotide occurs next to a guanine nucleotide) altered by chemical exposure. Methylation of CpG sites can turn a gene off.
Testing for gene signatures and profiles in NTP archival tissues [Merrick]	To determine if RNA can be extracted from fixed tissue blocks from the NTP Archives to measure gene signatures and profiles. Data will show future usefulness of NTP Archives for molecular measurements for chemical hazard assessment.
NTP WormTox Facility: assay development [Freedman]	Reproduction, growth, feeding, and locomotion assays measure the effects of toxicant exposure on complex biological phenotypes including development and neuron function. An in vivo stress-inducible gene expression assay that uses transgenic <i>Caenorhabditis elegans</i> (<i>C. elegans</i>) expressing fluorescence reporters measures stress pathway activation using high content imaging system. Two mitochondrial toxicity assays are in development: (1) an in vivo adenosine-5'-triphosphate assay, which provides real-time energetic status of the nematode and (2) a fluorescence dye-based mitochondrial membrane potential assay. Additionally, a low-throughput <i>C. elegans</i> mitochondrial DNA damage and repair assay has been developed.
NTP WormTox Facility: ToxCast phase 2 [Freedman]	To determine the effects of a 700-compound library on <i>C. elegans</i> development and compare the relative toxicities to those in higher organisms.
NTP WormTox Facility: ionic liquids [Freedman]	(1) To describe the effects of four ionic liquids commonly used as starting materials for other ionic liquids on <i>C. elegans</i> feeding, growth, and reproduction and (2) to compare the results in <i>C. elegans</i> to results in rodents.
NTP WormTox Facility: flame retardants [Freedman]	(1) To describe the effects of eight flame retardants on <i>C. elegans</i> feeding, growth, and reproduction and (2) to compare the results in <i>C. elegans</i> to results in rodents.
NTP WormTox Facility: mitochondrial toxicants [Freedman]	To determine the effects of the mitochondrial toxicant subset from the Tox21 10K library on <i>C. elegans</i> growth and in vivo adenosine-5'-triphosphate levels and membrane potential.
NTP WormTox Facility: fluorides [Freedman]	To compare the toxicities of three fluoride compounds commonly used in drinking water treatment processes on <i>C. elegans</i> feeding, growth, and reproduction.
Validation of high-throughput screening ER qHTS transactivation assay [Casey]	(1) To compare the quality and accuracy of the qHTS assay that evaluates transcriptional activation of the estrogen receptor in human ovarian cancer cells (BG1 ER TA assay) relative to the manual method that has been validated for regulatory use (U.S. EPA and OECD). (2) To compare the BG1 ER TA assay (full-length receptor) with the assay that evaluates transcriptional activation of the estrogen receptor in human embryonal kidney cells (HeK293 ER TA assay) that uses a transfected partial (ligand binding domain) receptor. (Once the quality of the data is deemed to be sufficient, results can be used to assess and further develop quantitative structure–activity relationship models for estrogen receptor binding.



NTP Project Title [Study Scientist]	Objective and/or Summary
Analysis of 52 compounds in EPA's ToxCast program [Casey]	The NTP selected compounds based largely on immunological relevance. NICEATM will use in vitro chemical profiling data to identify predictive signatures and adverse outcome pathways anchored to in vivo endpoints and toxicity pathways. These analyses will be used to enable chemical prioritization and hazard predictions.
Development of a database related to skin sensitization [Casey]	NICEATM, in concert with U.S. EPA and L'Oreal, aims to develop the world's largest public database for skin sensitization. This database will serve as a valuable source for reference data to help develop alternative toxicological methods, including quantitative structure–activity relationship models that can be used to eliminate the use of animals.

B. ICCVAM

The purpose of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) is to advance the regulatory acceptance of scientifically valid alternative test methods, those methods that replace, reduce, or refine (enhance animal well-being and lessen or avoid pain and distress) the use of animals (see page 11). The NICEATM was established in 1998. NICEATM administers ICCVAM, provides scientific support for ICCVAM activities, and conducts independent validation studies on promising test methods. NICEATM received contract support from Integrated Laboratory Systems, Inc.

Dr. William Stokes (Rear Admiral, U.S. Public Health Service) served as the NICEATM Director and Executive Director of ICCVAM during FY 2012. Dr. Stokes retired from the U.S. Public Health Service Commissioned Corps in December after over 30 years of dedicated federal service including over 20 years at NIEHS.

Information about NICEATM and ICCVAM is available on the ICCVAM website at <http://iccvam.niehs.nih.gov>. ICCVAM has contributed to the approval or endorsement of over 60 alternative safety or potency testing methods by Federal regulatory agencies since its first test method evaluation in 1998.

i. Workshops

NICEATM and ICCVAM organized two workshops in FY 2012. Presentations and summaries of the workshops are available on the ICCVAM website (<http://iccvam.niehs.nih.gov/meetings/schedule.htm>).



The *International Workshop on Alternative Methods for Human and Veterinary Rabies Vaccine Testing* was held on October 11–13, 2011, at the USDA National Centers for Animal Health in Ames, Iowa. The International Cooperation on Alternative Test Methods (ICATM) and the International Alliance for Biological Standardization cosponsored this workshop with ICCVAM and NICEATM. Over 90 experts in human and veterinary rabies vaccines from government, industry, and academia participated in the workshop. The objectives of the workshop included (1) to assess data gaps and research needed to allow implementation of available alternative methods for rabies vaccine potency testing, (2) to develop an implementation strategy to address these data gaps, (3) to assess ways to improve the current rabies potency test, (4) to evaluate available process control parameters and assays for demonstrating batch-to-batch consistency in conjunction with in vitro rabies potency tests, and (5) to identify best practices for minimizing the use of animals. A workshop report was published in September 2012 in the journal *Biologicals* (<http://dx.doi.org/10.1016/j.biologicals.2012.07.005>).

The *International Workshop on Alternative Methods for Leptospira Vaccine Potency Testing* was held on September 19–21, 2012, at the USDA National Centers for Animal Health in Ames, Iowa. In addition to ICATM and the International Alliance for Biological Standardization, the Animal Health Institute also cosponsored this workshop. Over 80 scientific experts from government, industry, and academia participated in the workshop. The objectives of the workshop were to (1) assess data gaps and research needed for implementation of available alternative methods for *Leptospira* vaccine potency testing and (2) develop an implementation strategy to address these data gaps and achieve global regulatory acceptance of these alternatives. A workshop report is in preparation for publication in 2013 in the journal *Biologicals*.

ii. Publications

Recent NICEATM and ICCVAM publications, test methods currently under review, and project status are presented in Tables 33, 34, and 35, respectively. A list of all ICCVAM publications is available at <http://ntp-apps.niehs.nih.gov/iccvampb/searchDoc.cfm>, and the list of articles published by NICEATM staff members and ICCVAM members in scientific journals is available at <http://iccvam.niehs.nih.gov/articles/publications.htm>. Further information on the status of nominations and submissions is available at <http://iccvam.niehs.nih.gov/SuppDocs/submission.htm>.

The following are NICEATM and ICCVAM publications from FY 2012.

- Report on the International Workshop on Alternative Methods to Reduce, Refine, and Replace the Use of Animals in Vaccine Potency and Safety Testing: State of the Science and Future Directions (dedicated issue of *Procedia in Vaccinology*), January 13, 2012.
- ICCVAM Test Method Evaluation Report - The LUMI-CELL® ER (BG1Luc ER TA) Test Method: An In Vitro Assay for Identifying Human Estrogen Receptor Agonist and Antagonist Activity of Chemicals, February 1, 2012.
- Validation of the 21st Century Toxicology Toolbox: Challenges, Opportunities, and the Way Forward (published in *ALTEX Proceedings*), March 1, 2012.
- BG1Luc ER TA Test Method: Results of an International Validation Study and Proposed Performance Standards (published in *ALTEX Proceedings*), March 1, 2012.
- Informational Brochure: “NICEATM–ICCVAM: Advancing Public Health and Animal Welfare”, March 6, 2012.
- Informational Brochure: “Nominations and Submissions to ICCVAM: A Guide for Test Method Developers and Sponsors”, March 6, 2012.
- ICCVAM Biennial Progress Report 2010-2011, June 13, 2012.
- Validation and regulatory acceptance of dermatotoxicology methods: Recent progress and the role of NICEATM and ICCVAM. Book chapter: *Dermatotoxicology*, 8th Edition, July 1, 2012.
- Report on The International Workshop on Alternative Methods for Human and Veterinary Rabies Vaccine Testing: State of the Science and Planning the Way Forward (published in *Biologicals*), September 1, 2012.



Table 33. Nominations or Submissions to NICEATM-ICCVAM in FY 2012

Test Method Nomination or Submission	Nominator or Sponsor/Activity Status
Electrophilic allergic screening assay for the detection of substances causing allergic contact dermatitis	NIOSH /under consideration
In vitro sensitivity assay for detection of substances that cause dermal sensitization	MB Research Labs/evaluation suspended; the assay is covered under recent FDA guidance on in vitro pyrogen testing and a separate evaluation is thus unnecessary

Table 34. ICCVAM Recommendations in FY 2012

Test Method	ICCVAM Recommendations/Agency Status
Use of the BG1Luc ER TA test method for endocrine disruptor chemical screening	ICCVAM evaluated the scientific validity of the BG1Luc estrogen receptor (ER) transactivation (TA) agonist and antagonist assays and recommended how they could be used to identify substances that induce or inhibit human ER activity in vitro. Agency responses received in FY 2012. http://iccvam.niehs.nih.gov/methods/endocrine/end_eval.htm#agencyresponses
Recommendations on the usefulness and limitations of the murine local lymph node assay for potency categorization of chemicals causing allergic contact dermatitis in humans	ICCVAM concluded that the murine local lymph node assay (LLNA) can be used to categorize substances as strong sensitizers. However, substances that are not identified as strong sensitizers using the LLNA require additional information to categorize them as other than strong sensitizers (Globally Harmonized System of Classification and Labeling of Chemicals Subcategory 1B). Agency responses received in FY 2012. http://iccvam.niehs.nih.gov/methods/immunotox/LLNAPotency.htm

iii. International Validation Activities

NICEATM and ICCVAM prepared, commented on, or otherwise contributed to the development of new test guidelines, revisions of existing test guidelines, and guidance documents considered by the Organisation for Economic Co-operation and Development (OECD).

- ICCVAM recommendations on the use of anesthetics, analgesics, and humane endpoints were incorporated into a 2012 update of the OECD test guideline describing animal tests to identify potential eye irritants.
- Results of a NICEATM-sponsored international validation study of the BG1Luc ER TA test method were the basis for a new OECD test guideline describing the BG1Luc ER TA test method and a revision of an existing test method for stably transfected transactivation in vitro assays to detect estrogen receptor agonists.
- NICEATM staff and ICCVAM committee members participated in expert meetings and provided comments on ongoing revisions of test guidelines for in vitro methods for identification of dermal corrosives.
- NICEATM staff and ICCVAM members participated as liaisons to the scientific advisory committee of the European Union Reference Laboratory for Alternatives to Animal Testing, European Centre for the Validation of Alternative Methods (EURL, ECVAM) for the meeting held October 2011 and March 2012.

- NICEATM staff attended the November 2011 meeting of the advisory council to the Japanese Center for the Validation of Alternative Methods (JaCVAM).

Ongoing International Cooperation on Alternative Test Methods (ICATM) (<http://iccvam.niehs.nih.gov/about/icatm.htm>) collaborations on validation studies are summarized in Table 35. NICEATM hosted a meeting of representatives of the ICATM partner organizations in September 2012, and NICEATM and ICCVAM representatives attended ICATM coordination meetings in March 2012.

Table 35. NICEATM Participation in International Validation Studies

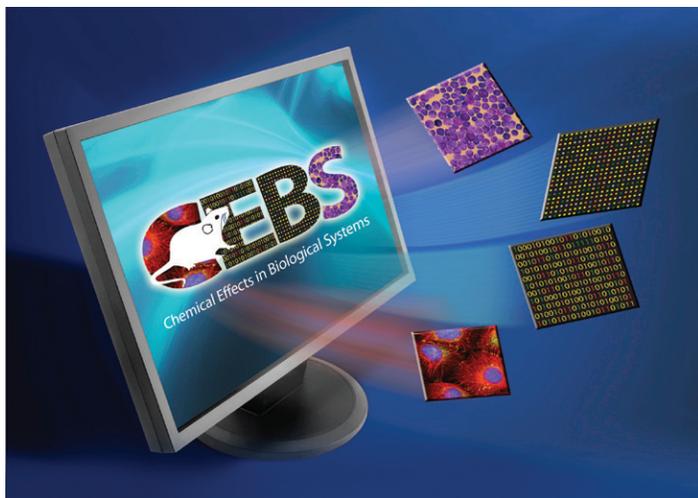
Test Method	Type of Test	Lead Organization	NICEATM-ICCVAM Involvement
CertiChem MCF-7 cell proliferation test method	Endocrine disruption	NICEATM	NICEATM coordinated an international validation study that included laboratories in the United States, Korea, and Japan
EpiOcular™ (MatTek) and SkinEthic™ (L'Oreal)	Ocular irritation	ECVAM	NICEATM and ICCVAM members served on the validation management team and provided comments on study design, chemical selection, and test method performance criteria.
Human cryopreserved HepaRG and cryopreserved hepatocytes cytochrome p450 induction test methods	Acute toxicity	ECVAM	NICEATM and ICCVAM members served on the validation management team and provided comments on study design, chemical selection, test method protocols, and study reports.
In vitro tests for assessing skin sensitization potential of chemicals	Allergic contact dermatitis	ECVAM	NICEATM and ICCVAM members served on the validation management team and provided comments on study design, chemical selection, and test method protocols
In vitro tests for assessing skin sensitization potential of chemicals	Allergic contact dermatitis	JaCVAM	NICEATM and ICCVAM members served on the validation management team and provided comments on study design, chemical selection, and test method protocols
In vitro crystal violet staining method using the rabbit cornea-derived cell line	Ocular irritation	JaCVAM	NICEATM and ICCVAM members served on the validation management team



7. Public Tools

The NTP provides a variety of resources for public use; those available in FY 2012 are described below. In FY 2012, the NTP Non-Neoplastic Lesion Atlas was in development and is scheduled for release in FY 2014. This is a database for non-neoplastic lesions organized by organ system employing a set of guidelines developed for consistent terminology.

A. Chemical Effects in Biological Systems (CEBS) Database



CEBS is a publicly accessible, NTP-integrated, data management system that houses biological study data deemed of interest to toxicologists and environmental health scientists. The CEBS database was designed as a reference repository that accepts studies from many sources. Governmental, academic, and pharmaceutical company laboratories contribute peer-reviewed studies to CEBS.

An important feature of the database is its flexibility—CEBS can house “any” type of biological measurements from “any” type of study design. This flexibility in CEBS allows data from different sources to be integrated into one place

to permit data mining and analysis. In addition, any one study can have different types of data associated with it such as blood chemistry, histopathology, and microarray—all viewed together underneath one study name. The investigator does not have to access different databases, each housing one specific type of data.

The NIEHS is continuing to add legacy NTP data to CEBS. Phase II Tox21 data will be publicly available through CEBS as the studies are released for reference and data mining. CEBS supports queries such as “show me all test articles that cause a particular pathology” or “show me all test articles positive in a particular genetic toxicology assay”, where ‘test articles’ is the database term used to refer to substances being tested such as chemicals or drugs.

CEBS captures the details of the study’s design and execution plus the biological responses of study subjects (i.e. animals, tissue culture cells). This enables the user to view the details of each study, search for particular studies or study subjects of interest based on treatment, response, or other characteristics; and then either analyze the data within CEBS or download for import into other tools. CEBS can be accessed at <http://cebs.niehs.nih.gov>.

B. NTP Archives

The NTP Archives is an important NIEHS-supported resource comprised of stained histopathology slides, paraffin tissue blocks, formalin-fixed tissues and organs, and selected frozen tissue from over 2,000 studies including toxicity, carcinogenicity, immunotoxicity, reproductive, and developmental studies. There are ongoing efforts to organize the NTP Archives to make it more electronically searchable for chemical exposure related to toxicity phenotype at the animal level and to recommend protocols consistent with best practices for biobanking and archival storage. There are also ongoing efforts to determine the usefulness

of archival materials for various types of molecular analysis including gene expression, epigenetics, and mutational analysis.

The first archival gene expression study by NIEHS/DNTP, published in FY 2012, showed that a gene expression signature, comprised of 14 different transcripts, could be reliably measured from RNA extracted from four-year-old formalin-fixed, paraffin-embedded (FFPE) liver tissues in an NTP 90-day rat study. FFPE RNA from liver and kidney were of sufficient quality for molecular analysis to measure gene expression by quantitative polymerase chain reaction that favorably compared to results of fresh frozen tissues from identical animals. FFPE RNA from lung performed less satisfactorily probably because of this organ's sensitivity to fixation conditions that degraded RNA into small fragments. This study also showed that the quality of FFPE RNA and its successful application to molecular analysis could be predicted by measuring the size range of the fragmented FFPE RNA. Secondly, very exciting results were obtained with FFPE RNA from these same rat livers that show accurate whole-genome transcript profiling could be successfully performed using transcriptome sequencing. Third, a different transcript profiling technique—qNPA—was used to compare transcripts from RNA isolated from fresh or FFPE brain and liver in mice. These results again demonstrated the usefulness of archival tissue blocks for gene profiling. A more systematic query of NTP archival materials from different organs and storage times is planned for the future to more precisely determine the value in transcript profiling.

C. The NCGC BioPlanet

No one, comprehensive, and uniform resource covers all known annotations of cellular pathways and no single platform allows integrated browsing, retrieval, and analysis of information from the many existing resources that do pathway mapping. Therefore, the NCGC (with support from the NIEHS through NTP, see page 16) built an integrated pathway resource that hosts information on ~1100 human pathways from manually curated and publicly available resources. The NCGC BioPlanet (<http://www.ncgc.nih.gov/pub/bioplanet/>) complements this pathway warehouse by allowing easy browsing, visualization, and analysis of the universe of pathways.

D. DrugMatrix® and ToxFX®

Related to the goal of developing analysis tools and approaches to allow an integrated assessment of high-throughput screening endpoints and associations with findings from traditional toxicology and cancer models, the NTP acquired DrugMatrix®—a toxicogenomics reference database and the accompanying extensive frozen tissue archives, and the informatics system. This resource expands the NTP's ability to develop predictive models for toxicological effects based on gene signatures, to provide additional tools for linking in vitro data to in vivo gene signatures and disease outcomes, and to provide additional tissue samples for NextGen-based investigations. DrugMatrix® and its companion automated analysis tool, ToxFX®, were made accessible to the international scientific community in early FY 2012 (available at <https://ntp.niehs.nih.gov/drugmatrix> and <https://ntp.niehs.nih.gov/toxfx/>). To date, over 300 researchers have registered to use the DrugMatrix® database. In addition, the data and biological samples from DrugMatrix® are a focal point in a number of collaborations between DNTP scientists and research groups from the FDA's National Center for Toxicological Research, the City of Hope, Stanford University, Boston University, U.S. EPA, Health Canada, Abbott Laboratories, Eli Lilly and Company, SAS, Maastrich University, GeneData, University of Massachusetts, and University of North Dakota. Samples from the DrugMatrix® frozen tissue bank have been analyzed through the MicroArray Quality Control/Sequencing Quality Control Consortium (<http://www.fda.gov/ScienceResearch/BioinformaticsTools/MicroarrayQualityControlProject/default.htm>) and in collaboration with researchers at Harvard University. Finally all the transcriptomics data from DrugMatrix® has been integrated in the NextBio, which is a database



and analysis tool allowing analysis of the data within the context of all existing genomic and transcriptomic data. Ultimately, the goal of these collaborations and data sharing is to use the DrugMatrix® data to better understand the molecular underpinnings of disease and toxicological pathology.

E. MetaDataViewer

Staff within the Office of Health Assessment and Translation, DNTP at NIEHS developed Meta Data Viewer, in collaboration with SRA International, to be a user-friendly program for creating figures with multiple columns of accompanying text, such as forest plots of epidemiology data or exposure response arrays of toxicology data. The program allows users to quickly sort, group, and filter subsets of data from a larger database to look at patterns of findings across a wide variety of studies or sets of results from a single study. Meta Data Viewer is a public resource. Users are welcome to use the program and any associated NTP data files for their own purposes, including for use in publications. Meta Data Viewer is available at http://ntp.niehs.nih.gov/go/tools_metadataviewer.

8. Appendices

A. Frequently Used Abbreviations

3TC	lamivudine	ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
ADME	absorption, distribution, metabolism, and excretion	IgE	immunoglobulin E
ATSDR	Agency for Toxic Substances and Disease Registry	IRIS	EPA's Integrated Risk Information System
AZT	zidovudine, 3'-Azido-3'-Deoxythymidine	JaCVAM	Japanese Center for the Validation of Alternative Methods
BPA	bisphenol A	KoCVAM	Korean Center for the Validation of Alternative Methods
BSC	Board of Scientific Counselors	LIFE	Longitudinal Investigation of Fertility and the Environment
CASRN	Chemical Abstracts Service Registry Number	LLNA	Local Lymph Node Assay
CDC	Centers for Disease Control and Prevention	miRNA	microRNA
CDMA	code division multiple access	MOU	Memorandum of Understanding
CEBS	Chemical Effects in Biological Systems	N/A	not applicable
CPSC	U.S. Consumer Product Safety Commission	NASH	nonalcoholic steatohepatitis
CYP	cytochrome P450	NCGC	NIH Chemical Genomics Center
ECVAM	European Centre for the Validation of Alternative Methods	NCI	National Cancer Institute
EGEHE	ethylene glycol 2-ethylhexyl ether	NCTR	National Center for Toxicological Research
EPA	U.S. Environmental Protection Agency	NICEATM	NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
ER	estrogen receptor	NHGRI	National Human Genome Research Institute
FDA	U.S. Food and Drug Administration	NIEHS	National Institute of Environmental Health Sciences
FFPE	formalin fixed, paraffin embedded	NIH	National Institutes of Health
FY	fiscal year	NIOSH	National Institute for Occupational Safety and Health
GABA	gamma-amino butyric acid	NTP	National Toxicology Program
GC-MSMS	gas chromatography-tandem mass spectrometry	NVP	Nevirapine
GD	gestational day	OECD	Organisation for Economic Co-operation and Development
GMM	genetically modified model	OSHA	Occupational Safety and Health Administration
GSM	global system for mobile communication	PCB	polychlorinated biphenyl
HHS	U.S. Department of Health and Human Services	PCBTf	chloro-4-(trifluoromethyl) benzene
HPRT	hypoxanthine-guanine phosphoribosyltransferase	PET	Positron Emission Tomography
IARC	International Agency for Research on Cancer	PFOA	perfluorooctanoic acid
ICATM	International Cooperation on Alternative Test Methods		



PFOS	perfluorooctane sulfonate	UPLC-MSMS	ultra-performance liquid chromatography-tandem mass spectrometry
Pig-A	phosphatidylinositol glycan complementation group A	UV	ultraviolet
PND	postnatal day	U.S.	United States
qHTS	quantitative high throughput screening	VOC	volatile organic compound
qNPA	quantitative nuclease protection assay		
QSDAR	quantitative spectrometric data-activity relationship		
RoC	Report on Carcinogens		
SACATM	Scientific Advisory Committee on Alternative Toxicological Methods		
SOT	Society of Toxicology		
TCAB	Tetrachloroazobenzene		
TiO ₂	titanium dioxide		
TOX	NTP Toxicity Report		
TR	NTP Technical Report		

B. Agency Staff and Contact Information

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