Welcome to the 2015 Annual Report

http://ntp.niehs.nih.gov/go/2015annualreport

"The NTP serves a critical role for our nation. It provides a unique consolidated venue for toxicology research, testing, and analysis to occur."
- Dr. Linda Birnbaum, NTP Director

Read the 2015 Letter from the NTP Director.

FY 2015 at a Glance

- West Virginia Chemical Spill Research Program
- 13th Report on Carcinogens Published
- Completed Technical Reports

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- NTP Board of Scientific Counselors
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Research and Testing

- Testing and Toxicology Studies
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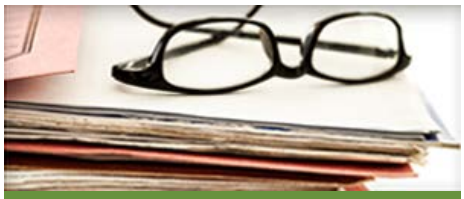
- Tox21
- ICCVAM



Literature Analysis

- Noncancer Research
- Report on Carcinogens

Partner Agency Research

- NTP at NIEHS
- NTP at NIOSH
- NTP at NCTR

Official Citation: National Toxicology Program. 2015. Annual Report for Fiscal Year 2015. Research Triangle Park, NC: National Toxicology Program. http://ntp.niehs.nih.gov/annualreport/2015

Director of Office of Liaison, Policy, and Review and Editor-in-Chief: Mary Wolfe
Managing Editor: Danica Andrews

Letter From the NIEHS and NTP Director

In fiscal year (FY) 2015, NTP continued to advance toxicology and inform public health policy by providing information about substances in our environment to decision makers and the public. Numerous studies were published on substances of public health concern, such as metals, nanomaterials, and widely used industrial chemicals. NTP improved testing methods and health assessments through collaborations with other federal agencies and international groups, refined methods, prepared a handbook for applying systematic review to environmental health research, and released a handbook of preparation instructions for the Report on Carcinogens. NTP also developed more efficient approaches to predict how chemicals may affect human health through the Tox21 initiative.

Dr. Birnbaum has served as the Director of the National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program (NTP) since 2009. (Photo courtesy of Steve McCaw)

On October 2, 2014, the U.S. Department of Health and Human Services Secretary Sylvia Burwell released the 13th Report on Carcinogens, which was prepared by NTP for the secretary. The report lists three new substances as reasonably anticipated to be a human carcinogen, and upgrades the listing of a fourth substance to known to be a human carcinogen. There are a total of 243 substances listed in the report.

In response to a request from the Centers for Disease Control and Prevention (CDC)/Agency for Toxic Substances and Disease Registry, NTP carried out research to evaluate the toxicity of chemicals spilled into the West Virginia Elk River. NTP regularly communicated its findings to the public and other federal agencies via a targeted website. Overall, NTP findings supported the drinking water screening levels established by CDC at the time of the chemical spill.

I invite you to read this report to learn about what we accomplished in FY 2015 to safeguard public health by informing policy with the best science.

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

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FY 2015 at a Glance

Timeline of Events

Highlighted activities of NTP in FY 2015.

West Virginia Chemical Spill Research Program

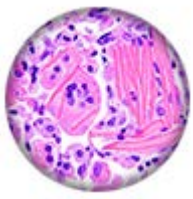
NTP published study findings of a research program to characterize the toxicity of the chemicals spilled into the West Virginia Elk River in 2014.

NTP Partners with EPA to Develop Testing Plan to Replace Animal Use

Scientists at EPA and NICEATM have developed and validated a new approach to replace tests currently used in the EPA Endocrine Disruptor Screening Program.

NTP Scientists Presented SAN Trimer Results at Toms River Public Meeting

EPA invited NTP scientists to discuss studies on the contaminant styrene-acrylonitrile trimer (SAN trimer), in Toms River, Ocean County, New Jersey, a Reich Farm Superfund site.



Nonneoplastic Lesion Atlas

The Web-based NTP Nonneoplastic Lesion Atlas contains hundreds of high-quality images and diagnostic guidelines for nonneoplastic lesions in experimental rodent models.

Diversity Outbred Mice May Predict Potential Human Responses to Chemical Exposures

NTP researchers found that a genetically diverse mouse model may better predict the potential range of response to chemical exposures observed among humans compared to traditional mouse models.

13th Report on Carcinogens Published

The 13th Report on Carcinogens was released in October 2014 by the U.S. Department of Health and Human Services (HHS) Secretary Sylvia M. Burwell.

Handbook for Preparing Report on Carcinogens Monographs

NTP released the Handbook for Preparing Report on Carcinogens Monographs which provides instructions related to potential listings in the report.

Handbook for Conducting Systematic Reviews

The Office of Health Assessment and Translation (OHAT) published the Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration.

Completed Technical Reports

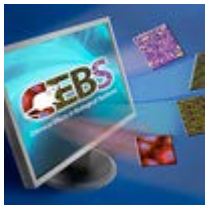
NTP studies are published in NTP report series after undergoing peer review. Technical reports that have been published in FY 2015, or are expected for peer review in FY 2016 are listed.

Evaluating the Impact of NTP: a Case Study on Hexavalent Chromium

NTP developed and applied a methodical approach to broadly assess the program's impact on stakeholders, using hexavalent chromium as a case study.

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.



Databases and Resources

NTP provides a variety of resources for public use including databases and software.

Additional Activities

Additional meetings with stakeholders and the scientific community in which NTP participated.

Publications

Full citations for NTP reports, journal publications, and book chapters published during FY 2015.

Timeline of Events

2014

October

- 13th Report on Carcinogens Published

December

- NTP Board of Scientific Counselors

2015

January

- Handbook for Conducting Systematic Reviews

February

- NTP Scientists Presented SAN Trimer Results at Toms River Public Meeting
- NICEATM FY 2015 Workshops

March

- NICEATM FY 2015 Workshops
- Additional Activities

May

- Noncancer Research

June

- NICEATM FY 2015 Workshops
- NTP Board of Scientific Counselors
- Completed Technical Reports

July

- Handbook for Preparing Report on Carcinogens Monographs
- Completed Technical Reports

September

- SACATM
- NICEATM FY 2015 Workshops

West Virginia Chemical Spill Research Program

In January 2014, a liquid used to wash coal was spilled into the West Virginia Elk River, a primary municipal water source serving about 300,000 people. NTP carried out a research program for toxicological characterization of the spilled chemicals, in response to a July 2014 nomination from the Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry (CDC/ATSDR). NTP used studies in rodents, toxicity tests in cells and other lower animal species such as fish and worms, and computer modeling to predict toxicity.

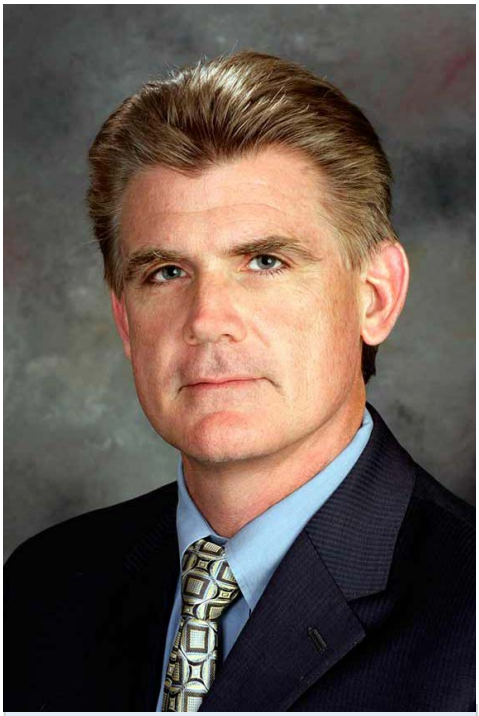
WVU researchers collect a water sample from the Elk River in Charleston, WV. (Photo courtesy of Raymond Thompson/West Virginia University)

Throughout a year of conducting these toxicity tests, NTP regularly updated the public and other federal agencies on study findings. NTP studies reconfirmed that 4-methylcyclohexanemethanol (MCHM), the main component of the spill, is a skin irritant. NTP also found that MCHM caused lower weights in fetuses of pregnant rats exposed to very high doses. Although this fetal growth effect in rats does not establish that MCHM would cause similar effects in humans, it identifies a potential vulnerable life stage. No significant health effects were found for the other spill chemicals. Collectively, NTP studies support adequacy of the drinking water screening levels established at the time of the chemical spill.

next article - "NTP Partners with EPA ..."

NTP Partners with EPA to Develop Testing Plan to Replace Animal Use

Scientists at the U.S. Environmental Protection Agency (EPA) and NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) developed and validated a new approach to replace tests currently used in the EPA Endocrine Disruptor Screening Program. In this program, EPA tests substances to identify chemicals in the environment that may interfere with the normal function of hormones and potentially cause health problems in humans and animals. Chemicals go through a screening phase, known as Tier 1, to assess the potential for them to interfere with normal hormone function resulting in their selection for the next testing phase. Using current assays, Tier 1 screening can take more than five years for a set of chemicals.



Dr. Casey, Director of NICEATM, was a co-author on the approach to replace animal use. (Photo courtesy of Steve McCaw)

The approach developed by EPA and NICEATM will replace three of the five assays currently used in Tier 1. Two of the assays being replaced required the use of animals. This new approach, which utilizes high throughput assays and computational methods, will accelerate the pace of screening chemicals, decrease costs, and reduce animal use. The approach is described in detail in a manuscript published in Environmental Science and Technology in FY 2015.

"West Virginia Chemical Spill ..." - previous article

next article - "NTP Scientists Presented SAN ..."

NTP Scientists Presented SAN Trimer Results at Toms River Public Meeting

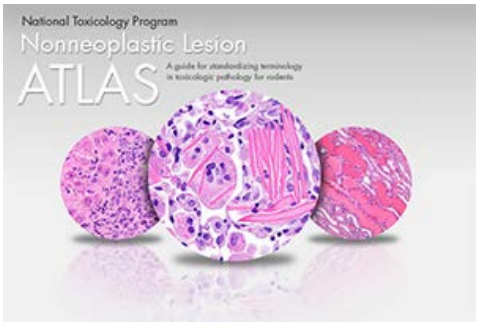
On February 4, 2015, the U.S. Environmental Protection Agency (EPA) held a public meeting to update the community about the Reich Farm Superfund site in Toms River, Ocean County, New Jersey. EPA invited NTP scientists to discuss their studies on styrene-acrylonitrile trimer, also known as SAN trimer. SAN trimer was one of the contaminants at the site and is a byproduct of manufacturing acrylonitrile styrene plastic.

Mamta Behl, Ph.D., a neurotoxicologist with NTP, was at the meeting to discuss the research on SAN trimer. Susan Elmore, D.V.M., a scientist in the NTP Pathology Group, presented the SAN trimer pathology findings. (Photo courtesy of Steve McCaw)

Due to a lack of scientific information about SAN trimer, EPA asked NTP to study the chemical. After an extensive design, study, and peer-review process, NTP published its results in 2012 in NTP Technical Report 573. NTP found no evidence that SAN trimer caused cancer in male and female rats. Some noncancer effects, such as peripheral nerve damage in the exposed male and female rats, were reported. EPA is using NTP findings, along with other data, to establish cleanup levels for the Superfund site.

"NTP Partners with EPA ..." - previous article
next article - "Nonneoplastic Lesion Atlas ..."

Nonneoplastic Lesion Atlas



In FY 2015, work continued on the NTP Nonneoplastic Lesion Atlas, a Web-based resource that currently contains hundreds, and will eventually contain thousands, of high-quality images and diagnostic guidelines for nonneoplastic lesions in experimental rodent models. While nonneoplastic lesions are not cancerous, nonneoplastic diseases, such as cardiovascular and pulmonary diseases, are a major cause of illness and death, and many are thought to have environmental causes. For example, forms of pulmonary fibrosis, a disease that causes lung scarring, have been linked to exposures to inorganic materials such as asbestos, vanadium, cobalt, nickel, beryllium, and sulfur dioxide; and organic materials such as dust from cotton, grain, and wood.

Diagnosing and recording nonneoplastic lesions can be challenging, and terminology and diagnostic strategies can vary among pathologists. The purpose of the NTP Nonneoplastic Lesion Atlas is to standardize the terminology, diagnostic strategy, and recording of nonneoplastic rodent lesions; improve consistency; and facilitate database searches, comparisons between studies, and generation of historical control data for nonneoplastic lesions. The atlas was launched in FY 2014. To date, 47 organs have been completed, and the atlas should be completed in FY 2016.

"NTP Scientists Presented SAN ..." - previous article

next article - "Diversity Outbred Mice May ..."

Diversity Outbred Mice May Predict Potential Human Responses to Chemical Exposures

NTP researchers found that a genetically diverse mouse model may better predict the potential range of response to chemical exposures observed among humans compared to traditional mouse models. Each Diversity Outbred mouse is genetically unique, and the extent of genetic variability among these mice is similar to the genetic variation seen among humans.

Jef French, Ph.D., who is now retired, devoted several years to studying in vivo animal models to explore individual variability in toxicity response. (Photo courtesy of Steve McCaw)

In this research project, the mice were exposed to benzene, and, like humans, each Diversity Outbred mouse responded to the effects of benzene exposure differently. Benzene is a common air pollutant and human carcinogen found in crude oil, gasoline, and cigarette smoke, and naturally produced by wildfires and volcanoes. Scientists assessed the biological response of the mice by measuring the frequency of micronucleated red blood cells, a blood-borne marker of chromosomal damage, which is a hallmark of benzene exposure.

Some mice demonstrated sensitivity to benzene exposure, while others showed no response. There was about a five-fold difference between lowest to highest response. Because the researchers knew the genetic makeup of each mouse, they could pinpoint the genomic regions involved in susceptibility or resistance to the chemical exposure, and then look for related genetic regions in human chromosomes.

These results may lead to further research to better understand genetically regulated responses to toxicity in humans, as well as mechanisms of susceptibility and resistance to environmental exposures as they relate to disease. The paper describing these findings was published in Environmental Health Perspectives in FY 2015.

"Nonneoplastic Lesion Atlas ..." - previous article

next article - "13th Report on Carcinogens ..."

13th Report on Carcinogens Published

In October 2014, the U.S. Department of Health and Human Services (HHS) Secretary Sylvia M. Burwell released the 13th Report on Carcinogens. The Report on Carcinogens is a congressionally mandated report prepared by NTP for the HHS secretary. The report identifies agents, substances, mixtures, and exposures in two categories: known to be a human carcinogen and reasonably anticipated to be a human carcinogen.

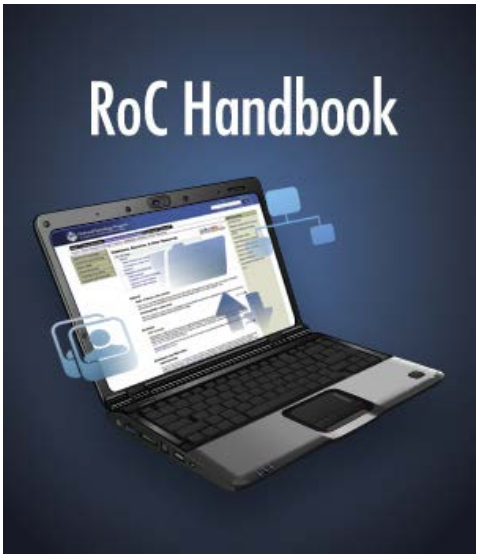
The 13th report includes 243 listings. Ortho-toluidine, used to make rubber chemicals, pesticides, and dyes, was reevaluated and is now listed as a known human carcinogen. Three substances were added as reasonably anticipated to be human carcinogens. They include 1-bromopropane, used as a cleaning solvent and spray adhesive; cumene, used to make phenol and acetone and found in fuel products and tobacco smoke; and the wood preservative mixture pentachlorophenol and by-products of its synthesis.

Additional Links for the RoC

- Report on Carcinogens
- RoC Activities in 2015
- Newly Reviewed Listings
- RoC Candidate Substances

"Diversity Outbred Mice May ..." - previous article
next article - "Handbook for Preparing Report ..."

Handbook for Preparing Report on Carcinogens Monographs



In FY 2015, NTP released the Handbook for Preparing Report on Carcinogens Monographs, which was prepared by the Office of the Report on Carcinogens. The handbook provides instructions for conducting cancer hazard evaluations and preparing monographs on substances NTP is evaluating for potential listing in the Report on Carcinogens. The handbook is based largely on, and expanded from, protocols used to prepare the monographs. As a living document, the handbook will be updated based on lessons learned from preparing monographs and may also incorporate new systematic review tools and harmonize systematic review methods used by other scientists.

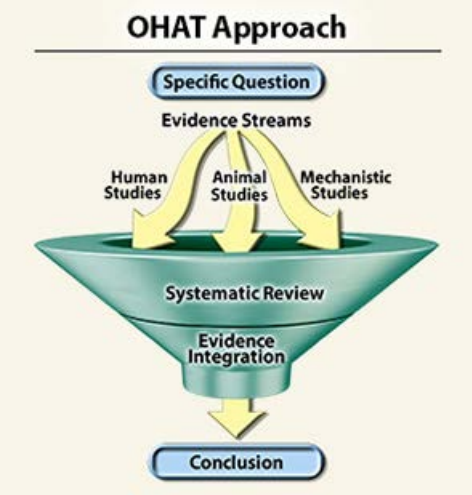
Additional Links for the RoC

- Report on Carcinogens
- RoC Activities in 2015
- Newly Revised Listings
- RoC Candidate Substances

"13th Report on Carcinogens ..." - previous article

next article - "Handbook for Conducting Systematic ..."

Handbook for Conducting Systematic Reviews



The Office of Health Assessment and Translation (OHAT) published the Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. This handbook provides standard operating procedures for the implementation of systematic review in OHAT evaluations. They are based on (1) lessons learned from developing protocols for two case studies for implementing systematic review, (2) consideration of public comments received on systematic review between 2012 and 2014, and (3) discussions with experts at other organizations and agencies working on applying methods of systematic review to environmental health and toxicology. The handbook is a living document that will be updated as methodological practices are refined and developed to improve the reliability, ease, and efficiency of conducting systematic reviews.

"Handbook for Preparing Report ..." - previous article

next article - "Completed Technical Reports ..."

Completed Technical Reports

The results of NTP studies undergo peer review and are published in NTP report series. Long-term toxicology and carcinogenicity studies, generally two-years in length, are reported in the NTP Technical Report (TR) series. Toxicity (TOX) reports are for shorter-term studies, generally up to 13 weeks. All peer reviewers are screened for conflict of interest prior to confirming their service. These reports are available on the NTP website and catalogued in PubMed.

NTP TRs published in FY 2015 are listed in the table below. NTP used established criteria to evaluate the findings and determine the strength of the evidence for conclusions regarding the carcinogenic activity of each substance. The conclusions for level of evidence of carcinogenic activity are included in the table. The final reports are available on the NTP website.

NTP anticipates two draft TRs will undergo peer review in FY 2015, as listed in the second table below.

Technical Reports Published During FY 2015 Reporting Levels of Evidence of Carcinogenic Activity

Chemical	Technical Report Number/ CASRN	Use	Male Rats	Female Rats	Male Mice	Female Mice
Cobalt	TR-581 7440-48-4	Used in the production of alloys, in nuclear medicine, and as a catalyst in organic reactions. Exposure to cobalt metal dust occurs in a variety of metalworking occupations. Associated with tobacco either as a natural component of tobacco, pyrolysis product in tobacco smoke, or additive for one or more types of	Clear evidence	Clear evidence	Clear evidence	Clear evidence

		tobacco products.				
CIMSTAR 3800	TR-586	Semisynthetic metal working fluid.	Equivocal evidence	Equivocal evidence	No evidence	Some evidence
Glycidamide	TR-588 5694-00-8	Metabolite of acrylamide. Associated with tobacco 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
Vinylidene chloride	TR-582 75-35-4	Copolymerized with vinylchloride or acrylonitrile for saran and saran fibers. A widely used chemical intermediate and monomer.	Clear evidence	Some evidence	Clear evidence	Clear evidence

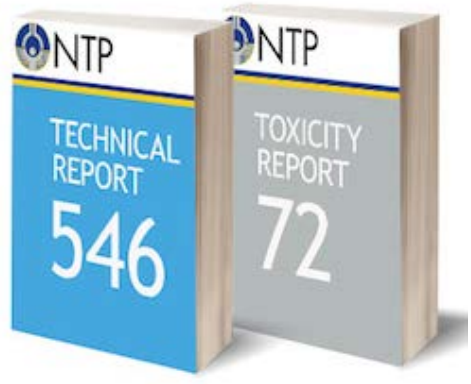
Technical Reports Expected to Undergo Peer Review in FY 2016

Chemical	Technical Report Number/CASRN	Use
Antimony trioxide	TR-590 1309-64-4	Flame retardant in fabrics, resins, and wood coatings; pigment and additive for opacity in glass, ceramics, and plastic; chemical intermediate for potassium antimony tartrate; raw material for manufacture of antimony metal.
Trim® VX	TR-591	Soluble oil and metalworking fluid.

"Handbook for Conducting Systematic ..." - previous article

next article - "Evaluating the Impact of ..."

Evaluating the Impact of NTP: a Case Study on Hexavalent Chromium



For over 35 years, NTP has conducted research and analysis activities and disseminated information about potential health hazards in our environment. NTP sought to develop and apply a methodical approach to broadly assess the program's impact on stakeholders, including academia, industry, federal agencies, state agencies, nongovernment groups, and international groups. NTP developed a logic model with defined outputs (activities and products) and outcomes (proximal, intermediate, and distal), and applied it retrospectively to the research program on hexavalent chromium (CrVI) as a case study. For proximal outcomes, views of, and requests for, NTP products by external stakeholders were measured. Bibliometric analysis was conducted to account for intermediate outcomes. For distal outcomes, Web and LexisNexis searches were conducted to find references to NTP work in documents related to legislation or regulation changes.

This approach identified awareness of NTP work on CrVI by external stakeholders and citations of NTP research in scientific publications, reports, congressional testimonies, and legal and policy documents. NTP research was key to the nation's first-ever drinking water standard for CrVI adopted by California in 2014. In applying this approach to a case study, NTP also found challenges to evaluating the outcomes of a research program.

This study was presented at the December 9-10, 2014, NTP Board of Scientific Counselors meeting. A manuscript is in preparation to describe this study's broad and objective approach for assessing the effectiveness of NTP, including methodological needs for more thorough and efficient impact assessments in the future.

"Completed Technical Reports ..." - previous article next article - "NTP Impact on Regulatory ..."

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. Below is a highlights listing of the NTP data and recommendations used by other agencies in FY 2015, a full listing is also available on the NTP website.

Use of NTP Study Data or Recommendations by Federal and State Regulatory Agencies in FY 2015

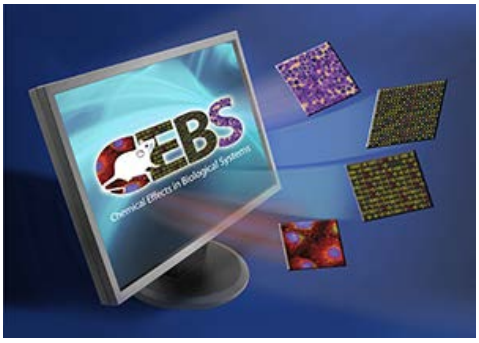
Notice	Summary of Notice	NTP Information Cited
Chemical listed effective June 19, 2015, as known to the state of California to cause reproductive toxicity: ethylene glycol (ingested)	Effective June 19, 2015, the Office of Environmental Health Hazard Assessment (OEHHA) is adding ethylene glycol (ingested) (CAS No. 107-21-1) to the list of chemicals known to the state to cause reproductive toxicity for purposes of Proposition 65. June 19, 2015 – Proposition 65	NTP-CERHR (2004). NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Ethylene Glycol. Research Triangle Park, NC, National Toxicology Program, Center for the Evaluation of Risks to Human Reproduction: NIH Publication No. 04-4481.
Chemical listed effective March 27, 2015, as known to the state of California to cause cancer: beta-myrcene	Effective March 27, 2015, the Office of Environmental Health Hazard Assessment (OEHHA) is adding beta-myrcene (CAS No. 123-35-3) to the list of chemicals known to the state to cause cancer for purposes of Proposition 65 March 24, 2015 – Proposition 65	NTP (2010). Toxicology and Carcinogenesis Studies of β-Myrcene (CAS No. 123-35-3) in F344/N Rats and B6C3F1 Mice (Gavage Studies). Technical Report Series No. 557, NIH Publication No. 10-5898. U.S. Department of Health

		and Human Services, NTP, Research Triangle Park, NC.
Final rule: addition of 1-bromopropane; community right-to-know toxic chemical release reporting	The U.S. Environmental Protection Agency (EPA) is adding 1-bromopropane to the list of toxic chemicals subject to reporting under section 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA) of 1986 and section 6607 of the Pollution Prevention Act (PPA) of 1990. 1-Bromopropane was classified by NTP in the 13th Report on Carcinogens as 'reasonably anticipated to be a human carcinogen.' EPA has determined that 1-bromopropane meets the EPCRA section 313(d)(2)(B) criteria because it can reasonably be anticipated to cause cancer in humans. November 23, 2015 – 80 FR 72906	NTP (2014). Report on Carcinogens, Thirteenth Edition. Released October 2, 2015. U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, Research Triangle Park, NC 27709. NTP (2013). Report on Carcinogens Monograph on 1-Bromopropane. Office of the Report on Carcinogens, Division of the National Toxicology Program, National Institute of Environmental Health Sciences, U.S. Department of Health and Human Services. NIH Publication No. 13-5982, September 25, 2013.

"Evaluating the Impact of ..." - previous article

next article - "Databases and Resources ..."

Databases and Resources



NTP provides a variety of resources for public use. Several of these tools are actively being improved, with new features scheduled to be released in the future. The tools provided by NTP include:

- Nonneoplastic Lesion Atlas
- Chemical Effects in Biological Systems (CEBS) Database
- NTP Archives
- NIH Chemical Genomics Center (NCGC) BioPlanet (scheduled release 2016)
- DrugMatrix and ToxFX
- Meta Data Viewer

"NTP Impact on Regulatory ..." - previous article

next article - "Additional Activities ..."

Additional Activities

NTP participated in a number of meetings with stakeholders and the scientific community. At the 2015 annual meeting of the Society of Toxicology in San Diego, staff from NTP and NIEHS participated in more than 45 workshops, symposia, platform sessions, education and information sessions, and poster sessions. The full program, including all NTP and NIEHS activities, can be found at on the Society of Toxicology website.

When Yun Xie, Ph.D., left, of NTP, Chad Blystone, Ph.D., center, of NTP, and Tammy Collins, Ph.D., head of the NIEHS Office of Fellows' Career Development, were not presenting posters or leading sessions, they were available at the NIEHS exhibit, giving advice to postdoctoral researchers or answering questions about ongoing research efforts. (Photo courtesy of Robin Mackar)

NTP also hosts symposiums and workshops to discuss the state of the science, and advances to the field. For example, the 2015 annual NTP Satellite Symposium, Pathology Potpourri, will be held in Minneapolis, Minnesota, October 17, at the American College of Veterinary Pathologists, American Society for Veterinary Clinical Pathology, and Society of Toxicologic Pathology combined annual meeting. The goal of this annual symposium is to present current diagnostic pathology or nomenclature issues to the toxicologic pathology community, including diagnostically difficult, interesting, or rare lesions, or challenging nomenclature issues. Proceedings of the symposium will be published in the journal Toxicologic Pathology, along with summaries of presentations on diagnostic or nomenclature issues, and specific pathologic images that were used for audience voting and discussion.

NTP postdoctoral fellow Erin Quist, D.V.M., at computer monitor, gave hands-on tutorials on the NTP Atlas. (Photo courtesy of Robin Mackar)

NTP also hosted four workshops in FY 2015 related to alternative methods development:

- Technical Discussion on In Vitro Testing Strategies to Assess Inhalation Toxicity of Nanomaterials.
- In Search of Acceptable Alternatives to the HIST: What is Possible and Practical?

- Workshop on Good Cell Culture Practices for Induced Pluripotent Stem Cells.
- Alternative Approaches for Identifying Acute Systemic Toxicity: Moving From Research to Regulatory Testing.

"Databases and Resources ..." - previous article next article - "Publications ..."

Publications

NTP Reports and Documents

National Toxicology Program. 2015. Handbook for Conducting a Literature-Based Health Assessment Using Office of Health Assessment and Translation (OHAT) Approach for Systematic Review and Evidence Integration. Research Triangle Park, NC: National Toxicology Program. http://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf

National Toxicology Program. 2015. Handbook for Preparing Report on Carcinogens Monographs. Research Triangle Park, NC: National Toxicology Program. http://ntp.niehs.nih.gov/ntp/roc/handbook/roc_handbook_508.pdf

National Toxicology Program. 2015. National Toxicology Program Monograph On Identifying Research Needs For Assessing Safe Use Of High Intakes Of Folic Acid. Research Triangle Park, NC: National Toxicology Program. http://ntp.niehs.nih.gov/ntp/ohat/folicacid/final_monograph_508.pdf

National Toxicology Program. 2015. National Toxicology Program Technical Report on the Toxicology and Carcinogenesis Studies of CIMSTAR® 3800 (CASRN CIMSTAR3800) in Wistar Han Rats and B6C3F1 Mice (Inhalation Studies). TR 586. Research Triangle Park, NC: National Toxicology Program. http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr586_508.pdf

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[1] Funded by the NIEHS/NIOSH Interagency Agreement

[2] Funded by NIOSH voluntary allocations to the NTP

[3] Funded by the NIEHS/NCTR Interagency Agreement

[4] Funded by NCTR voluntary allocations to the NTP

[5] Funded by NIEHS voluntary allocations to the NTP

[6] Funded by the NIEHS/EPA Interagency Agreement

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Learn About Us

Mission and Goals

NTP was established in 1978 in response to concerns about potential human health effects of chemicals in our environment.

Organizational Structure and Oversight

Three agencies form the core for NTP: NIOSH, NCTR, and NIEHS.

Funding

The total NTP budget for FY 2015, and contracts that support NTP research.

Interagency Agreements

In FY 2015, NIEHS provided support for NTP activities through interagency agreements with other federal agencies.

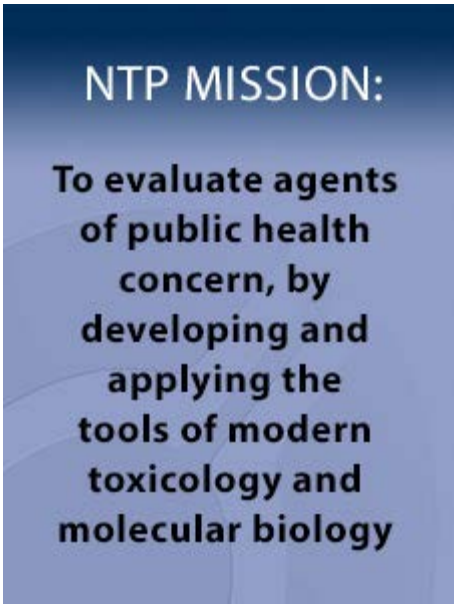
Training Opportunities

NTP offers postdoctoral training fellowships designed to prepare trainees for careers in science.

Program Contact Information

General inquiries, websites, and staff directory information.

Mission and Goals



NTP was established in 1978 by the U.S. Department of Health, Education, and Welfare, now the U.S. Department of Health and Human Services (HHS), in response to concerns about potential human health effects of chemicals in our environment. Specifically, NTP goals were to:

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

NTP provides scientific data, interpretation, and guidance in the appropriate uses of these data to regulatory agencies and other health-related research groups. The American people and government agencies, at state and federal levels, rely on NTP to provide a strong scientific basis for making credible decisions that will protect public health. In the past 37 years, NTP has studied and shared information on the health effects of more than 2,500 substances, including dietary supplements, industrial chemicals, consumer products, and complex mixtures.

In following government-wide efforts to increase access to the results of federally funded scientific research, NTP maintains open communications and dialogue with federal and state agencies, industry, nongovernmental organizations, academia, and the public. The NTP website provides the public with a variety of information, including Federal Register notices, status of and data from NTP

studies, access to NTP reports and journal publications, and notifications through media releases, a calendar of upcoming events, and the NTP Update 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. In addition, requests for information can be made through the Central Data Management office via email or calling 919-541-3419, or Freedom of Information Act coordinator.

NTP welcomes input on its programs and priorities. This input can be submitted in response to formal requests for public comment in Federal Register notices or informal submissions to the Office of Liaison, Policy, and Review (919-541-7539 or ntpinfo@niehs.nih.gov).

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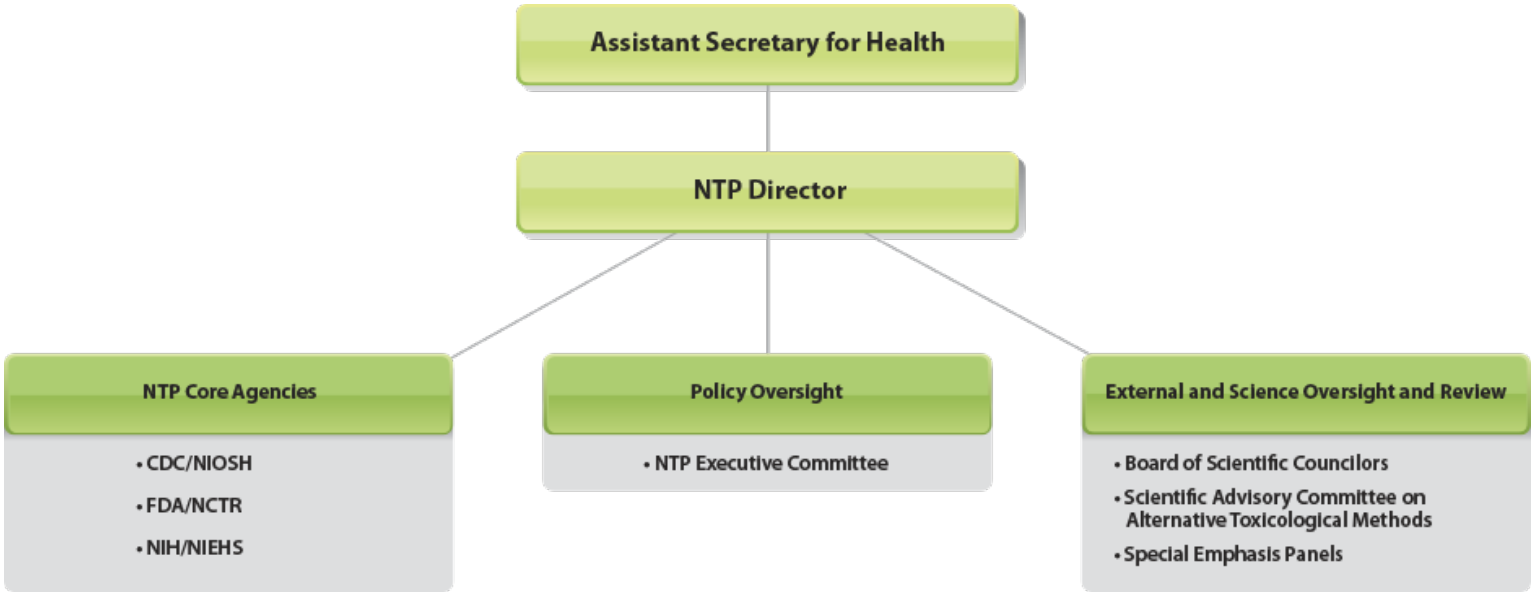
Organizational Structure and Oversight

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



NTP is located administratively at NIEHS, and Linda Birnbaum, Ph.D., serves as director of both NIEHS and NTP. John Bucher, Ph.D., is NTP associate director and director of the NTP Division at NIEHS, herein referred to as NIEHS/NTP, which is the focal point for NTP activities. NIEHS and NTP utilize best research practices and embrace developments in technology to discover how the environment affects people, maintaining leadership in the field of environmental health sciences by applying innovative research to address public health issues.

John Howard, M.D., is director of NIOSH, and Elizabeth Whelan, Ph.D., chief of the Industrywide Studies Branch of the Division of Surveillance, Hazard Evaluations, and Field Studies, manages NTP activities within NIOSH, herein referred to as NIOSH/NTP. Staff from three NIOSH divisions participate in NTP: the Division of Surveillance, Hazard Evaluations, and Field Studies, and the Division of Applied Research and Technology; Education and Information Division; and Health Effects Laboratory Division.

NIOSH’s mission 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 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., Ph.D., is director of NCTR, and Paul Howard, Ph.D., associate director of the Office of Scientific Coordination, manages NTP activities within NCTR, herein referred to as NCTR/NTP. 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. NCTR conducts an array of studies that reflect the NTP mission and are critical in supporting FDA product centers and their regulatory roles.

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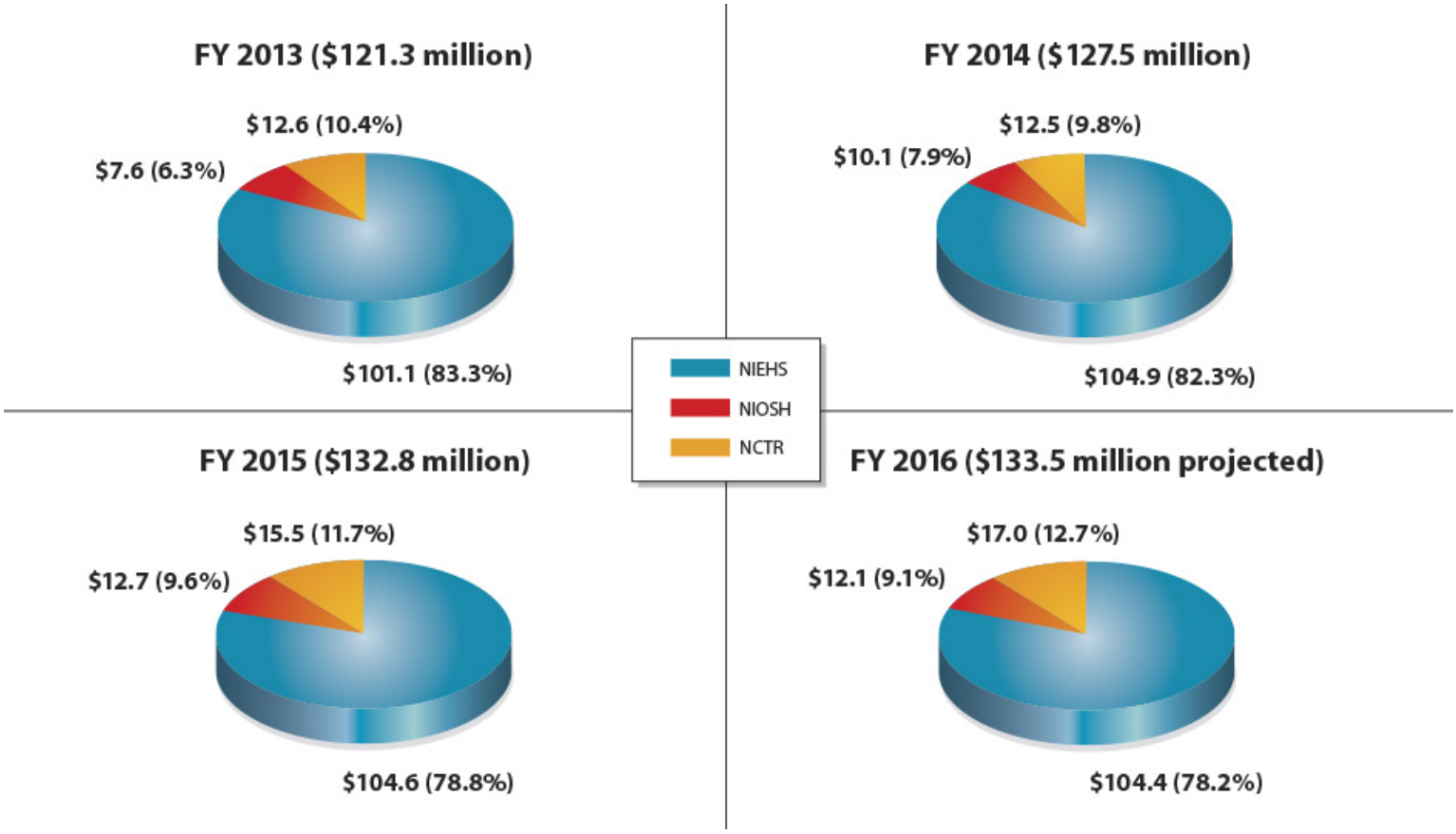
Funding

NTP relies on voluntary allocations from the 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 the figure, the total NTP budget for FY 2015 was $132.7 million.



NTP conducts its research studies through contract laboratories, in-house at the three core agencies, or through interagency agreements with other agencies. In FY 2015, NIEHS funded 36 contracts, listed in the table below, held four workshops, three special emphasis panel peer-review meetings, and three scientific advisory meetings for NTP. There may be additional contracts at the other agencies that support some of their voluntary NTP efforts.

NIEHS Contracts That Supported NTP Activities in FY 2015

Description	Contractor
Absorption, Distribution, Metabolism Excretion	Lovelace Biomedical Research Triangle Institute
Acute System Toxicity Testing by NICEATM	Palladian Partners, Inc.
Analysis of Bisphenol A in Zebrafish	Oregon State University
Analytical Chemistry Services	Midwest Research Institute Battelle Memorial Research Triangle Institute
Archives and Specimen Repository	Experimental Pathology Laboratories
Bioinformatics Methylation Project	Laboratory Corp of America
Carcinogenic Potential of Cellphone Radio Frequency	IIT Research Institute
Computational and bioinformatics support	Kelly Scientific
Evaluate Toxicity Following Early Life Exposure	Southern Research Institute
Evaluation of Alternative Toxicological Methods	Integrated Laboratory Systems
Evaluation the Toxicity of Selected Chemicals	Battelle Memorial
Genetic Toxicity Testing Support Services	Integrated Laboratory Systems
Immunotoxicity Potential of Environmental and Therapeutic Agents	Burleson Research Technologies
In Life Data Collection and Management System	INSTEM, LSS
NTP Computer and User Support	Vistronix Inc.
NTP Information Systems Support	Signature Consulting Group, LLC
NTP Statistical and Computer Support	SRA International
NTP Technical Reports Preparation Support Services	Biotechnical Sciences, Inc.
OHAT Literature-Based Evaluations	ICF, Inc.
	PAI/Charles River

Pathology Support	Laboratories Experimental Pathology Laboratories Integrated Laboratory Systems
Polycyclic Aromatic Compounds Residue Analysis	Oregon State University
Production of B6C3F1 Mice	Taconic Farms
Productive Assessments by Continuous Breeding	Research Triangle Institute
Provision for Animals and Specialized Services	Charles River, Jax, Taconic
Quality Assessment Support/Audits & Inspections	Dynamac CSS-Dynamac Corporation
Research on InhalationToxicology of Environ Chemicals	Alion Science & Technology
Screening for Potential Persisting Neurobehavioral Effects in Zebrafish (Flame Retardants)	Duke University
Support for GeneCo Database (MetaDrug)	Thomson Reuters
Support for preparation of the Report on Carcinogens	Integrated Laboratory Systems
Toxicological and Carcinogenic Potential of Chemicals	Battelle Memorial

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Interagency Agreements

In FY 2015, NIEHS provided support for NTP activities through interagency agreements with other federal agencies.

FDA/NCTR

In December 1992, NIEHS and FDA established a formal interagency agreement (IAA) to conduct toxicology studies on FDA-regulated agents nominated to NTP and studies at NCTR. These studies are designed to provide FDA and other regulatory agencies with hazard identification and dose-response data to support risk assessment and risk management decisions that could affect public health.

This IAA has supported studies on endocrine active agents, dietary supplements, food contaminants, AIDS therapeutics, pediatric medicines, electromagnetic radiation, cosmetics, and nanoscale materials. Studies in these areas have produced 18 published NTP Technical Reports and over 200 peer-reviewed journal publications. Some of the data from the IAA-supported studies have led to an increased understanding of the pharmacokinetics, mechanism of action, or dose-response of substances. Other data have led to refinement of risk assessment models.

CDC/NIOSH

NIEHS/NTP has two interagency agreements (IAAs) with NIOSH. One IAA was established in the early 1990s in response to increased efforts by NTP to study noncancer endpoints. NIOSH and NTP have conducted studies to assess the potential toxicity of exposures to substances such as fungi, mycotoxins, volatile organics, lead, latex, nickel, isocyanates, and beryllium. Studies have included workers such as miners, farmers, health care workers, autoworkers, and firefighters, exposed to mixtures of chemicals. There have also been a number of studies examining how genetic variability in immune-inflammatory-antioxidant responses contributes to the development and severity of inflammatory and allergic disease in people of different occupations.

The second IAA involves multiple projects. NIEHS/NTP and NIOSH have worked to establish methodologies to assess complex mixtures, such as asphalt fume, welding fume, and tungsten fibers. NIOSH and NIEHS/NTP are jointly supporting two large initiatives that evaluate emerging issues in

nanotechnology. One project focuses on identifying workplaces engaged in the development, production, and use of engineered nanomaterials, the first objective is to determine the potential for worker exposure to selected engineered nanoparticles. The second objective is to evaluate potential toxicity from workplace exposures to engineered nanomaterials. Another study with similar purpose and design to evaluate occupational exposure to bisphenol A is also in progress.

Many studies performed under these IAAs are published in the peer-reviewed literature and have been used for hazard identification, and regulatory and intervention purposes.

CDC/DLS

NIEHS/NTP and CDC/Division of Laboratory Sciences (DLS) are participating in a pilot study to characterize exposure profiles in a subset of 50 Danish women, who will be enrolled in a larger study of 500 women. The pilot study is designed to assess whether exposure to several common endocrine-disrupting chemicals is related to reproductive health problems, such as infertility, risk of miscarriage, and low birth weight, or childhood obesity or other health outcomes in the children. Endocrine-disrupting chemicals from the organotins and phthalates classes will be evaluated. Blood and urine samples will be collected three times from each woman, once prior to pregnancy and twice during pregnancy. This collaboration between NIEHS/NTP and CDC/DLS facilitates common goals in understanding individual exposure profiles for multiple chemicals in woman of reproductive age.

The chemical analysis has been completed and statistical analysis of co-patterns of exposure is underway. In FY 2015, a paper was published from this study in the journal Talanta about a method for simultaneous determination of organotins in human serum. A second paper about organotin and tin levels in Danish women was submitted.

NIH/NCATS/DPI

This IAA supports ongoing and anticipated studies conducted at the National Center for Advancing Translational Sciences (NCATS)/Division of Pre-Clinical Innovation (DPI), to evaluate high throughput and high content screening assays in support of Tox21. Tox21 is an ongoing collaboration among federal agencies to characterize the potential toxicity of chemicals by using cells and isolated molecular targets instead of laboratory animals. This collaboration between NIEHS/NTP and NCATS/DPI should produce data for substances lacking needed toxicological information that can be used to prioritize substances for further studies, including toxicological evaluation, mechanisms of action investigation, and development of predictive modeling for biological response. The use of the assays should greatly increase the number of substances tested and decrease the cost of testing.

Additional Agreements

NTP also established several smaller interagency agreements to conduct research, listed in the table below.

Additional Interagency Agreements in FY 2015

Study-Agency	Description
Sisters Collaborative Study - EPA	Research exposure patterns of personal care product use and the association with breast cancer and associated risk factors.
Folic Acid Expert Panel - NIH Office of Dietary Supplements	Provide support for conduct of an expert panel to identify research needs related to the safe use of high intakes of folic acid based on consideration of the state of the science.
Addressing Challenges in the Assessment of Botanical Dietary Supplement Safety Workshop - NIH	Provide support for conduct of a workshop in FY 2016 to identify potential adverse effects of these agents after both short-term exposure and long-term exposure. More information can be found here on the NTP website.

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Training Opportunities

NIEHS/NTP offers a limited number of postdoctoral training fellowships to prepare trainees for careers in pharmaceutical and chemical industries, regulatory agencies, and academia. Full details on opportunities, benefits, and the application process can be found on the NIEHS training website. The training program has six focal 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 2015, NIEHS/NTP staff mentored 19 postdoctoral fellows at NIEHS.

NIEHS/NTP Training Program Postdoctoral Fellows in FY 2015

Training Program	Fellow
Applied toxicology and carcinogenesis	Natasha Catlin In Ok Surh Brian Sayers Kristen Ryan Georgia Hinkley
Biomolecular screening and computational toxicology	Jui-Hua Hsieh Sreenivasa Ramaiahgari
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	Tanasa Osborne Erin Quist

"Interagency Agreements ..." - previous article

next article - "Program Contact Information ..."

Program Contact Information

For general inquiries, contact:

Central Data Management
P.O. Box 12233, MD K2-05
Research Triangle Park, NC 27709
919-541-3419
cdm@niehs.nih.gov (or use our contact form).

A **Staff Directory** is available.

"Training Opportunities ..." - previous article

Scientific and Public Input Opportunities

Nominations

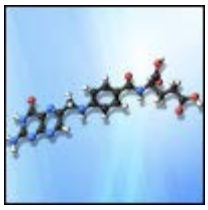
NTP nominations are open to the public, and continually accepted from the NTP website.

NTP Board of Scientific Counselors

The NTP Board of Scientific Counselors (BSC) provides scientific oversight to NTP on the scientific merit of its programs and activities.

SACATM

Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) provides advice on priorities and activities related alternative toxicological test methods.



Special Emphasis Panels

NTP uses ad hoc scientific panels to provide independent scientific peer review and advice on targeted issues including the review of NTP technical reports and monographs.

NTP Executive Committee

The NTP Executive Committee provides programmatic and policy oversight to the NTP director.

Nominations

NTP continually accepts and reviews nominations for studies in its research and testing program. The NTP nomination process is open to the public, and nominations can be submitted via the NTP website. Agencies represented on the NTP Executive Committee also identify and forward nominations to NTP. For new studies or research projects of substantial scope and complexity, NTP research concepts or project plans are prepared to facilitate external review as part of a multi-step process with input from NTP participating federal agencies, Board of Scientific Counselors (BSC), and the public.

In July 2014, NTP received a nomination from the Centers for Disease Control and Prevention (CDC)/Agency for Toxic Substances and Disease Registry (ATSDR) to conduct toxicity studies on the predominant chemicals known to be involved in the West Virginia Elk River chemical spill. In response, NTP formulated plans to conduct a number of studies to provide more information about the chemicals and their potential health effects. The NTP Research Project Plan was released and presented to the Board of Scientific Counselors (BSC) in December 2014.

NTP also conducts new studies to extend or explain findings observed in previously conducted studies and address new nominations that are closely aligned with current research efforts. An update on testing nominations was presented to the BSC in December 2014. New studies initiated or approved in FY2015 in response to several recent nominations are provided below.

Questions about the nomination, review, and selection process can be sent to Scott Masten, Ph.D., at masten@niehs.nih.gov.

Research and Testing Projects Initiated in FY 2015

Project CASRN* Study Scientist	Nomination Rationale and Project Aims
Decabromodiphenylethane 84852-83-9 Dunnick	Due to increased demand and use as an alternative to decabromodiphenyl ether, decabromodiphenylethane is widely detected in indoor and outdoor environments, biota, and consumer products. Subacute and subchronic toxicology studies in rats indicate the liver is a

	target organ. This compound is included along with other brominated flame retardants as part of a short-term toxicogenomic evaluation.
Firemaster 550 and constituents: 2-Ethylhexyl-2,3,4,5-tetrabromobenzoate 183658-27-7 Bis(2-ethylhexyl) tetrabromophthalate 26040-51-7 Triphenyl phosphate 115-86-6 Isopropylated phenol phosphate 68937-41-7 Behl	A widely used flame retardant alternative to polybrominated diphenyl ethers, Firemaster 550 is a mixture of brominated aromatic and aromatic phosphate components and has been widely detected in the environment, biota, and indoor dust. Activity at nuclear hormone receptors has been demonstrated from in vitro studies, yet there is very limited in vivo data for the commercial mixture and some of its components. The two phosphate components (115-86-6 and 68937-41-7) are included in the ongoing aromatic phosphate flame retardant research program. The other two components (183658-27-7 and 26040-51-7) are included along with other brominated flame retardants as part of a short-term toxicogenomic evaluation.
Microcystin-LR 101043-37-2 McIntyre	Microcystins are among the most common cyanobacterial toxins that contaminate recreational water and drinking water sources, with documented adverse human health effects and a robust literature on hepatotoxicity and mechanisms of action in animal models. There are no long-term rodent toxicity studies and existing data indicate concern for potential adverse effects during sensitive periods of development. NTP has previously conducted toxicogenomic studies following acute exposure. A new study to provide a comprehensive assessment of developmental, reproductive, and general toxicity following subchronic drinking water exposure is under development.

*CASRN = Chemical Abstracts Service Registry Number

next article - "NTP Board of Scientific ..."

NTP Board of Scientific Counselors

The NTP Board of Scientific Counselors (BSC), a federally chartered advisory group, provides scientific oversight to NTP on the scientific merit of its programs and activities. The HHS secretary 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 NTP activities. The BSC charter and current roster are available on the NTP webpage. Lori White, Ph.D., serves as the designated federal officer and manager of the BSC. Below is the roster for FY 2015.

The BSC met twice in FY 2015. During the meeting on December 9-10, 2014 the BSC:

- Reviewed the NTP Toxicology Branch and its chief Paul Foster, Ph.D.
- Voted on two contract concepts: (1) Scientific Information Management and Literature-based Evaluations for NTP and (2) Support for Toxicological Data for NTP.
- Heard an update on NTP testing program nominations and NTP activities assessing the West Virginia Elk River chemical spill.
- Heard a report on the Report on Carcinogens peer-review meeting on trichloroethylene, held in August 2014.
- Heard an update on Office of Health Assessment and Translation activities, and reviewed the draft concept Immunotoxicity Associated with Exposure to Perfluorooctane Acid and Perfluorooctane Sulfonate.
- Heard a report on draft NTP Technical Reports peer reviewed in May 2014, including green tea extract, indole-3-carbinol, CIMSTAR 3800, and bromodichloroacetic acid.
- Heard the presentation Assessing the Biological Relevance of In Vitro Data: A Case Study using Estrogen Pathway Signaling.
- Learned about NTP evaluation activities in the talk Assessing NTP's Effectiveness: A Case Study on Hexavalent Chromium.
- Heard an update on NIOSH NTP projects.

The second BSC meeting was held June 16, 2015. During this meeting, the BSC:

- Voted on two contract concepts: (1) Statistical Support and (2) Conduct of Studies to Evaluate the

Toxicologic Potential of Selected Test Agents for NTP.

- Heard an update on progress of the NTP response to the Elk River chemical spill.
- Heard a report on the May 2015 expert panel meeting Identifying Research Needs for Assessing Safe Use of High Intakes of Folic Acid.
- Heard a report on NTP tools and approaches for enhancing evaluation and communication of analysis activities, which included (1) systematically searching the literature, (2) SWIFT: A text-mining workbench for systematic review, (3) Environmental influences on the epigenome: using SWIFT text-mining toll to explore the state of the science, and (4) Health Assessment Workplace Collaborative (HAWC).
- Heard about a research study to update NTP level of concern categories.

BSC members and NTP staff at the June 2015 BSC meeting

NTP Board of Scientific Counselors Membership Roster FY 2015

Name and Title	Affiliation	Term Ends
Milton L. Brown, M.D., Ph.D. Director Drug Discovery Program	Georgetown University Medical Center Washington, D.C.	07/21/15

Robert E. Chapin, Ph.D. Laboratory Director	Pfizer Groton, Connecticut	06/30/15
George B. Corcoran, Ph.D., A.T.S. Chair and Professor Department of Pharmaceutical Sciences Eugene Applebaum College of Pharmacy and Health Sciences	Wayne State University Detroit, Michigan	06/30/16
David C. Dorman, D.V.M., Ph.D. Professor College of Veterinary Medicine	North Carolina State University Raleigh, North Carolina	06/30/15
Mary Beth Genter, Ph.D. Associate Professor Department of Environmental Health	University of Cincinnati Goshan, Ohio	06/30/17
Jack R. Harkema, D.V.M., Ph.D., D.A.C.V.P. Distinguished Professor Department of Pathobiology and Diagnostic Investigation	Michigan State University East Lansing, Michigan	06/30/15
Dale Hattis, Ph.D. Research Professor George Perkins Marsh Institute	Clark University Worcester, Massachusetts	06/30/15
Steven Markowitz, M.D., Dr.P.H. Professor and Director Center for the Biology of Natural Systems	Queens College City University of New York Flushing, New York	06/30/17
Lisa A. Peterson, Ph.D. (BSC Chair) Professor Division of Environmental Health Sciences and Masonic Center School of Public Health	University of Minnesota Minneapolis, Minnesota	06/30/16
Sonya Sobrian, Ph.D. Associate Professor Department of Pharmacology	Howard University Washington, D.C.	06/30/15
Iris G. Udasin, M.D. Professor Department of Environmental and Occupational Medicine	Rutgers – Robert Wood Johnson Medical School Piscataway, New Jersey	06/30/16

"Nominations ..." - previous article

next article - "SACATM ..."

SACATM

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) is a federally chartered advisory committee established 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. 285l-3(d)). SACATM advises ICCVAM, the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), and the director of NIEHS and NTP regarding statutorily mandated duties of ICCVAM and activities of NICEATM. 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 on the NTP website. The table below provides the roster for FY 2015. SACATM typically meets once a year and members serve rotating terms of up to four years. Lori White, Ph.D., serves as the designated federal officer and manager of SACATM.

SACATM met once during FY 2015 on September 2, 2015, at NIEHS. At the meeting, ICCVAM and NICEATM updated SACATM on the activities since the last meeting, including information on (1) in vitro to in vivo extrapolation, (2) fit-for-purpose validation, (3) integrated analysis of data, (4) endocrine disruptor testing, (5) skin sensitization testing, and (6) acute toxicity testing. ICCVAM members provided an update on international activities and metrics for quantifying animal usage. SACATM heard a proposal for creating a 3Rs (replacement, reduction, or refinement of animal use in testing and research) roadmap and strategy. SACATM provided input on the reports from four federal agencies: the U.S. Department of Agriculture, FDA, EPA, and NIEHS.

Members of SACATM, ICCVAM, and staff from NIEHS and NTP at the September 2015 SACATM meeting

NTP SACATM Membership Roster FY 2015

Name and Title	Affiliation	Term Ends
Lauren E. Black, Ph.D. Senior Scientific Advisor Navigators Services	Charles River Laboratories Reno, Nevada	11/30/16
Tracie E. Bunton, D.V.M., Ph.D. Consultant	Eicarte LLC Gettysburg, Pennsylvania	06/30/15
Joy Cavagnaro, Ph.D., D.A.B.T., R.A.C., A.T.S., R.A.P.S. President and Founder	Access BIO LC Boyce, Virginia	11/30/14
Joan M. Chapdelaine, Ph.D. Senior Immunologist and Director, Business Development	Calvert Laboratories, Inc. Scott Township, Pennsylvania	06/30/15

Mark G. Evans, D.V.M., Ph.D., A.C.V.P. Research Fellow La Jolla Laboratories	Pfizer San Diego, California	06/30/15
William P. Janzen (Chair starting December 2014) Executive Director of Lead Discovery	Epizyme, Inc. Cambridge, Massachusetts	06/30/17
Michael D. Kastello, D.V.M., Ph.D. Vice President and Global Head Animal Research and Welfare Disposition, Safety and Animal Research	Sanofi Bridgewater, New Jersey	11/06/14
Safdar A. Khan, D.V.M., M.S., Ph.D., D.A.B.V.T. Associate Director Global Pharmacoavigilance	Zoetis Kalamazoo, Michigan	11/30/16
Ricardo Ochoa, D.V.M., Ph.D., A.C.V.P. President and Principal	Pre-Clinical Safety, Inc. Niantic, Connecticut	11/30/14
Catherine E. Willett, Ph.D. Director Regulatory Toxicology, Risk Assessment and Alternatives	The Humane Society of the United States Gaithersburg, Maryland	11/30/17
Daniel M. Wilson, Ph.D., D.A.B.T. (Chair) Mammalian Toxicology Consultant Toxicology and Environmental Research and Consulting	The Dow Chemical Company Midland, Michigan	11/30/14
Wei Xu, Ph.D. Associate Professor Department of Oncology McArdle Laboratory for Cancer Research	University of Wisconsin at Madison Madison, Wisconsin	11/30/17

"NTP Board of Scientific ..." - previous article

next article - "Special Emphasis Panels ..."

Special Emphasis Panels

NTP uses ad hoc scientific panels, referred to as special emphasis panels, to provide independent scientific peer review and advice on targeted issues, such as agents of public health concern, new and revised toxicological test methods, and other issues. These panels help ensure transparent, unbiased, and scientifically rigorous input to NTP 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 Report Peer-Review Panels

NTP Technical Reports (TRs) are published results of long-term studies, generally two-year rodent toxicology and carcinogenesis studies. NTP convenes external scientific panels to peer review draft TRs at public meetings held at NIEHS. All reviews provide the opportunity for public comment. For each TR, the panel is charged with peer reviewing the scientific and technical elements and presentation of the study, and determining whether the study's experimental design and conduct support the NTP conclusions regarding the carcinogenic activity of the substance tested. There was one TR meeting in FY 2015.

NTP convened a meeting on June 25, 2015, to peer review the draft TR on pentabromodiphenyl ether mixture (DE-71 (technical grade)). The peer-review panel included individuals with expertise in molecular carcinogenesis, pathology, statistics, toxicology, and reproductive and developmental toxicology. Yun Xie, Ph.D., served as designated federal officer for the meeting.

The meeting was open to the public with time scheduled for oral public comment. The charge to the panel was to (1) review and evaluate the scientific and technical elements of the study and its presentation; and (2) determine whether the study's experimental design, conduct, and findings support the NTP conclusions regarding the carcinogenic activity and toxicity of the substance tested. The panel agreed with the NTP conclusions in the draft TR. Additional information about peer-review meetings is available here.

NTP Monograph Peer-Review Panels

Monographs are publications on a single, detailed specific topic. There were no monograph review meetings in FY 2015. Additional information about NTP monograph peer-review meetings is available here.

Report on Carcinogens Peer-Review Panels

NTP follows an established, four-part process for preparation of the Report on Carcinogens (RoC). RoC monographs are prepared for each candidate substance selected for review and consist of a cancer evaluation component and a substance profile. NTP convenes external scientific panels to peer review draft RoC monographs. These meetings are open to the public with time scheduled for oral public comment. The panels are charged with commenting on whether the draft cancer evaluation component is technically correct and clearly stated, whether NTP objectively presents and assesses the scientific evidence, and whether the scientific evidence is adequate for applying the listing criteria. For the draft substance profile, panels are charged with commenting on whether the scientific justification presented supports the preliminary NTP policy decision on the RoC listing status.

On July 22, 2015, NTP convened a panel at NIEHS to peer review the draft RoC monograph on cobalt and certain cobalt compounds. The panel voted on the draft level of evidence for carcinogenicity determination, based on the available scientific evidence in experimental animals and human cancer studies, and whether the information cited in the draft substance profile supported The NTP preliminary listing recommendation in the RoC. The review covered the chemical properties and human exposure, cancer studies in experimental animals, metabolism and mechanistic data, human cancer studies, an overall cancer evaluation, and the draft substance profile. Lori White, Ph.D., served as designated federal officer for the peer-review meeting. After the meeting, the input from the panel was considered in finalizing the monograph. Additional information about this meeting and other RoC monograph peer-review meetings is available here.

NTP Expert Panels

NTP expert panels provide independent advice to NTP on agents of public health concern, new and revised toxicological test methods, or other topics. NTP convened an expert panel meeting on May 11-12, 2015, to identify research needs for assessing the safe use of high intakes of folic acid. This meeting was open to the public with time scheduled for oral public comment. The panel was charged to carry out a state-of-science evaluation for four general health effect categories to identify areas for further research. The four health effect categories were (1) cancer, (2) cognition in conjunction with vitamin B12 deficiency, (3) hypersensitivity-related outcomes, and (4) thyroid and diabetes-related outcomes. To address this charge, the expert panel was asked to (1) identify the areas of consistency and areas of uncertainty in the available science, (2) identify research needs based on review of the available science, and (3) propose research approaches for addressing the research needs and gaps in the available science. The expert panel included individuals with expertise in cancer prevention, epidemiology, food science, nutrition, gastroenterology, cardiovascular disease, bio-analytical chemistry, folate, immunotoxicology, biochemistry, and pediatric allergy. The panel was divided into four subpanels according to the four health effect categories and made research recommendations based on the literature reviewed. The full panel agreed with the recommendations of the four subpanels. The expert panel report, final monograph, and other meeting materials can be found here.

"SACATM ..." - previous article

next article - "NTP Executive Committee ..."

NTP Executive Committee

The NTP Executive Committee provides programmatic and policy oversight to the NTP director. The 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. Consumer Product Safety Commission
- U.S. Department of Defense
- U.S. Environmental Protection Agency
- U.S. Food and Drug Administration
- National Cancer Institute
- National Center for Environmental Health/Agency for Toxic Substances and Disease Registry
- National Institute of Environmental Health Sciences
- National Institute for Occupational Safety and Health
- Occupational Safety and Health Administration

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

"Special Emphasis Panels ..." - previous article

Research and Testing

Tox21

The Toxicology in the 21st Century (Tox21) program is a federal collaboration that uses automated high throughput screening methods to quickly test chemicals across a battery of assays.

NICEATM

The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), an office within NIEHS/NTP, supports the development and evaluation of new, revised, and alternative methods to identify potential hazards to human health and the environment, with a focus on replacing, reducing, or refining animal use.

ICCVAM

The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) is a permanent interagency committee of NIEHS.

Testing and Toxicology Studies

The NTP testing program evaluates substances for a variety of health-related effects, generally using rodent models for study.

Tox21

The Toxicology in the 21st Century (Tox21) program is a federal collaboration that uses automated high throughput screening (HTS) methods to quickly and efficiently test chemicals for activity across a battery of assays that target cellular processes. These assays are useful for rapidly evaluating large numbers of chemicals to provide insight on potential human health effects.

In June 2015, the Memorandum of Understanding (MOU) for High Throughput Screening, Toxicity Pathway Profiling, and Biological Interpretation of Findings was renewed to support continuation of the Tox21 program. Through this MOU, NIEHS/NTP has partnered with the NIH Chemical Genomics Center (NCGC) now part of National Center for Advancing Translational Sciences (NCATS), the EPA National Center for Computational Toxicology, and FDA, to foster the advancement of toxicology to a more predictive science, based on development and implementation of the most relevant and meaningful tools of modern molecular biology and chemistry. This partnership 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.

A central component of the Tox21 MOU is to explore the use of quantitative high throughput screening and quantitative high content screening (qHTS/qHCS) assays; assays using phylogenetically lower animal species, such as fish and worms; as well as high throughput, gene expression, and analytical methods to evaluate mechanisms of toxicity. Through Tox21, these agencies hope to develop, validate, and translate innovative test methods that will better predict how chemicals may affect humans and the environment with the intent to use results from these methods to:

- Prioritize substances for further in-depth toxicological evaluation.
- Identify mechanisms of action for further investigation, such as disease-associated pathways.

Related Links

Tox21 Projects in 2015

- Develop models that better predict how chemicals will affect biological responses.

Tox21 research is being conducted in three phases. In Phase I, from 2005 to 2010, the partners at NCGC performed qHTS testing on 2,870 compounds in 140 assays, representing 77 predominately cell-based qHTS assays. Phase II started in 2011 and is ongoing. In this phase, the partners expanded the chemical library from Phase I to greater than 10,000 compounds, and testing these compounds at NCATS using a HTS robotics system sponsored by NIEHS/NTP. More than 200 databases of chemicals and drugs in the U.S. and abroad were analyzed to select the compounds for testing. This chemical library includes industrial and consumer products, food additives, drugs, and mixtures.

In 2011, NIEHS, NCATS, the University of North Carolina at Chapel Hill, and Sage Bionetworks, sponsored the NIEHS-NCATS-UNC DREAM Toxicogenetics Challenge, the first-ever crowdsourcing challenge of its kind. Interested groups were challenged to use Tox21 data to create prediction models for how genetically diverse human populations may respond to environmental toxicants based on interindividual differences in sensitivity, and predict the response of a toxicant based on similar toxicants. The results of this challenge were published in two papers (Abdo et al. 2015. Environ Health Perspect 123:458-566; and Eduati et al. 2015. Nat Biotechnol 33:933-940).

Tox21 Phase III was initiated in FY 2013 to improve biological coverage and relevance of screening activity by (1) focusing on more physiologically relevant in vitro cell systems, such as human stem cell-derived differentiated cell populations; (2) incorporating cell types, such as HepaRG, in 2-D and 3-D in vitro models that incorporate xenobiotic metabolism and allow for longer-term exposures; (3) increasing the characterization and use of computational models to predict metabolism and toxicity; (4) increasing the testing of compounds in alternative animal models such as zebrafish and *Caenorhabditis elegans* (*C. elegans*); and (5) developing and implementing a high throughput transcriptomics platform for human, rat, mouse, zebrafish, and *C. elegans*.

next article - "NICEATM ..."

Tox21 Projects

Also see:

Tox21 Background

This table describes the NTP Tox21 projects in FY 2015 that are being carried out by NIEHS/NTP staff.

View Research Areas in

Assay Development
Assay Interpretation
Data Analysis
Testing Projects
NTP WormTox Laboratory Projects

Show All

Search Projects

Search Projects

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Assay Development

Project & Study Scientist	Project Summary
Developing a stable cell line to screen compounds that affect the estrogen-related receptor/peroxisome proliferator-activated receptor coactivator pathway Study Scientist: Merrick, Teng	To develop an assay that will detect compounds that interfere with the estrogen-related receptor/peroxisome proliferator-activated receptor gamma coactivator pathway, a critical pathway for metabolic homeostasis. Stable human cell lines expressing the appropriate reporter construct were successfully generated, and qHTA screening efforts with the 10K library initiated in FY 2015.

High content screening with HepaRG cells Study Scientist: Ferguson, Ramaiahgari	To establish metabolically functional human HepaRG liver cells in 96-well or 384-well format for carrying out multiplex, high-content screening assays in collaboration with the NIH Chemical Genomics Center (NCGC). In FY 2015, the focus was on establishing metabolically competent HepaRG cells grown in 2-D and 3-D formats. Studies to characterize the metabolism of xenobiotic compounds in these cells will begin in FY 2015.
Testing for gene signatures and profiles in NTP archival tissues project Study Scientist: Merrick	To determine if RNA can be extracted from fixed tissue blocks, produced from NTP studies and located in the NTP Archives, and used to measure gene signatures and develop chemically induced transcriptomics profiles. The goal is to measure molecular changes caused by chemical exposures in different organs of the rat and mouse. An effort to establish a relational database to allow identification and linkage of all tissues in the NTP Archives is underway.
Stem Cell Projects Study Scientist: Ferguson, Parham, Hsieh, Behl	To screen for chemical toxicity in human or mouse stem cell lines (undifferentiated or differentiated) by quantitative high throughput screening (qHTS) at NCGC, or by using lower throughput assays at NIEHS. Initially, the project focuses 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 will be employed with larger sets of chemicals for hazard identification and chemical prioritization for toxicity testing. Data have been generated on a library of 80 predominantly developmental neurotoxicants evaluated for effects on neurite outgrowth in a human stem cell-derived neural cell population, cytotoxicity in different neural populations derived from human stem cells, and effects on the beating of human stem cell derived cardiomyocytes. Dose-response analysis has been carried out on the data from these assays and manuscripts are in preparation for publication in FY 2016.
Use of high throughput assays and	To develop an approach using validated ToxCast and

computational models to replace current EPA Endocrine Disruptor Screening Program Tier 1 tests Study Scientist: Casey (NICEATM)	Tox21 high throughput assays, and an associated computational model, to replace three Tier 1 tests currently used to assess estrogenic activity in the EPA Endocrine Disruptor Screening Program. The approach was developed and validated by EPA and NICEATM scientists, and EPA solicited public comments on the plan in June 2015. A description of the method has been published.

Assay Interpretation

Project & Study Scientist	Project Summary
Validation of high throughput screening estrogen receptor (ER) quantitative high throughput screening (qHTS) transactivation assay (TA) Study Scientist: Casey (NICEATM)	To compare the quality and accuracy of the quantitative high throughput screening (qHTS) assay that evaluates transcriptional activation of the estrogen receptor (ER) in human ovarian cancer cells (BG1 ER transactivation assay [TA] assay) relative to the manual method that has been validated for regulatory use by EPA and listed as a test guideline by the Organisation for Economic Co-operation and Development. The results of this evaluation indicate that the performance of the high throughput screening method is equivalent to the manual method. These results have been published.

Data Analysis

Project & Study Scientist	Project Summary
Modeling mixtures of androgen receptor-active and estrogen receptor-active compounds screened in Tox21 quantitative high throughput screening (qHTS) assays Study Scientist: Parham	To determine (1) which mathematical models can best describe the toxicity of mixtures of these compounds; and (2) whether the behavior of the mixtures can be predicted from the behavior of individual components.
Analysis of Tox21 quantitative high throughput screening (qHTS) assay data Study Scientist: Hsieh	To develop data analysis pipelines for Tox21 Phase II quantitative high throughput screening (qHTS) data to determine the activity of compounds in assays. The developed ranking or calling procedure takes into account

compound potency, efficacy, and data reproducibility. A manuscript describing this pipeline was published in FY 2015.

Prioritization of Tox21 compounds for genotoxicity

Study Scientist: Hsieh

To develop a prioritization approach that includes compounds that show clear evidence of activity in the quantitative high throughput screening (qHTS) genotoxic assays and those compounds that are weakly active based on chemical structure-activity relationship analysis. A manuscript is in preparation using this data.

Design of Tox21 data exploration graphical user interface

Study Scientist: Hsieh

To develop two graphical user interfaces for viewing Tox21 data. One graphical user interface is to explore the concentration-response data in a line chart, and the second graphical user interface is to explore compound similarity relationships in terms of their activities in Tox21 quantitative high throughput screening (qHTS) assays and their chemical structures. Prototype graphical user interfaces were developed during FY 2013 and made public in FY 2015.

Low-dose extrapolation for Tox21 Phase I quantitative high throughput screening (qHTS) data

Study Scientist: Parham

To determine points of departure for low-dose extrapolation by using signal-to-noise ratios and a benchmark-dose method. Data generated by this approach will be used to help prioritize compounds for more extensive toxicological testing.

Unsupervised, data-driven analysis of Tox21 assay data project

Study Scientist: Auerbach

To employ unsupervised data analysis methods (data organization based on patterns and performed by software) to identify chemicals that exhibit biological properties similar to those of well-characterized toxicants from the quantitative high throughput screening (qHTS) assays used to screen the 10K library. The results are being used to help prioritize compounds for more extensive toxicological testing.

Next generation sequencing in toxicology project

Study Scientist: Merrick

To develop bioinformatics pipelines for genomic and transcriptomic gene expression and mutational analysis on a genome-wide level, using next generation sequencing technologies to build signatures of toxicity and chemical exposure.

Development of a reference database for estrogenic activity

Study Scientist: Casey-NICEATM

To support future validation of high throughput in vitro test methods and in silico models of estrogenic activity. NICEATM created a comprehensive database of high quality in vivo data from over 1,000 scientific articles describing uterotrophic assay experiments for over 2,660 different combinations of chemicals, studies, and protocols. These data have potential utility for leading to development of adverse outcome pathways or models of estrogenic activity, prioritizing chemicals for further testing, or evaluating species-specific responses to chemicals. The database is described in a manuscript in press.

In vitro to in vivo extrapolation using Tox21 data

Study Scientist: Casey-NICEATM

To quantitatively correlate in vitro and in vivo dosimetry for estrogen receptor reference chemicals. Using collective results of 16 Tox21 and ToxCast estrogen receptor pathway related assays, NICEATM developed and applied one-compartment or physiologically based pharmacokinetic models to quantitatively correlate in vitro and in vivo dosimetry for estrogen receptor reference chemicals. This approach highlights the importance of pharmacokinetic considerations in assessing and ranking endocrine-active chemicals based on in vitro high throughput screening assays. The initial approach and results are described in a published manuscript. Refinements to the approach are ongoing.

Evaluation of Tox21 data for predicting acute oral toxicity

Study Scientist: Casey-NICEATM

To determine the potential of high throughput screening data to reduce animal use for acute oral toxicity testing. NICEATM analyzed high throughput screening data from Tox21 and ToxCast for correlation and model fitting to rat oral LD50 data. The goal of the analysis is to determine which tests or combinations of tests best characterize the rat oral toxicity data. The analysis, presented at the 2015 Annual Meeting of the Society of Toxicology (SOT), suggests that combinations of in vitro assays and data from small model organisms, such as zebrafish, offer promise for predicting outcomes of rat acute oral toxicity tests.

In silico prediction of metabolism project

Study Scientist: Ferguson

To evaluate various in silico methods for predicting the extent of xenobiotic metabolism, identity metabolites, and prioritize chemicals in the Tox21 10K library. Computational methods will be used to partition the 10K library and develop subsets of chemicals that are likely to be appreciably metabolized in humans. The results of these predictions are being summarized in a manuscript for submission in FY 2016.

Selection of a target set of genes for use in a high throughput transcriptomics screen

Study Scientist: Paules

To identify patterns of exposure-induced biological responses, in order to characterize toxicity and disease pathways and facilitate extrapolation of findings from model species to humans. An effort has been initiated to select a set of 1,500 sentinel genes, or the S1500 set of genes, that best captures and represents the full biological response to exposures and disease for use in a high throughput transcriptomics screening assay. Additional genes, which were identified as being particularly informative to toxicological processes, were added to the S1500 set, giving rise to the S1500+ set of approximately 2,750 genes. Criteria were developed for selecting the best target set of genes representing humans, rats, mouse, zebrafish, and perhaps Caenorhabditis elegans. The human list was released for public comment via the Federal Register in April 2014, and a finalized list was released September 2015.

Development of domain-specific quantitative structure-activity relationship (QSAR) models to predict estrogen receptor binding and activity

Study Scientist: Casey-NICEATM

To explore whether domain-specific, quantitative, structure–activity relationship (QSAR) models might provide improved predictions of activity and potency of estrogenic activity. Using data from Tox21 and ToxCast assays, NICEATM is working with scientists at EPA and the University of North Carolina at Chapel Hill to develop QSAR models to predict specific activity and relative potency of phenolic compounds. The domain-specific models consistently yield higher balanced accuracies, sensitivity, and specificity than global models. Results from this evaluation were presented at the Society of Toxicology (SOT) FutureTox III meeting in November 2015 and described in a manuscript that will be submitted

	in FY 2016.
Development of a computational model for androgen receptor pathway activity Study Scientist: Casey-NICEATM	To integrate data from nine Tox21 and ToxCast assays into a computational model that predicts agonist and antagonist activity against the androgen receptor pathway. The preliminary results from this model were presented at the December 2014 meeting of the EPA Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel, and the model is undergoing refinement. A manuscript is in preparation.
Development of quantitative structure-activity relationship (QSAR) models to predict androgen receptor binding and activity Study Scientist: Casey-NICEATM	To develop quantitative structure-activity relationship (QSAR) models to predict androgen receptor (AR) binding and activity. Using the computational model of the AR pathway described above, NICEATM developed QSAR models to predict AR binding and activity. These QSAR models are currently being refined, with a goal of using them to predict AR pathway activity of chemicals in the EPA Endocrine Disruptor Screening Program. Results from this evaluation were presented at FutureTox III in September 2015 and are described in a manuscript that will be submitted in FY 2016.
Development of a reference database for androgen receptor activity Study Scientist: Casey-NICEATM	To develop a reference chemical list for in vitro androgen receptor binding and transactivation assay activity. NICEATM is conducting literature reviews to identify information about in vitro androgen receptor binding and transactivation assays for 127 putative androgen-active or androgen-inactive chemicals. The final database will be made available to the public on the NTP website. A parallel EPA data curation effort is focusing on in vivo androgen activity data. These data were presented at FutureTox III in September 2015, and will be used for evaluating high throughput screening (HTS) approaches, testing strategies, and further development of alternative test methods.
Development of a bioactivity-based read-across approach Study Scientist: Casey-NICEATM	To use bioactivity data from ToxCast to characterize untested environmental chemicals based on their similarities to chemicals with known toxicological effects. NICEATM used computational methods to create clusters

of tested chemicals based on their activity in ToxCast assays. Clusters containing known toxicants were examined to identify similar in vitro bioactivity patterns in environmental chemicals lacking in vivo data. This work, which was described in a platform presentation at the 2015 Society of Toxicology (SOT) Annual Meeting, is included as a case study in a manuscript on good read-across practices being prepared in collaboration with the Johns Hopkins University Center for Alternatives to Animal Testing and other partners from industry, government, and academia.

Testing Projects

Project & Study Scientist	Project Summary
Epigenetic changes in chemical toxicity project Study Scientist: Merrick	To determine methylation patterns on a genome-wide basis and validate 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, while demethylation can cause transcriptional activation. A generalized approach for methylated DNA enrichment, by MBD2 capture following bisulfite reduction and sequencing, has been developed, and a manuscript describing the findings was submitted for publication in late FY 2015.
Polycyclic aromatic hydrocarbon (PAH) Study Scientist: Ferguson	To evaluate approximately 20 PAHs considered relevant to human exposure in metabolism-competent HepaRG cells (derived from a human hepatic progenitor cell line), using multiplexed high content screening assays and gene expression platforms. Studies are in progress.
Analysis of 52 compounds in the EPA ToxCast Phase II program Study Scientist: Casey-NICEATM	To screen 52 compounds nominated by NTP, identified based largely on immunological relevance, in the EPA ToxCast program. NICEATM used in vitro chemical profiling data to examine activity profiles in primary human cell systems and identify predictive signatures anchored to in vivo endpoints and toxicity pathways. These analyses will be used to develop adverse outcome pathways, to enable chemical prioritization and hazard predictions. A webcast seminar on this work was

presented in December 2014.

NTP WormTox Laboratory Projects

Project & Study Scientist	Project Summary
Assay development Study Scientist: Boyd	To develop reproduction, growth, feeding, and locomotion assays that measure the effects of toxicant exposure on complex biological phenotypes, including development and neuron function. These assays have been developed, in addition to an inducible gene expression fluorescence assay, for use in transgenic Caenorhabditis elegans (C. elegans) to measure stress pathway activation using a high-content imaging system. Two mitochondrial toxicity assays were developed, including (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 C. elegans mitochondrial DNA damage and repair assay has been developed.
Mitochondrial toxicants project Study Scientist: Boyd	To determine the effects of the mitochondrial toxicant subset from the Tox21 10K library on Caenorhabditis elegans growth and in vivo adenosine-5'-triphosphate levels and membrane potential. Compounds for testing were received in late FY 2014. Testing occurred in FY 2015, and a manuscript reporting the findings is in preparation for publication.
Fluorides project Study Scientist: Boyd	To compare the toxicities of three fluoride compounds commonly used in drinking water treatment processes on Caenorhabditis elegans feeding, growth, and reproduction. The in vivo studies have been completed and the resulting manuscript was accepted for publication in FY 2014.

NICEATM

The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), an office within NIEHS/NTP, supports the development and evaluation of new, revised, and alternative methods to identify potential hazards to human health and the environment, with a focus on replacing, reducing, or refining animal use. NICEATM activities include the following:

- Conducting and publishing analyses and evaluations of data from new, revised, and alternative testing approaches.
- Providing information to test method developers, regulators, and regulated industry, through their website and other communications, and by organizing workshops and symposia on topics of interest.
- Coordinating and providing logistical support for the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) committee meetings, webinars, teleconferences, working groups, and public forums.
- Providing bioinformatics and computational toxicology support to NIEHS/NTP projects, especially those related to Tox21.

Warren Casey, Ph.D., is director of NICEATM. NICEATM receives contract support from Integrated Laboratory Systems Inc.

Related Links

Activities and Resources
Publications
Reports

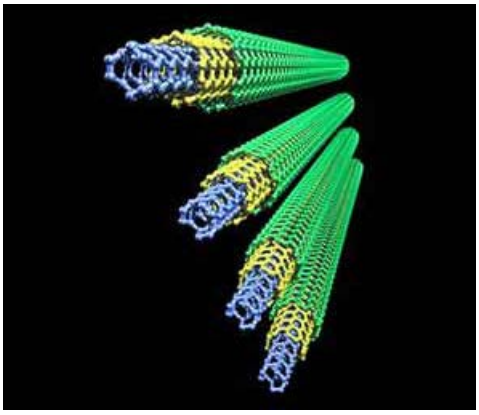
Related Annual Report Pages:

- FY 2015 NICEATM Workshops
- NICEATM Support of Tox21
- Additional NICEATM Activities

"Tox21 ..." - previous article

next article - "NICEATM FY 2015 Workshops ..."

NICEATM FY 2015 Workshops

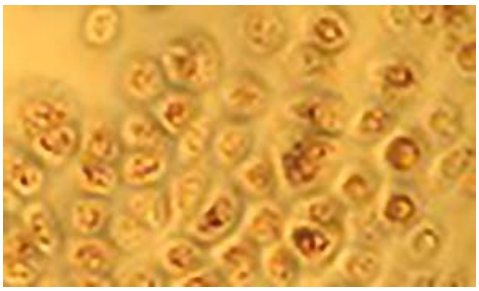


Nanomaterials

NICEATM and the PETA International Science Consortium (PISC) co-organized a Technical Discussion on In Vitro Testing Strategies to Assess Inhalation Toxicity of Nanomaterials Feb. 24-25, 2015, at the EPA in Washington, D.C. At this meeting, specifications were defined for the development and evaluation of an in vitro system to assess inhalation toxicity of multiwalled carbon nanotubes. Recommendations were made for the system to include a variety of lung cells cocultured at an air-liquid interface, and relevant human dosimetry and nanomaterial lifecycle transformations were considered. These recommendations were central to a subsequent request for research proposals, issued by PISC, to develop an appropriate testing system, and funding was awarded in September 2015. A workshop report is in preparation.

Pertussis vaccines

NICEATM supported a workshop to review data from a multilaboratory study to evaluate an in vitro alternative to the murine histamine sensitization test for safety testing of acellular pertussis vaccines. The In Search of Acceptable Alternatives to the HIST: What is Possible and Practical? workshop was held in London March 4-5, 2015, and organized in collaboration with the U.K. National Centre for the 3Rs (replacement, reduction, or refinement of animal use in testing and research). Workshop participants concluded that the relevance and reliability of the in vitro test were sufficient, and recommended that vaccine manufacturers begin using the in vitro test, alongside current mouse tests, to demonstrate its validity for their specific products. Participants also discussed implementing an approach that would



allow manufacturers to waive testing entirely under certain circumstances. A report on the workshop is in preparation for publication in FY 2016.

Induced Pluripotent Stem Cells

NICEATM co-organized the Workshop on Good Cell Culture Practices for Induced Pluripotent Stem Cells held in Baltimore June 1-3, 2015. Its goal was to develop consensus standards and foster international standardization on the use of induced pluripotent stem cells. Existing standards on the use for cell and tissue culture systems served as a guide, as attendees considered the unique properties and challenges of pluripotent stem cells compared to traditional in vitro systems. Attendees developed a framework for a guidance document specific to pluripotent stem cells that addresses quality of materials and methods, documentation, protection of workers and the environment from hazards, compliance with laws and ethical principles, and education and training. The guidance document is planned for publication in FY 2016.

Acute Systemic Toxicity

The workshop Alternative Approaches for Identifying Acute Systemic Toxicity: Moving From Research to Regulatory Testing brought together representatives from regulatory agencies, academia, and industries to develop strategies for advancing alternative methods for product safety testing that meet the needs of regulatory agencies. The workshop, co-organized by NICEATM, PISC, and the Physicians Committee for Responsible Medicine, was held Sept. 24-25, 2015, at NIH in Bethesda, Maryland. During the workshop, several resources were identified as necessary for meaningful progress in identifying and implementing alternatives to animal use: high quality reference data, training on use and interpretation of computational approaches, and global harmonization of testing requirements. Breakout groups explored different approaches to reducing or replacing animal use for acute toxicity testing, and each group crafted a roadmap and a strategy for implementation within a three-year timeframe. NICEATM will coordinate the creation of, and provide support for, a working group of workshop participants charged with implementing the

strategies. Workshop proceedings are being prepared for submission for publication in FY 2016.

Related Annual Report Pages:

- NICEATM Support of Tox21
- Additional NICEATM Activities
- About NICEATM

"NICEATM ..." - previous article

next article - "NICEATM Support of Tox21 ..."

NICEATM Support of Tox21

NICEATM conducted the following Tox21 projects. Full descriptions of those projects.

- Use of high throughput assays and computational models to replace current Tier 1 Endocrine Disruptor Screening Program (EDSP) tests.
- Validation of high throughput screening estrogen receptor transactivation assay.
- Development of a reference database for estrogenic and androgenic activity.
- In vitro to in vivo extrapolation using Tox21 data.
- Evaluation of Tox21 data for predicting acute oral toxicity.
- Development of domain-specific, quantitative structure-activity relationship (QSAR) models to predict estrogen receptor binding and activity.
- Development of a computational model for androgen receptor pathway activity.
- Development of QSAR models to predict androgen receptor binding and activity.
- Development of a bioactivity-based read-across approach.
- Analysis of the NTP-provided 52 compounds in the EPA ToxCast Phase II program.

Related Annual Report Pages:

- FY 2015 NICEATM Workshops
- Additional NICEATM Activities
- About NICEATM

"NICEATM FY 2015 Workshops ..." - previous article

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Additional NICEATM Activities

NICEATM is conducting a retrospective analysis to determine if acute oral toxicity data can be used reliably to assign EPA acute dermal hazard classifications, potentially reducing the number of animals needed for pesticide testing. NICEATM obtained high-quality data for 910 pesticide-active ingredients and formulations from EPA toxicity reports, peer-reviewed publications, and databases. Oral hazard classifications based on rat oral LD50 values were compared to dermal hazard classifications based on rat dermal LD50 values. Results suggest that acute oral hazard categories are sufficiently protective for acute dermal hazard classification. EPA will use these analyses to support guidance for waiving acute dermal toxicity tests currently required for pesticide formulations. The analysis is described in an abstract submitted to the 2016 Society of Toxicology (SOT) Annual Meeting.

NICEATM staff collaborated with scientists at the Procter and Gamble Company to develop an approach for identifying potential skin sensitizers and characterizing skin sensitization potency without conducting animal tests. The collaboration produced a widely available, open source version of a previously published integrated testing strategy. Revisions of the original strategy improved overall accuracy of the approach and enabled consideration of the variability in reference data. A poster describing improvements to the strategy was presented at the 2015 Society of Toxicology annual meeting. Other improvements to simplify model inputs and refine potency estimates are described in a submitted manuscript.

NICEATM is collaborating with scientists at the University of North Carolina at Chapel Hill to develop QSAR models to support identification of potential human skin sensitizers without using animals. Two papers published in FY 2015 described QSAR models developed for skin penetration and to predict results for animal tests to identify sensitizers. More recent efforts have focused on developing QSAR models to predict human skin sensitization. A manuscript describing these models is in preparation.

NICEATM staff used structure-activity relationship methods to predict toxicity of chemicals that spilled into the Elk River in West Virginia in January 2014. These studies of 4-methylcyclohexanemethanol, the major component of the spill, might cause skin or eye irritation or affect development of offspring of pregnant subjects. These results were used to help select subsequent toxicology studies. A summary of activities carried out to determine toxicity of chemicals involved in the Elk River spill is available on the NTP website.

NICEATM is collaborating with the test method developer CertiChem Inc. on evaluation of an MDA-Kb2 androgen receptor activity assay. This medium-throughput in vitro test measures androgen receptor agonist and antagonist activity. This project is a proof-of-concept evaluation of the method for a blinded set of chemicals. Testing began in September 2015, and was completed in October 2015. Data analysis will be conducted in FY 2016.

NICEATM is part of an NTP effort to systematically evaluate the application of zebrafish in NTP toxicology studies (SEAZIT). This effort will provide fundamental knowledge on the use of zebrafish in toxicology.

NICEATM is working with other NTP scientists at NIEHS to establish a list of developmental toxicants that cause subtle effects, as opposed to being potent or multisite teratogens. The toxicants identified will be candidates for testing in in vitro assays using primary cells, stem cells, or cell lines, as well as in vivo assays using lower order organisms such as zebrafish or Caenorhabditis elegans (C. elegans). Results from this testing may be compared to available in vivo mammalian data from rodents, rabbits, and humans. The toxicant list is being constructed with input from experts from industry, academia, and government, and is expected to include agrochemicals, pharmaceuticals, and other chemicals.

NICEATM is participating on the Acute Toxicity Working Team of the European Partnership for Alternative Approaches to Animal Testing. This team is investigating methods that could circumvent the need for in vivo acute lethality testing when determining acute classification and labeling of new agrochemical and biocide active substances, and industrial chemicals.

NICEATM is collaborating with the Cosmetics Europe Skin Tolerance Task Force to evaluate the integrated approaches to testing and assessment (IATA) of skin sensitization that have been submitted to the Economic Co-operation and Development (OECD). NICEATM has evaluated seven IATAs against a naïve set of chemicals with in vitro and in silico data provided by Cosmetics Europe. Manuscripts describing the datasets and the outcome of the IATA analyses are in preparation.

Related Annual Report Pages:

- FY 2015 NICEATM Workshops
- NICEATM Support of Tox21
- About NICEATM

"NICEATM Support of Tox21 ..." - previous article next article - "ICCVAM ..."

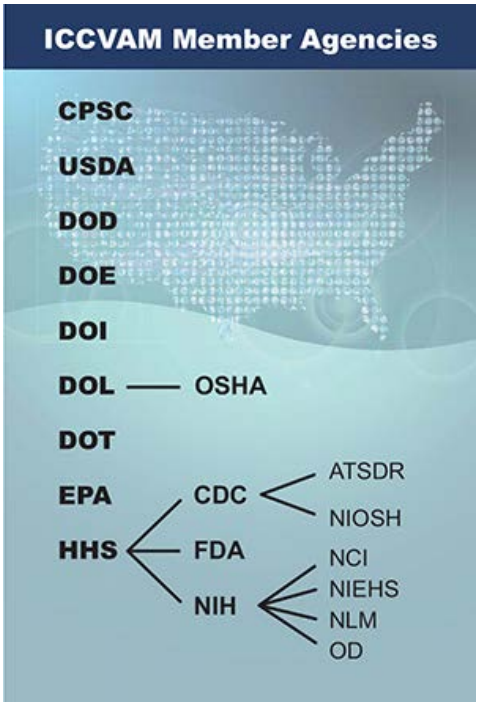
ICCVAM

The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) is a permanent interagency committee of NIEHS under NICEATM. Established by the ICCVAM Authorization Act of 2000 (42 U.S.C. 285*i*-3), its purpose 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."

ICCVAM is composed of representatives from 15 U.S. federal regulatory and research agencies that generate or use toxicological and safety testing information. Warren Casey, Ph.D., serves as administrative director of ICCVAM.

Related Annual Report Pages:

- FY 2015 ICCVAM Activities
- ICCVAM Test Method Evaluation
- International Validation Activities



Related Links

Information on ICCVAM Activities

Complete list of articles on ICCVAM activities published in scientific journals

"Additional NICEATM Activities ..." - previous article next article - "ICCVAM Activities ..."

ICCVAM Activities

NICEATM provided support for seven teleconferences and two in-person meetings held by ICCVAM in FY 2015. NICEATM also supported two ad hoc ICCVAM working groups, one focused on skin sensitization and the other on reference chemicals for validation of in vitro androgen receptor assays.

The first ICCVAM Communities of Practice webinar was held on January 27, 2015. The webinar focused on the development and application of reverse toxicokinetic models for extrapolation of high throughput screening data to in vivo dosimetry. John Wambaugh, Ph.D. from the EPA National Center for Computational Toxicology (NCCT), provided an overview of the development of reverse toxicokinetic models. Barbara Wetmore, Ph.D., from the Hamner Institutes for Health Sciences discussed the consideration of population variability and sensitive subpopulations in the use of these models. NICEATM and NCCT hosted the webinar on behalf of ICCVAM. Slide presentations and a video recording of the webinar are available on the NTP website.

ICCVAM, with NICEATM support, held its second public forum May 27, 2015, at NIH in Bethesda, Maryland. This meeting provided an opportunity for public interaction with representatives from the 15 member agencies of ICCVAM. ICCVAM members provided information about their agency's activities relevant to the development and use of alternative test methods. Individuals and groups interested in promoting alternative methods or reducing animal use in testing presented public comments. The agenda and presentations are available on the NTP website.

ICCVAM agency activities that support replacement, reduction, and

Related Links

Information on ICCVAM Activities

Complete list of articles on ICCVAM activities published in scientific journals

refinement of animal use can be found on the NTP website. NICEATM is also working with the NIEHS Office of Communications and Public Liaison to explore how social media, such as Twitter and LinkedIn, might be used to improve communication with stakeholders and facilitate collaboration.

Related Annual Report Pages:

- FY 2015 ICCVAM Activities
- ICCVAM Test Method Evaluation
- International Validation Activities

"ICCVAM ..." - previous article

next article - "ICCVAM Test Method Evaluation ..."

ICCVAM Test Method Evaluation Activities

ICCVAM received no formal test method nominations or submissions in FY 2015. ICCVAM welcomes submissions of innovative test methods, which may be acceptable for specific regulatory use and for which adequate validation studies have been completed. However, to maximize the potential for effective implementation of new test methods or approaches, ICCVAM only conducts evaluations and prepares recommendations on test method submissions proposed for regulatory uses that align with ICCVAM member agencies needs and priorities. More information on ICCVAM test method submissions is available. NICEATM and ICCVAM test method evaluation activities in FY 2015 are summarized in the table below.

Test Method Evaluation Activities in FY 2015

Test Method	ICCVAM Recommendations/Agency Status
ICCVAM integrated decision strategy for skin sensitization	ICCVAM developed integrated decision strategies using in vitro, in chemico, and in silico information based on an established skin sensitization adverse outcome pathway. Three manuscripts describing different strategies and targets are in preparation.
Electrophilic allergen screening assay	This test method, nominated by NIOSH, is an in chemico assay intended to identify potential skin sensitizers. NICEATM worked with the sponsor to address technical issues with the assay.
OptiSafe ocular irritation test	NICEATM is coordinating the validation of the in vitro Optisafe ocular irritation test method. In this method, a test substance is applied to a semipermeable membrane and damage to macromolecules in the membrane is measured to assess the substance's potential of the substance to cause eye irritation. NICEATM staff and ICCVAM Ocular Toxicity Working Group members will serve on a validation management team to provide oversight and direction for a multilaboratory validation study. Testing should be completed in FY 2016, along with a study report detailing the results.

Related Annual Report Pages:

- FY 2015 ICCVAM Activities
- ICCVAM Test Method Evaluation
- International Validation Activities

"ICCVAM Activities ..." - previous article

next article - "International Validation Activities ..."

International Validation Activities

NICEATM and ICCVAM participate in international test method validation activities through the Organisation for Economic Co-operation and Development (OECD), and collaborate with countries that are members of the International Cooperation on Alternative Test Methods (ICATM), including the European Union, Japan, Korea, and Health Canada. ICATM collaborations address three critical areas of cooperation: test method validation studies, independent peer review of validation studies, and the development of formal recommendations on alternative testing methods.

In FY 2015, ICCVAM agencies commented on draft OECD documents through the U.S. National Coordinator for the OECD Test Guidelines Programme, who is an ex officio ICCVAM member. NICEATM and ICCVAM collaborated with international colleagues on drafting a proposal for a new test guideline describing an in vitro assay for measuring induction of human cytochrome P450. They are also participating in an OECD drafting group for a guidance document on integrated approaches to testing and assessment for skin sensitization. Representatives of NICEATM and ICCVAM attended a meeting of the drafting group in November 2014.

The table below lists ongoing international validation studies led by ICATM member organizations that include NICEATM or ICCVAM participants. NICEATM and ICCVAM representatives attended an ICATM coordination meeting in June 2015 and attended a coordination meeting planned in November 2015.

Participation in International Validation Studies

Test Method	Type of Test	Lead Organization	NICEATM-ICCVAM Involvement
IL-8 in vitro test for assessing skin sensitization potential	Allergic contact dermatitis	JaCVAM*	NICEATM staff served on the validation management team and provided comments on study design, chemical selection, and test method protocols.
Vitrigel-SST assay for assessing skin	Allergic contact	JaCVAM	NICEATM staff served on the validation management team.

sensitization potential	dermatitis		
Vitrigel-EIT assay for eye irritation testing	Ocular irritation	JaCVAM	NICEATM staff served on the validation management team.
Hand1-luc in vitro test for assessing reproductive toxicity potential	Reproductive toxicity	JaCVAM	NICEATM staff served on the validation management team.
SIRC-CVS assay for eye irritation testing	Ocular irritation	JaCVAM	NICEATM staff served on the validation management team.

*Japanese Center for the Validation of Alternative Methods

Related Annual Report Pages:

- FY 2015 ICCVAM Activities
- ICCVAM Test Method Evaluation
- International Validation Activities

"ICCVAM Test Method Evaluation ..." - previous article

next article - "Testing and Toxicology Studies ..."

Testing and Toxicology Studies

The NTP testing program evaluates substances for a variety of health-related effects, generally using rodent models for study. For each test article studied, a study scientist designs a comprehensive testing strategy to address the identified research and testing needs to fully characterize its toxic potential, and a project review committee evaluates the strategy. Reports and summaries of NTP toxicity studies including carcinogenicity, and effects on development and reproduction, are available on the NTP website.

The following Division of NTP branches at NIEHS are involved in the testing program: Biomolecular Screening Branch, led by Raymond Tice, Ph.D. until his retirement in December 2014, and now led by acting chief Rick Paules, Ph.D.; Cellular and Molecular Pathology Branch, led by Robert Sills, D.V.M., Ph.D.; NTP Laboratory, led by acting chief Michael Devito, Ph.D.; Program Operations Branch, led by Michelle Hooth, Ph.D.; and Toxicology Branch, led by Paul Foster, Ph.D.

New studies that implement plans outlined in research concepts from prior years are listed in this section. Of note are the multiple study types initiated, scheduled, or approved: aromatic phosphates including isopropylated phenol phosphate and triphenyl phosphate; bisphenol S; C9 alkylbenzenes including cumene, 2-ethyltoluene, 3-ethyltoluene, and 4-ethyltoluene; ethylene glycol 2-ethylhexyl ether; polycyclic aromatic compounds including benzo(a)pyrene and phenanthrene; sulfolane; and valerian root extract.

Related Links

Disposition, Metabolism, and Toxicokinetic Studies
Genetic Toxicity
Organ System Toxicity
Modified One-Generation Reproduction Studies
Toxicology and Carcinogenicity Studies
Toxicogenomic Studies
Project Review Committee Approved

Disposition, Metabolism, and Toxicokinetic Studies

Complete dosimetry of a chemical or physical agent describes its absorption, distribution, metabolism, and excretion in the body in both humans and test animals at differing levels of exposure, over all ages, via several routes of exposure, and under varying genetic backgrounds. Substances evaluated during FY 2015 are listed in the table below.

Chemical	CASRN*	Species	Route	Study Scientist	Status
Bisphenol A	80-05-7	Rats	In-vitro	Declos	Completed
Bisphenol S	80-09-1	Mice, Rats	Gavage, Intravenous	Sutherland	Ongoing
1,3-Dichloro-2-propanol	96-23-1	Mice, Rats	Gavage	Chan	Completed
Ethylene glycol 2-ethylhexyl ether	1559-35-9	Mice, Rats	Gavage	Blystone	Completed

*CASRN = Chemical Abstracts Service Registry Number

Related Links:

- Disposition, Metabolism, and Toxicokinetic Studies
- Genetic Toxicity
- Organ System Toxicity
- Toxicology and Carcinogenicity Studies
- Modified One-Generation Reproduction Studies
- Toxicogenomic Studies
- Project Review Committee Approved

"Testing and Toxicology Studies ..." - previous article

next article - "Genetic Toxicity ..."

Genetic Toxicity

Genetic toxicity test results are used to help interpret general toxicity, carcinogenicity, or other in vivo test results, and provide a database for use in structure-activity relationship analysis. Substances tested for genetic toxicity during FY 2015 are listed in the table below.

Genetic Toxicity Studies During FY 2015

Test Article	CASRN*	Species	Testing Battery	Status
Aspergillus fumigatus mold	N/A	*Salmonella*	*Salmonella*	Completed
Aspergillus fumigatus mold	N/A	Mice	Micronucleus	Initiated
3'-Azido-3'-deoxythymidine	30516-87-1	*Salmonella*	*Salmonella*	Completed
Bisphenol AF	1478-61-1	Rats	Micronucleus	Completed
Black cohosh	84776-26-1	*Salmonella*	*Salmonella*	Ongoing
n-Butyl glycidyl ether	2426-08-6	Mice	Micronucleus	Ongoing
n-Butyl glycidyl ether	2426-08-6	Rats	Micronucleus	Ongoing
1-Butyl-3-methylimidazolium chloride	79917-90-1	Rats	Micronucleus	Completed
1-Butyl-3-methylimidazolium chloride	79917-90-1	Mice	Micronucleus	Completed
1-Butyl-1-methylpyrrolidinium chloride	479500-35-1	Rats	Micronucleus	Completed
1-Butyl-1-methylpyrrolidinium chloride	479500-35-1	Mice	Micronucleus	Completed
N-Butylpyridinium chloride	1124-64-7	Mice	Micronucleus	Completed
N-Butylpyridinium chloride	1124-64-7	Rats	Micronucleus	Ongoing
Corn oil	8001-30-7	Rats	Micronucleus	Ongoing

Dimethyl 1,4-cyclohexanedicarboxylate	94-60-0	*Salmonella*	*Salmonella*	Completed
1,4-Cyclohexanedimethanol	105-08-8	*Salmonella*	*Salmonella*	Completed
Dimethylamine borane	74-94-2	*Salmonella*	*Salmonella*	Completed
2,2'-Dimorpholinodiethyl ether	6425-39-4	*Salmonella*	*Salmonella*	Initiated
Dipropylene glycol phenyl ether	51730-94-0	*Salmonella*	*Salmonella*	Completed
Dowanol DiPPh glycol ether	N/A	*Salmonella*	*Salmonella*	Completed
Echinacea purpurea extract	90028-20-9	*Salmonella*	*Salmonella*	Initiated
1-Ethyl-3-methylimidazolium chloride	65039-09-0	Rats	Micronucleus	Completed
1-Ethyl-3-methylimidazolium chloride	65039-09-0	Mice	Micronucleus	Completed
4-Methoxymethylcyclohexylmethanol	98955-27-2	*Salmonella*	*Salmonella*	Completed
4-Methylcyclohexanemethanol, crude	N/A	Rats	Micronucleus	Completed
4-Methylcyclohexanemethanol, crude	N/A	*Salmonella*	*Salmonella*	Completed
Methyl 4-methylcyclohexanecarboxylate	51181-40-9	*Salmonella*	*Salmonella*	Completed
2-Methylcyclohexanemethanol	2105-40-0	*Salmonella*	*Salmonella*	Completed
4-Methylcyclohexanemethanol	34885-03-5	Rats	Micronucleus	Completed
4-Methylcyclohexanemethanol	34885-03-5	*Salmonella*	*Salmonella*	Completed
2-Nitro-2-ethyl-1,3-propanediol	597-09-1	*Salmonella*	*Salmonella*	Ongoing
Perfluorodecanoic acid	335-76-2	Rats	Micronucleus	Ongoing
2-Nitro-1-propanol	2902-96-7	*Salmonella*	*Salmonella*	Completed
Propylene glycol phenyl ether	770-35-4	Rats	Micronucleus	Completed
Propylene glycol phenyl ether	770-35-4	*Salmonella*	*Salmonella*	Completed
Sulfolane	126-33-0	Mice	Micronucleus	Completed
Sulfolane	126-33-0	Rats	Micronucleus	Completed
Tris(Chloropropyl)phosphate	13674-84-5	*Salmonella*	*Salmonella*	Completed
Vinpocetine	42971-09-5	*Salmonella*	*Salmonella*	Completed
Vinpocetine	42971-09-5	Mice	Micronucleus	Initiated

Zinc carbonate, basic	5263-02-5	Rats	Micronucleus	Ongoing

*CASRN = Chemical Abstracts Service Registry Number

Related Links:

- Disposition, Metabolism, and Toxicokinetic Studies
- Genetic Toxicity
- Organ System Toxicity
- Toxicology and Carcinogenicity Studies
- Modified One-Generation Reproduction Studies
- Toxicogenomic Studies
- Project Review Committee Approved

"Disposition, Metabolism, and Toxicokinetic ..." - previous article

next article - "Organ System Toxicity ..."

Organ System Toxicity

NTP studies toxicity of environmental substances on organ systems for development, reproduction, and the immune system. NTP immunotoxicity studies address adverse effects on the immune system that may result from exposure to environmental chemicals, biological materials, or therapeutic agents. Identifying substances with the potential to alter immune system function is critical to the public health field as these substances may lead to increased incidence of hypersensitivity disorders, autoimmune disease, infectious disease, or neoplasia. The table below lists organ systems toxicity studies during FY 2015.

Neurotoxicity, Developmental Toxicity, and Reproductive Toxicity Studies During FY 2015

Test Article	CASRN*	Species	Testing Battery	Length	Route	Study Scientist	Status
Acrylamide	79-06-1	Rats	Neurotoxicology assessment	3, 6, 12 and 24 months	Gavage	Beland	Ongoing
Benzo(a)pyrene	50-32-8	Mice	Immunotoxicity	28 days	Gavage	Rider	Initiated
Dimethylethanolamine	108-01-0	Rats	Conventional teratology	GD** 6 to GD 20	Gavage	McIntyre	Completed
2-Hydroxy-4-methoxybenzophenone	131-57-7	Rats	Developmental toxicity	GD 6 to GD 15	Feed	Hansen	Ongoing
2-Hydroxy-4-methoxybenzophenone	131-57-7	Rats	Developmental toxicity	GD 6 to PND*** 21	Feed	Hansen	Ongoing
4-Methylcyclohexanemethanol	34885-03-5	Rats	Conventional teratology	GD 6 to GD 20	Gavage	Auerbach	Completed
4-Methylcyclohexanemethanol	34885-03-5	Mice	Immunotoxicity	7 days	Topical application	Auerbach	Initiated

4-Methylcyclohexanemethanol, crude	N/A	Mice	Immunotoxicity	7 days	Topical application	Auerbach	Initiated
4-Methylcyclohexanemethanol, crude	N/A	Mice	Immunotoxicity	7 days	Topical application	Auerbach	Initiated
Phenanthrene	85-01-8	Mice	Immunotoxicity	28 days	Gavage	Rider	Initiated
Sulfolane	126-33-0	Mice	Immunotoxicity	13 weeks	Gavage	Blystone	Initiated
Sulfolane	126-33-0	Rats	Immunotoxicity	13 weeks	Gavage	Blystone	Initiated
Vinpocetine	42971-09-5	Rats	Teratology pilot studies	GD 6 to GD 20	Gavage	Catlin	Completed
Vinpocetine	42971-09-5	Rats	Conventional teratology	GD 6 to GD 20	Gavage	Catlin	Initiated
Vinpocetine	42971-09-5	Rabbits	Conventional teratology	GD 7 to GD 28	Gavage	Catlin	Initiated

*CASRN = Chemical Abstracts Service Registry Number

Related Links:

- Disposition, Metabolism, and Toxicokinetic Studies
- Genetic Toxicity
- Organ System Toxicity
- Toxicology and Carcinogenicity Studies
- Modified One-Generation Reproduction Studies
- Toxicogenomic Studies
- Project Review Committee Approved

"Genetic Toxicity ..." - previous article

next article - "Modified One-Generation Reproduction Studies ..."

Modified One-Generation Reproduction Studies

NTP modified one-generation study design emphasizes a full evaluation of the first generation offspring animals, and uses fewer animals than the classical multigenerational study design. These studies generate information on the effects of substances on prenatal development, postnatal development, and reproduction. The table below lists planned or ongoing modified one-generation studies.

Modified One-Generation Studies in FY 2015

Test Article	CASRN*	Species	Planned Cohorts	Study Scientist	Route	Status
Isopropylated phenol phosphate	68937-41-7	Rats	Dose range finding [1]	Behl	Feed	Initiated
Resveratrol	501-36-0	Rats	F0 generation [2]	Germolec	Gavage	Initiated
Simvastatin	79902-63-9	Rats	Dose range finding [1]	McIntyre	Gavage	Initiated
Triphenyl phosphate	115-86-6	Rats	Dose range finding [1]	Behl	Feed	Initiated
Valerian (*Valeriana officinalis L.*) root extract	8057-49-6	Rats	Dose range finding [1]	Roberts	Gavage	Initiated
Wyeth 14,643 (WY)	50892-23-4	Mice, Rats	Dose range finding [1]	Blystone	Gavage	Completed

*CASRN = Chemical Abstracts Service Registry Number
[1] Dose range-finding: to find the ideal dose for toxicological studies.
[2] F0 generation: parental generation.

Related Links:

Disposition, Metabolism, and Toxicokinetic Studies
- Genetic Toxicity
- Organ System Toxicity
- Toxicology and Carcinogenicity Studies
- Modified One-Generation Reproduction Studies
- Toxicogenomic Studies
- Project Review Committee Approved

"Organ System Toxicity ..." - previous article

next article - "Toxicology and Carcinogenicity Studies ..."

Toxicology and Carcinogenicity Studies

NTP performs toxicity studies to provide dose-setting information for chronic studies and address specific deficiencies in the toxicology database for the chemical. Toxicology and carcinogenicity studies fall into two categories: prechronic toxicity studies and two-year toxicology and carcinogenicity studies. Studies are generally conducted in rats and mice. Each study type 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 (January 2011). The tables below list toxicity studies, and chronic toxicity and carcinogenicity studies, that were initiated, ongoing, or completed during FY 2015.

Study Tables Below:

- Prechronic Studies
- Chronic Studies

Prechronic Toxicology and Carcinogenicity Studies FY 2015

Test Article	CASRN*	Species	Length	Route	Study Scientist	Status
AZT drug combinations, transplacental/neonatal study	N/A	Mice	28 days	Gavage	Beland	Ongoing
N-Butylbenzenesulfonamide	3622-84-2	Mice	14 days	Feed	Rider	Ongoing
1-Butyl-3-methylimidazolium chloride	79917-90-1	Mice, Rats	90 days	Water	Ryan	Ongoing
1-Butyl-1-methylpyrrolidinium chloride	479500-35-1	Mice, Rats	90 days	Water	Ryan	Ongoing
N-Butylpyridinium chloride	1124-64-7	Mice, Rats	90 days	Water	Ryan	Ongoing

Cobalt	7440-48-4	Mice, Rats	2 weeks, 13 weeks	Inhalation	Behl	Completed
4-Methylcyclohexanemethanol, crude	N/A	Rats	5 days	Gavage	Auerbach	Ongoing
Cumene	98-82-8	Mice, Rats	14 days	Inhalation	Roberts	Initiated
Dimethylamine borane	74-94-2	Mice, Rats	2 weeks	Dermal	Germolec	Ongoing
N,N-Dimethyl-*p*-toluidine	99-97-8	Rats	5 days	Gavage	Dunnick	Ongoing
1-Ethyl-3-methylimidazolium chloride	65039-09-0	Mice, Rats	90 days	Water	Ryan	Ongoing
2-Ethyltoluene	611-14-3	Mice, Rats	14 days	Inhalation	Roberts	Scheduled
3-Ethyltoluene	620-14-4	Mice, Rats	14 days	Inhalation	Roberts	Scheduled
4-Ethyltoluene	622-96-8	Mice, Rats	14 days	Inhalation	Roberts	Initiated
Garcinia cambogia extract	90045-23-1	Mice, Rats	14 days	Feed	Rider	Ongoing
Glycidamide	5694-00-8	Mice, Rats	14 days, 90 days	Water	Beland	Completed
Isopropylated phenol phosphate	68937-41-7	Mice	2 weeks	Feed	Behl	Initiated
Carbon nanotube, 1020 long multiwalled	N/A	Mice, Rats	30 days	Inhalation	Germolec	Scheduled
Melamine and cyanuric acid combination	N/A	Rats	90 days	Gavage	Gamboa	Ongoing
4-Methylcyclohexanemethanol	34885-03-5	Rats	5 days	Gavage	Auerbach	Ongoing
Nanoscale silver	7440-22-4	Rats	13 weeks	Gavage	Boudreau	Ongoing

Pentabromodiphenyl oxide (technical) (DE-71)	32534-81-9	Rats	GD** 6 to PND*** 21	Gavage	Dunnick	Ongoing
3,3,4,4,5-Pentachlorobiphenyl (PCB 126)	57465-28-8	Rats	GD 6 to PND 21	Gavage	Dunnick	Initiated
Perfluorodecanoic acid	335-76-2	Rats	28 days	Gavage	Blystone	Completed
Perfluorohexane sulfonate potassium salt	3871-99-6	Rats	28 days	Gavage	Blystone	Ongoing
Phenobarbital	50-06-6	Rats	13 weeks, GD 6 to PND 21	Gavage	Dunnick	Initiated
Propylene glycol phenyl ether	770-35-4	Rats	5 days	Gavage	Auerbach	Ongoing
Sodium metavanadate	13718-26-8	Mice, Rats	14 days	Water	Roberts	Completed
Sulfolane	126-33-0	Guinea Pigs, Mice, Rats	28 days	Gavage	Blystone	Completed
2,2',4,4'-Tetrabromodiphenyl ether (BDE-47)	5436-43-1	Rats	GD 6 to PND 21, GD 6 to GD 20, GD 6 to PND 21	Gavage	Dunnick	Ongoing
p-Toluidine	106-49-0	Rats	5 days	Gavage	Dunnick	Ongoing
Triclosan	3380-34-5	Mice	90 days	Dermal	Fang	Ongoing
Triphenyl phosphate	115-86-6	Mice	2 weeks	Feed	Behl	Initiated

Tungsten	7440-33-7	Rats	28 days	Intratracheal	Behl	Ongoing
Tungsten suboxide fibers	N/A	Rats	28 days	Intratracheal	Behl	Ongoing
Usnea lichen	N/A	Mice, Rats	2 weeks	Feed	Leakey	Ongoing
(+)-Usnic acid	7562-61-0	Mice, Rats	2 weeks, 90 days	Feed	Leakey	Ongoing
Valerian (*Valeriana officinalis L.*) root extract	8057-49-6	Mice	14 days	Gavage	Roberts	Initiated
Vanadyl sulfate	27774-13-6	Mice, Rats	14 days	Water	Roberts	Completed
Vinylidene chloride	75-35-4	Mice, Rats	2 weeks, 13 weeks	Inhalation	Wyde	Completed

*CASRN = Chemical Abstracts Service Registry Number
**GD: gestational day
***PND: postnatal day

Chronic Toxicity and Carcinogenicity Studies Ongoing During FY 2015

Test Article	CASRN*	Species	Length	Route	Study Scientist	Status
Aging cohort study, mouse strains: • 129S1/SvImJ • B6C3F1 (Jackson) • C3H/HeJ • C57BL/6J (Jackson) • CAST/EiJ (*M. m. castaneus*) • NZO/HiLtJ • PWK/PhJ • WSB/EiJ (*M. m. domesticus*)	N/A	Mice	2 years	N/A	Dunnick	Ongoing

- A/J
- NOD. B10Sn-H2(b)/J

alpha-Pinene	80-56-8	Mice, Rats	2 years	Inhalation	Rider	Initiated
Antimony trioxide	1309-64-4	Mice, Rats	2 years	Inhalation	Stout	Ongoing
AZT drug combinations, transplacental/neonatal study	N/A	Mice	2 years	Gavage	Beland	Ongoing
AZT drug combinations, transplacental/carcinogenesis study	N/A	Mice	2 years	In utero	Beland	Ongoing
Bisphenol A	80-05-7	Rats	2-years	Gavage	Delclos	Ongoing
Black cohosh	84776-26-1	Mice, Rats	2 years	Gavage	Blystone	Ongoing
2,3-Butanedione	431-03-8	Mice, Rats	2 years	Inhalation	Morgan	Ongoing
Cell phone radiation: CDMA**	N/A	Mice, Rats	2 years	Whole body exposure	Wyde	Ongoing
Cell phone radiation: GSM***	N/A	Mice, Rats	2 years	Whole body exposure	Wyde	Ongoing
p-Chloro-a,a,a-trifluorotoluene	98-56-6	Mice, Rats	2 years	Inhalation	Stout	Ongoing
Dibutyl phthalate	84-74-2	Mice, Rats	2 years	Feed	Blystone	Ongoing
Di(2-ethylhexyl) phthalate	117-81-7	Rats	Perinatal and 2 years	Feed	Foster	Ongoing
Furan	110-00-9	Rats	2 years	Gavage	Beland	Ongoing
2-Hydroxy-4-methoxybenzophenone	131-57-7	Mice, Rats	2 years	Feed	McIntyre	Ongoing

Insertional mutagenesis, definitive vector study	N/A	Mice	14 months	Intravenous	Germolec	Ongoing
Trim VX	N/A	Mice, Rats	2 years	Inhalation	Ryan	Ongoing
Pentabromodiphenyl oxide (technical) (DE-71)	32534-81-9	Mice, Rats	2 years	Gavage	Dunnick	Ongoing
Perfluorooctanoic Acid	335-67-1	Rats	2 years	Feed	Blystone	Ongoing
Resveratrol	501-36-0	Mice, Rats	2 years	Gavage	Germolec	Ongoing
Sodium tungstate dihydrate	10213-10-2	Mice, Rats	2 years	Water	Behl	Ongoing
Sulfolane	126-33-0	Mice, Rats	2 years	Water	Blystone	Initiated
Triclosan	3380-34-5	Mice	2 years	Dermal	Fang	Ongoing
Tris(chloropropyl)phosphate	13674-84-5	Mice, Rats	2 years	Feed	Ryan	Ongoing
Zinc carbonate, basic	5263-02-5	Rats	2 years	Feed	Wyde	Ongoing

*CASRN = Chemical Abstracts Service Registry Number
**CDMA: code division multiple access
***GSM: global system for mobile communication

Related Links:

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"Modified One-Generation Reproduction Studies ..." next article - "Toxicogenomic Studies ..."

- previous article

Toxicogenomic Studies

NTP is incorporating the latest toxicogenomic technologies into its testing program to gain further insight regarding the toxicity of environmental substances. Toxicogenomics examines how the entire genetic structure, or genome, is involved in an organism's response to environmental toxicants. Microarray, next-generation (NextGen) sequencing, proteomics, and metabolomics are among the advanced technologies that 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 may be useful for identifying biomarkers of disease or exposure to toxic substances, and for understanding individual genetic susceptibilities. Once 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 provide a genetic signature. In one FY 2015 study, NTP initiated microRNA profiling of lung tissue after chemical inhalation to understand the mechanisms of pulmonary fibrosis that may lead to better biomarkers in lung tissue or blood.

NTP is researching if gene expression pattern analysis can provide indicators of toxicity (1) at earlier time points and (2) at lower doses than is possible for traditional toxicology parameters. Evaluating patterns of gene expression may provide more than just a link between genetics and morphology. It is also expected to provide insights into the pathogenesis of the disease and how different rodent models respond to toxicants. 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.

Several FY 2015 toxicogenomic studies used NextGen sequencing technologies, which provided improvements to gene expression analysis, including base-pair level resolution of accuracy and increased sensitivity compared to microarray platforms. While micorarrays are a stable and well understood technology for assaying gene expression, NextGen sequencing methods like RNA-Seq should become more common as sequencing costs drop, and bioinformatic pipelines become standardized and integrated with genomic sequencing. A promising area of research is the use of exome sequencing (Exome-Seq) that can be applied to either frozen or formalin fixed, paraffin embedded (FFPE) tissues. DNA can be extracted from either frozen or archival tissues. Coding portions of DNA, or exons, are captured by libraries of hybridization-based probes targeting over 200,000 exons and transcriptionally active regions. Exon-enriched DNA can be sequenced by DNA-Seq and then genomically aligned to find: mutations; indels, which are insertions or deletions; and other genetic abnormalities associated with disease. Three NTP studies are using Exome-Seq as a means for mutation profiling at a genome-wide scale to understand differences between spontaneous and chemically induced tumors.

NTP is evaluating study conditions that may contribute to differential gene expression, such as animal and tissue variability, methods for tissue sampling, and standards for conducting toxicogenomic studies under laboratory conditions. Efforts have been made to optimize methods for DNA and RNA extraction from archival tissues for

molecular analysis, as the NTP archives has a large amount of materials available. FY 2015 planned or ongoing NTP toxicogenomic studies are listed in the table below.

Toxicogenomic Studies Planned or Ongoing in FY 2015

Chemical	CASRN*	Species/ Cell Line	Route	Length	Test Type (Platform)	Study Scientist
Aging cohort study, mouse strains: • 129S1/SvImJ • B6C3F1 (Jackson) • C3H/HeJ • C57BL/6J (Jackson) • CAST/EiJ (*M. m. castaneus*) • NZO/HiLtJ • PWK/PhJ • WSB/EiJ (*M. m. domesticus*) • A/J • NOD. B10Sn-H2(b)/J	N/A	Mice	N/A	2 years	NextGen sequencing Exome-Seq (Illumina)	Dunnick
Arsenite	7784-46-5	Human prostate cell lines	Cell culture	30 weeks	NextGen sequencing DNA-Seq, RNA-Seq (Illumina)	Merrick
Black cohosh	84776-26-1	Mice	Gavage	90 days	Microarray (Affymetrix)	Cora
Bromodichloroacetic acid Methyleugenol***	5589-96-8 93-15-2	Mice	Gavage	2 years	NextGen sequencing Exome-Seq (Illumina)	Pandiri
DE-71 PCB-126 Phenobarbital***	32534-81-9 57465-28-2 50-06-6	Rats	Gavage	GD** to PND 22	Microarray (Affymetrix)	Dunnick
N,N-Dimethyl-*p*-toluidine	99-97-8	Rats	Gavage	5 days, 90	Microarray	Dunnick

				days	(Affymetrix)	
Dong quai (*Angelica sinensis*) root extract	299184-76-2	Mice	Gavage	90 days	Microarray (Affymetrix)	McIntyre
Elk River spilled chemicals: • Dipropylene glycol phenyl ether • 4-Methylcyclohexane methanol (MCHM) • 4-Methylcyclohexane methanol, crude/mixture • Propylene glycol phenyl ether	51730-94-0 34885-03-5 N/A 770-35-4	Rats	Gavage	5 days	Microarray (Affymetrix)	Auerbach
Phosphate flame retardants: • *tert*-Butylphenyl diphenyl phosphate • 2-Ethylhexyl diphenyl phosphate • Isodecyl diphenyl phosphate • Isopropylated phenol phosphate	56803-37-3 1241-94-7 29761-21-5 68937-41-7	Rats	Gavage	5 days	Microarray (Affymetrix) Metabolomics	Auerbach
Ginkgo biloba extract	90045-36-6	Rats	Gavage	5 days	Microarray (Affymetrix)	Rider/ Auerbach
2-Hydroxy-4-methoxybenzophenone	131-57-7	Rats	Feed	90 days	Microarray (Affymetrix)	Auerbach
Methyleugenol extract *Ginkgo biloba* extract***	93-15-2 90045-36-6	Mice	Gavage	2 years NextGen sequencing Exome-Seq RNASeq (Illumina)	NextGen sequencing Exome-Seq RNA-Seq (Illumina)	Auerbach/Merrick

2,3-Pentanedione	600-14-6	Rats	Inhalation	14 and 28 days	microRNA Microarray (Affymetrix)	Morgan
Polycyclic aromatic compounds: • Acenaphthenequinone • Benzo[b]fluoranthene • Benzo(a)pyrene • Dibenz[a,h]anthracene • 9-Methylanthracene • 1-Methylfluorene • Perinaphthenone • Phenanthrene • Pyrene	82-86-0 205-99-2 50-32-8 53-70-3 779-02-2 1730-37-6 548-39-0 85-01-8 129-00-0	Human hepatocyte cell line	In vitro exposure	48 hours	Cytotoxicity Gene expression by quantitative polymerase chain reaction (qPCR)	Rider/ Tokar
BDE Toxicogenomics Studies: • 2,2’,4,4’,5-Pentabromodiphenyl ethers • Pentabromodiphenyl oxide (technical) (DE-71) • 3,3,4,4,5-Pentachlorobiphenyl • 2,2'4,4'-Tetrabromodiphenyl ether (DE-47)	5436-43-1 32534-81-9 57465-28-8 5436-43-1	Rats, Mice	Gavage	GD** 6 through 3 weeks	Microarray (Affymetrix)	Dunnick
Tetrabromobisphenol A	79-94-7	Rats	Gavage	90 days	Microarray (Affymetrix)	Dunnick/ Merrick
p-Toluidine	106-49-0	Rats	Gavage	5 days and 90 days	Microarray (Affymetrix)	Dunnick

* Chemical Abstracts Service Registry Number
**GD: gestational day

*** This study will compare toxicogenomic effects among the chemicals listed together.

Related Links:

- Disposition, Metabolism, and Toxicokinetic Studies
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- Project Review Committee Approved

"Toxicology and Carcinogenicity Studies ..." - previous article

next article - "Project Review Committee Approved ..."

Project Review Committee Approved

The table below lists studies that were approved by either the internal NIEHS/NTP protocol approval committee or the internal NIEHS/NTP project review committee, but were not started during FY 2015.

Protocol Title	Study Scientist
Evaluation of the immunotoxicity of sulfolane (CASRN* 126-33-0) in B6C3F1/N mice treated for 90-days via oral gavage	Germolec
Evaluation of the immunotoxicity of sulfolane (CASRN 126-33-0) in harlan sprague dawley rats following perinatal exposure via dosed drinking water	Germolec
Toxicokinetic studies of sulfolane (CASRN 126-33-0) in harlan sprague dawley rats and B6C3F1/N mice following administration via gavage, intravenous, and drinking water	Waidyanatha/ Blystone
Chronic toxicity and carcinogenicity studies of 1020 long multiwalled carbon nanotubes in harlan sprague dawley rats and B6C3F1/N mice exposed via whole body inhalation	Germolec
Evaluation of the immunotoxicity of 1020 long multiwalled carbon nanotubes in harlan sprague dawley rats exposed via whole body inhalation for 30-days and B6C3F1/N mice exposed via whole body inhalation for 30-days or 3-months	Germolec
Acute toxicity studies of trimethylsilyldiazomethane (TMSD) (CASRN 18107-18-1) in male harlan sprague dawley rats and B6C3F1/N mice exposed via nose only inhalation	Gwinn
Evaluation of the prechronic toxicity of Valerian (*V. officinalis*) in B6C3F1/N mice treated via gavage	Roberts
Evaluation of a perinatal dose range finding study of Valerian (*V. officinalis*) in harlan sprague dawley rats administered daily via gavage	Roberts
Toxicokinetic studies of vinpocetine (CASRN 42971-09-5) in pregnant harlan sprague dawley rats following gavage administration	Catlin

Perinatal dose range-finding study of 2,2’ –dimorpholinodiethyl ether (DMDEE) (CASRN 6425-39-4) in harlan sprague dawley rats exposed via gavage	Roberts
4-week toxicity study of 2,2’ –dimorpholinodiethyl ether (DMDEE) (CASRN 6425-39-4) in B6C3F1/N mice treated via gavage	Roberts
Combined prenatal and perinatal dose range-finding study of efavirenz (CASRN 154598-52-4) in CD-1 mice exposed via gavage	McIntyre
Combined prenatal and perinatal dose range-finding study of tenofovir disoproxil fumarate (CASRN 202138-50-9) in CD-1 mice exposed via gavage	McIntyre
Perinatal dose range-finding study of bisphenol S (CASRN 80-09-1) in harlan sprague dawley rats exposed via dosed feed	Sutherland
Two-week toxicity of bisphenol S (CASRN 80-09-1) in B6C3F1/N mice exposed via dosed feed	Sutherland
Subchronic toxicity of *Aspergillus versicolor* in B6C3F1/N mice exposed via nose only inhalation	Germolec
Prenatal toxicity study of vinpocetine (CASRN 42971-09-5) in new zealand white rabbits administered via gavage	Catlin
Perinatal dose range-finding study of triclocarban (CASRN 101-20-2) in harlan sprague dawley rats exposed via oral gavage	Sutherland
Two-week toxicity of triclocarban (CASRN 101-20-2) in B6C3F1/N mice exposed via oral gavage	Sutherland
Perinatal dose range-finding study of triclosan (CASRN 3380-34-5) in harlan sprague dawley rats exposed via oral gavage	Sutherland
Absorption, distribution, metabolism, and excretion (ADME) studies of bisphenol S (CASRN 80-09-1) in harlan sprague dawley rats and B6C3F1/N mice following gavage administration and intravenous administration of [14C]bisphenol S and for investigating clearance and metabolism of selected bisphenol S derivatives in vitro	Sutherland
Subchronic toxicity of *Stachybotrys chartarum* (CASRN 67892-26-6) in B6C3F1/N mice exposed via nose only inhalation	Germolec
Perinatal dose range-finding study of *Echinacea purpurea* extract (CASRN 90028-20-9) in harlan sprague dawley rats exposed via oral gavage	Ryan
Prechronic toxicity of N-butylbenzenesulfonamide (CASRN 3622-84-2) in B6C3F1/N mice exposed via dosed feed	Rider
Five-day toxicity and toxicogenomics study of five lots of *Ginkgo biloba* extract (CASRN	

90045-36-6), goldenseal extract (CASRN 84603-60-1) and green tea extract, and toxicokinetic study in one lot of *Ginkgo biloba* extract in F344/NTac rats treated via oral gavage	Rider
Five-day toxicity and toxicogenomics study of brominated flame retardants in male harlan spraque dawley rats treated via oral gavage	Dunnick
Perinatal study to investigate the endocrine toxicity of tris(4-chlorophenyl)methane (CASRN 27575-78-6) in harlan sprague dawley rats exposed via dosed feed	Catlin

*CASRN = Chemical Abstracts Service Registry Number

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"Toxicogenomic Studies ..." - previous article

Literature Analysis

Noncancer Research

NTP conducts evaluations to assess the evidence that substances cause adverse health effects and provides opinions on whether these substances may be of human concern.

Report on Carcinogens

The Report on Carcinogens (RoC) is a congressionally mandated listing of substances that either are known to be human carcinogens or may reasonably be anticipated to be human carcinogens, and to which a significant number of persons residing in the U.S. are exposed.

Noncancer Research

NTP has made a commitment to studying noncancer health effects, and conducts evaluations to assess the evidence that environmental chemicals, physical substances, or mixtures, collectively referred to as substances, cause adverse health effects. NTP also provides opinions on whether these substances may be of concern, given what is known about current human exposure levels. The Office of Health Assessment and Translation (OHAT) conducts health hazard assessments, workshops, and state-of-the-science evaluations, which are published as NTP monographs, and hosts workshops to address important issues in environmental health sciences. Kristina Thayer, Ph.D. serves as deputy division director for analysis, Division of NTP, NIEHS, and is director of OHAT.

In FY 2015, OHAT published the Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration, which identifies the standard operating procedures used in evaluations. The table below lists literature analysis projects that were initiated, ongoing, or completed in FY 2015.

View Research Areas in Noncancer Research

Ongoing Noncancer Health Effects Projects

Show All

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Results: Reset

Ongoing Noncancer Health Effects Projects

Project & Study Scientist	Project Summary
Identifying research needs for assessing safe use of high intakes of folic acid; state of the	NTP, in conjunction with the NIH Office of Dietary Supplements, convened an expert panel to identify

science evaluation Study Scientist: Boyles	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 effects from high intakes of folic acid. The expert panel discussed the areas of consistency and inconsistency in the literature at a public meeting at NIH on May 11-12, 2015, in Bethesda, Maryland. An NTP monograph was published in August 2015, which identifies research needs and informs the development of a research agenda for evaluating the safe use of high intakes of folic acid.
Evaluation of inflammation-based atherosclerosis associated with environmental exposures Study Scientist: Rooney	There is growing evidence that the environment plays a role in a wide range of diseases that involve inflammation. The extent to which environmental exposures ultimately lead to these adverse health effects through an inflammatory pathway remains unclear. This evaluation will examine the evidence that environmental substances contribute to inflammation, which ultimately leads to atherosclerosis, and identify biomarkers of the inflammation involved. Atherosclerosis was selected for investigation because of the significant public health impact of the disease, and the well-established role for inflammation in the disease process leading to atherosclerosis. The draft concept was reviewed at the December 2014 Board of Scientific Counselors meeting, and the evaluation has been initiated.
Evaluation of immunotoxicity associated with exposure to perfluorooctanoic acid (PFOA) or perfluorooctane sulfonate (PFOS) Study Scientist: Rooney	Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) are extremely persistent chemicals and are widely distributed in the environment as a result of extensive use over the last 60 years. Although exposures have been dramatically reduced, the persistence and bioaccumulation of both PFOA and PFOS result in detectable levels in the U.S. population. Recent publications have linked PFOA and PFOS exposure in humans to functional immune changes that are consistent

with evidence of PFOA- and PFOS-related immunotoxicity reported in animal studies. OHAT is conducting a systematic review to evaluate the evidence for an association between exposure to PFOA or PFOS and immunotoxicity or immune-related health effects. The draft concept was reviewed at the June 2015 Board of Scientific Counselors meeting, and the evaluation has been initiated.

Exposure to chemicals in consumer products: an NIEHS and EPA collaborative methods demonstration and evaluation pilot study

Study Scientist: Taylor

There is concern about the endocrine-disrupting potential of some chemicals found in personal care products and other consumer products. Given the large number of co-occurring chemicals in these products, new strategies and techniques need to be developed, and existing tools need to be evaluated, for their utility in assessing the extent of human exposure to tens of thousands of chemicals. NIEHS is collaborating with EPA to perform a small-scale, longitudinal pilot study, to evaluate the performance of existing survey, measurement, and modeling methods for assessing exposures to chemicals in a number of consumer product categories, including personal and child care, household cleaning, lawn and garden, home improvement, and food packaging products. The pilot study addresses a number of research needs related to the measurement and modeling of human exposures. The draft concept was reviewed at the June 2015 Board of Scientific Counselors meeting, and the NIEHS Institutional Review Board (IRB) for the Protection of Human Subjects in Research has approved the project. This evaluation has been initiated.

State of the science for transgenerational inheritance of health effects

Study Scientist: Walker

Transgenerational inheritance is the phenomenon in which an individual's exposures have far-reaching consequences, affecting multiple generations removed from the original insult. The traditional belief suggests that negative effects of exposure to environmental chemicals are reset in each generation, such that subsequent generations are unaffected by the exposure history of their parents and grandparents. This state-of-the-science evaluation will examine the robustness of the evidence for transgenerational inheritance of health effects

associated with exposure to a wide range of stressors, such as environmental chemicals, drugs of abuse, nutrition and diet, pharmaceuticals, infectious agents, and stress in humans and animals. A Federal Register Notice was published in May 2013 soliciting public comments. The evaluation has been initiated.

Evaluation of children's health and traffic-related air pollution

Study Scientist: Howdeshell

Research on traffic-related air pollution and children's health has increased in the past decade with improvements in air monitoring technology and exposure methodology. Traffic-related air pollution has been measured in many different ways, including direct traffic measures, such as proximity or density of traffic; environmental gases, such as ozone and nitrogen dioxide; particulate matter, including coarse particles (PM10) and fine particles (PM2.5); and select components of traffic-related pollution, including benzene, diesel exhaust, and polycyclic aromatic hydrocarbons (PAHs). This topic is being addressed in a series of evaluations on the evidence for an association between traffic-related air pollution and health outcomes impacting fetal outcome and children, including gestational hypertension and neurological development and function in children. The draft concept was reviewed at the April 2014 Board of Scientific Counselors meeting, and the evaluation has been initiated.

Evaluation of adverse health effects and occupational exposure to cancer chemotherapy agents

Study Scientist: Howdeshell

Cancer chemotherapy agents are cytotoxic drugs, and many of these agents are known mutagens and developmental toxicants. Occupational exposure to cancer chemotherapy agents may occur in various professions including medical, veterinary, and manufacturing. While improved handling procedures and engineering controls have reduced contamination, surface contamination persists in pharmacy and nursing areas of some hospital-based cancer centers. This evaluation will examine the evidence that occupational exposure to cancer chemotherapy agents is associated with adverse health effects and focus on nonreproductive health. NIOSH recently published a review of

occupational exposure to anti-neoplastic drugs and reproductive health effects. The draft concept was reviewed at the April 2014 Board of Scientific Counselors meeting, and the evaluation has been initiated.

Biological activity of bisphenol A (BPA) structural analogues and functional alternatives

Study Scientist: Pelch

Bisphenol A (BPA) is a high production volume chemical used in the manufacture of polycarbonate plastic, thermal paper, dental resins, and other composite materials used in consumer products. Recent studies report widespread use and exposure to a variety of chemicals with structural or functional similarity to BPA, referred to as BPA analogues. This evaluation will examine the extent of the human, animal, and in vitro evidence of biological activity of BPA analogues of emerging public health concern. It will be further addressed by additional in vitro laboratory experiments and external collaborations to evaluate in vivo activity in two model organisms, zebrafish and *Caenorhabditis elegans*. The concept was announced in June 2015 to the Board of Scientific Counselors, and the evaluation and research have been initiated.

Environmental influences on the epigenome: a scoping report

Study Scientist: Pelch

NIEHS is interested in understanding the effects of the environment on epigenetic regulation of biological and pathological processes. Of the various epigenetic modifications, the alteration of DNA methylation patterns has been the most widely studied and highly funded modification to date. This evaluation will leverage newly developed text mining and machine learning tools to carry out scoping activities exploring the extent of the evidence linking environmental exposures to health outcomes via genome-wide alterations in DNA methylation. The concept was announced in June 2015 to the Board of Scientific Counselors, and the evaluation has been initiated.

Shift work at night, light at night, and circadian disruption

Study Scientist: Thayer

Circadian disruption occurs when endogenous circadian rhythms, which are daily and predictable variations in biological, physiological, and behavioral processes, are out of phase with the external environment or with each other. People, by virtue of the nature of their work, lifestyle choices, or residence, are subjected to

interruptions in the natural light-dark cycles, leading to the potential for circadian disruption. This project is being undertaken in conjunction with an analysis by the Office of the Report on Carcinogens (RoC) for cancer hazard evaluation. The draft concept was reviewed at the April 2014 Board of Scientific Counselors meeting, and activity is underway working with the Office of the Report on Carcinogens to define the relevant exposures.

Report on Carcinogens

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

The RoC is a cumulative report and consists of substances newly reviewed, in addition to those listed in previous editions. NTP follows an established four-part process for preparing the report.

1. NTP selects nominations for RoC evaluation, referred to as candidate substances.
2. Office of RoC conducts cancer hazard evaluations on candidate substances.
3. Draft RoC monographs are released for public comment and peer review before finalization.
4. NTP submits the proposed listing of newly reviewed substances, whose cancer evaluations are completed, to the U.S. Department of Health and Human Services (HHS) secretary for review, approval, and release to the public and congressional members.

Each substance listed in the RoC has a profile, which contains the listing status, determined by using established listing criteria; and a summary of the cancer studies supporting the listing status, information on human exposure, and federal regulations to reduce exposure.

Preparation of the RoC is conducted by the Office of the Report on Carcinogens, under the direction of Ruth Lunn, Dr.P.H. Contract support for preparation of the RoC in FY 2015 was provided by Integrated Laboratory Systems Inc.

Additional Links for the RoC

- Report on Carcinogens
- RoC Activities in 2015
- Newly Reviewed Listings
- RoC Candidate Substances

next article - "RoC Activities in FY ..."

RoC Activities in FY 2015

On October 2, 2014, HHS released the 13th RoC. This cumulative report contains 243 listings, of which four were newly reviewed. The newly reviewed listings, also listed in the table below, include ortho-toluidine, listed as known to be a human carcinogen, and three substances: 1-bromopropane, cumene, and pentachlorophenol and byproducts of its synthesis (hereinafter referred to as pentachlorophenol), all listed as reasonably anticipated to be human carcinogens.

Other RoC activities in FY2015 were related to conducting the cancer hazard evaluations of several candidate substances, listed in the second table below. The cancer hazard evaluation of trichloroethylene was completed, including preparation of the revised draft monograph and response to the peer-review report, and the NTP Board of Scientific Counselors was updated on the peer-review meeting in December 2014. The final monograph was published on the NTP website in January 2015. In July 2015, NTP convened a panel of experts to peer review the draft RoC monograph on cobalt and certain cobalt compounds. The monograph is being revised based on the peer-review comments. The Office of the Report on Carcinogens has also worked on the preparation of a series on monographs for five viruses. The peer-review meeting is scheduled for December 17, 2015. Cancer hazard evaluations are ongoing for two other candidate substances: (1) goldenseal and (2) shift work at night, light at night, and circadian disruption.

The Handbook for Preparing Report on Carcinogens Monographs was published in July 2015. It lays out the methods for conducting the cancer hazard evaluation, from the planning and problem formulation stage to reaching a preliminary listing recommendation. The handbook is a living document and incorporates principles of systematic review.

Key elements related to increasing the transparency of RoC reviews include methods to evaluate risk of bias and sensitivity of cancer studies in humans and experimental animals, and guidelines for synthesizing evidence across the studies to reach preliminary level of evidence conclusions.

Additional Links for the RoC

- Report on Carcinogens
- RoC Activities in 2015
- Newly Reviewed Listings
- RoC Candidate Substances

"Report on Carcinogens ..." - previous article

next article - "Newly Reviewed Listings in ..."

Newly Reviewed Listings in the 13th RoC

Candidate Substance CASRN* Study Scientist	Primary Uses/Exposures	Listing Status and Rationale
1-Bromopropane 106-94-5 Spencer	Halogenated alkane used as a solvent for cleaning or adhesives in a variety of industrial sectors including: • Spray adhesives • Vapor degreasing • Aerosol solvents • Dry-cleaning People are primarily exposed to 1-bromopropane by inhalation or through the skin in workplaces that use or produce 1-bromopropane.	Reasonably anticipated to be a human carcinogen. Sufficient evidence of carcinogenicity from studies in experimental animals.
Cumene 98-82-8 Jahnke	Alkylated benzene found in fossil fuels and used primarily to produce phenol and acetone. People are exposed to cumene in workplaces that produce or use cumene, or in gasoline transport related jobs. In their everyday lives, people can be exposed from breathing contaminated air or cigarette smoke.	Reasonably anticipated to be a human carcinogen. Sufficient evidence of carcinogenicity from studies in experimental animals.
Pentachlorophenol and byproducts of its synthesis 87-86-5 Jahnke	Complex mixture primarily used as wood preservatives in the U.S. People are exposed to the mixture in workplaces that treat wood, use treated wood, or in the past have produced it.	Reasonably anticipated to be a human carcinogen. Limited evidence of carcinogenicity from

	In their everyday lives, people can be exposed by breathing contaminated outdoor air, indoor air, and indoor dust; from the soil; and by ingesting water or food.	studies in humans (non-Hodgkin lymphoma). Sufficient evidence of carcinogenicity from studies in experimental animals.
ortho-Toluidine 95-53-4 Lunn	Arylamine used as an intermediate to manufacture herbicides, dyes, pigments, and rubber chemicals. The highest exposure to ortho-toluidine occurs to people using it in the workplace. People are exposed to lower levels in their everyday lives from consumer products, medical products, cigarette smoke, and possibly the environment.	Known to be a human carcinogen. Sufficient evidence of carcinogenicity from studies in humans.

* Chemical Abstracts Service Registry Number

Additional Links for the RoC

- Report on Carcinogens
- RoC Activities in 2015
- Newly Reviewed Listings
- RoC Candidate Substances

"RoC Activities in FY ..." - previous article

next article - "RoC Candidate Substances ..."

RoC Candidate Substances

Candidate Substance CASRN* Study Scientist	Primary Uses/Exposures	Listing Status and Rationale
Cobalt 7440-48-4 Spencer	A naturally occurring element that is present in different forms, such as a metal and salts. Cobalt metal and cobalt compounds are used in the production of metal alloys for a variety of commercial applications, as a pigment for dying pottery and colored glass, and in green energies.	Peer-review meeting July 22, 2015.
Goldenseal root powder Lunn	Member of the plant family *Ranunculaceae*; the root is used as an alternative medicine to treat a variety of ailments. People are exposed to this botanical by ingesting one of over 150 products, such as dietary supplements and herbal remedies that contain goldenseal root powder.	NTP Board of Scientific Counselors review of draft concept, April 2014. Planning of cancer hazard evaluation initiated.
Shift work at night, light at night, and circadian disruption Lunn	Circadian disruption occurs when endogenous circadian rhythms, daily and predictable variations in biological, physiological, and behavioral processes, are out of phase with the external environment or with each other. People, by virtue of the nature of their work, lifestyle choices, or residence, are subjected to interruptions in the natural light-dark cycles, leading to the potential for circadian disruption.	NTP Board of Scientific Counselors review of draft concept, June 2013. Cancer hazard evaluation initiated, and working with Office of Health Assessment and Translation (OHAT) to define the exposures.

Trichloroethylene** 79-01-6 Lunn	Halogenated alkene used primarily for degreasing metals.	Peer-review meeting August 12, 2014. Revised draft monograph posted on RoC website.
5 Selected viruses: • Epstein-Barr virus (EBV) • Human immunodeficiency virus type 1 (HIV) • Human T-cell lymphotrophic virus type 1 (HTLV-1) • Kaposi's sarcoma-associated herpes virus (KSHV) • Merkel cell polyoma virus (MCV) Jahnke	EBV and KSHV: herpes viruses (enveloped; double-stranded DNA genome). Exposure occurs through saliva. HIV and HTLV-1: retroviruses (enveloped; single-stranded RNA genome). Exposure occurs via breast feeding and perinatal, parenteral, and sexual transmission. MCV: polyomavirus (nonenveloped, double-stranded DNA genome). It is not known how people are infected with the virus.	Peer-review meeting scheduled for December 17, 2015.

* Chemical Abstracts Service Registry Number
** Currently listed as reasonably anticipated to be a human carcinogen in the RoC.

Additional Links for the RoC

- Report on Carcinogens
- RoC Activities in 2015
- Newly Reviewed Listings
- RoC Candidate Substances

"Newly Reviewed Listings in ..." - previous article

Partner Agency Research

NTP at NIEHS

Research activities in the Division of NTP at NIEHS are conducted through the several branches: Biomolecular Screening Branch, Cellular and Molecular Pathology Branch, NTP Laboratory, Program Operations Branch, and Toxicology Branch.

NTP at NIOSH

NIOSH research projects for NTP to assess the effects of exposures to substances, following its mandate to protect workers' health and safety.

NTP at NCTR

NCTR provides innovative technology, methods development, vital scientific training, and technical expertise to the NTP program.

NTP at NIEHS

The following Division of NTP branches at NIEHS are actively involved in NTP research activities: Biomolecular Screening Branch, led by Raymond Tice, Ph.D. until his retirement in December 2014, and now led by acting chief Rick Paules, Ph.D.; Cellular and Molecular Pathology Branch, led by Robert Sills, D.V.M., Ph.D.; NTP Laboratory, led by acting chief Michael Devito, Ph.D.; Program Operations Branch, led by Michelle Hooth, Ph.D.; and Toxicology Branch, led by Paul Foster, Ph.D.

NIEHS/NTP Staff

Biomolecular Screening

Genetic and epigenetic differences between individuals in the human population are proposed as major factors for individual susceptibility to environmental stressors. Environmental and drug safety assessments are currently conducted with a small number of commonly used animal models, which have limited genetic diversity. Further, there are many layers of biological regulation that can influence individual genetic susceptibility to chemical and drug toxicity. Animal models have inherent limitations in extrapolating results to human toxicity and disease, and this program is working toward development of more sophisticated analyses in epigenetics to make better use of current animal models, and adopt biological systems that are more appropriate for modeling human toxicity and disease. The NTP Biomolecular Screening Branch conducts in-house projects aimed at understanding individual susceptibility.

In FY 2015, work continued on the mouse methylome project by Alex Merrick, Ph.D., and Paul Wade, Ph.D. Epigenetics involves the study of modifications to DNA, like methylation, and related cellular structures, such as histones, that affect gene expression and an organism’s ability to adapt to the environment. NTP

designed an epigenetic study to examine DNA methylation and its possible relationship with the susceptibility of mouse strains to develop liver tumors. Male and female C57BL/6N mice were crossed with C3H/HeN mice. Five tissues — brain, liver, cardiac and skeletal muscle, brown and white fat, and epididymal sperm — from the first generation offspring were collected, at the average age NTP starts mice in a subchronic toxicity study, and flash frozen for DNA/RNA isolation and liver sequencing. Progress in FY 2015 involved computational analysis on sites of genomic methylation in relation to known genes and transcriptionally active regions in both parental strains and the resulting first generation offspring. The relationship of DNA methylation to gene expression and possible heredity in offspring is being determined, and the genomic variation between mouse strains, genders, and F1 offspring is being catalogued. The epigenetic landscape is being carefully described in these two mouse strains and offspring to help interpret the contribution of differences in DNA methylation to their differential susceptibility to hepatic malignancy. A manuscript is in preparation to be followed by public release of the methylome data. Additional studies in 2015 have been initiated that will address the impact of sex hormone signaling on DNA methylation at a genome-wide level, and the impact of DNA methylation at distal regulatory regions.

NTP Laboratory

The NTP Laboratory, within the NIEHS Division of NTP, 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, and methods development to advance the NTP mission. The NTP Laboratory also focuses on the study of the developmental origins of adult diseases. The table below includes projects in the NTP Laboratory in FY 2015.

View Research Areas in

NTP Laboratory Projects in FY 2015

Show All

Search Projects

Search Projects

Results: Reset

NTP Laboratory Projects in FY 2015

Project & Study Scientist	Project Summary
Development of in vitro models of metal carcinogenesis Study Scientist: Tokar	To develop in vitro cell transformation models with target relevant cells using arsenic and cadmium.

Epigenetics in malignant transformation
Study Scientist: Thayer

To assess the epigenome of a series of isogenic cell lines transformed by genotoxic or epigenetic carcinogens, and perform gene-specific methylation analyses. This project has been completed and a paper published in FY 2015 (Pelch 2015).

Formaldehyde in p53 knockout mice
Study Scientist: Morgan

To define the role of formaldehyde inhalation in hematopoietic tumor induction.

Formaldehyde-induced transformation of human myeloid progenitor cells
Study Scientist: Morgan

To perform a proof of concept study of in vitro formaldehyde-induced malignant transformation in hematopoietic stem cells. Companion study to the p53 study mentioned above.

Incorporating metabolism into high throughput screening assays
Study Scientist: DeVito

To develop in vitro methods that incorporate xenobiotic metabolism.

Indium-tin-oxide and indium compounds
Study Scientist: Morgan

To perform various in vivo inhalation or in vitro toxicity studies. This project has been completed and resulted in one new publication in FY 2015 (Gwinn 2015).

Metalloestrogens and uterine/breast response
Study Scientist: Dixon, Fenton

To retest the ability of reported metalloestrogens, like cadmium and arsenic, to cause estrogen receptor stimulation in the uterus as a mode of action towards cancer development.

Method for assessing biological impact of metal particle dissolution
Study Scientist: Morgan

(1) To develop an in vitro transwell method with metal particles and macrophages in one well and cells of interest, such as lung epithelium, in the other; and (2) define the ability of various types of macrophages to release different metals from different particles. This project has been completed, manuscripts are in preparation.

Methods in histopathology of mammary gland development
Study Scientist: Fenton

To develop standardized methods to quantitatively assess chemical insult on mammary gland development.

Refinement of developmental neurotoxicology methods

Study Scientist: Harry

To improve methods for various efforts including genetic signatures, stem cells, inflammation, behavior, and conditioning.

Role of microRNAs in malignant transformation

Study Scientist: Tokar

To study genes of interest involved in the epigenetics of malignant transformation, using in vitro human model systems of carcinogenesis. MicroRNAs are thought to be a key epigenetic or posttranscriptional gene expression control mechanism.

Stem cells in toxicology and carcinogenesis

Study Scientist: Tokar

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.

Toxicants and mammary gland development

Study Scientist: Fenton

To determine the effects of different toxicants, including atrazine, on mammary gland development in rats and mice.

Using *Caenorhabditis elegans* (*C. elegans*.) for screening mitochondrial toxicants

Study Scientist: Boyd

To study the effects of mitochondrial toxicants in *C. elegans*. This project has been completed, and a manuscript has been accepted for publication.

Using *Caenorhabditis elegans* (*C. elegans*.) as screens for toxicity of flame retardants

Study Scientist: Boyd

To study the effects of flame retardants in *C. elegans*. This project has been completed, and a paper published in FY 2015 (Behl 2015).

Using in vitro screens to evaluate potential obesogens

Study Scientist: Fenton

To develop orthogonal assays to evaluate findings from Tox21 that identified potential obesogens.

Using in vitro screens to evaluate polyaromatic compounds

Study Scientist: DeVito

To apply in vitro assays to assess and categorize the biological effects of polyaromatic compounds.

Application of in vitro assays to evaluate botanicals Study Scientist: DeVito	To determine if in vitro assays and chemical analysis of botanicals can aid in selecting botanicals for in vivo testing.

NTP at NIOSH

Assessing Exposure to Substances in the Workplace

In following its mandate to protect workers' health and safety, NIOSH carries out research projects for NTP to assess the effects of exposure to substances, through an interagency agreement with NIEHS. Setting priorities in occupational toxicological research is based upon several sources of information that NIOSH develops and maintains. 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 and alerts, other technical reports, and information profiles on chemical hazards.

NIOSH Staff: Health Effects Laboratory Division; Education and Information Division; Division of Applied Research and Technology and the Division of Surveillance, Hazard Evaluations, and Field Studies

Related NIOSH Research:

Comprehensive Assessment of Occupationally-Relevant Exposures
Immunotoxicology Research

The table below lists NIOSH/NTP projects in FY 2015.

View Research Areas in

Biomonitoring, Biomarker Dev. & Health Assesment
Environmental Monitoring
Exposure Assessment

Search Projects

Search Projects

Results: Reset

Immunotoxicity and Immunology Genetics

Show All

Biomonitoring, Biomarker Dev. & Health Assesment

Project & Study Scientist	Project Summary
Reproductive health assessment of male workers Study Scientist: Schrader	To evaluate reproductive health hazards, using a health profile consisting of biomarkers for assessing male fecundity. Current research involves a multiyear study with Emory University to evaluate the reproductive health of adult men accidently exposed to endocrine disruptors in utero through mothers living and working on family farms in Michigan.
Exposure assessment research and support Study Scientist: Striley	To support multiple branch and interdivisional projects through the management and planning of field sample collection, the development of new classical and immunochemical biomonitoring methods, and the validation and adaptation of existing methods. 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.
Ultraviolet native fluorescence-based monitor for workplace exposures Study Scientist: Snawder	To develop and evaluate a readily adaptable, next generation, direct reading, personal monitor 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 semivolatile workplace chemicals will be

	helpful in rapidly assessing chemical exposure, resulting in more realistic occupational exposure assessments, allowing for rapid interventions leading to reduced worker exposures, and aiding prevention of occupational illness and disease.
Evaluation of welding fumes as a lung carcinogen in mice exposed by inhalation Study Scientist: Erdely	To investigate both carcinogenic-metal and non-carcinogenic-metal containing welding fumes as lung carcinogens using a two-stage initiation-promotion mouse model. The findings will establish if welding fume inhalation at relevant occupational exposure levels increases lung tumorigenesis. The project will also generate valuable data regarding the carcinogenic potential of fumes from different types of welding activities that may or may not contain carcinogenic metals. In addition, the project will establish knowledge on which subcomponents of the total welding fume have the greatest carcinogenic potency. The results will be important for the potential reevaluation of welding fume by the International Agency for Research on Cancer (IARC).
Systematic assessment of cobalt oxide (CoO) and lanthanum oxide (La2O3) in pulmonary disease Study Scientist: Qian	To investigate cobalt oxide (CoO) and lanthanum oxide (La2O3) nanoparticle–induced (1) pulmonary injury in vivo and (2) cellular toxicity in vitro. This project will reveal the toxicological mode of actions of CoO and La2O3 nanoparticles. Metal oxide nanoparticles are an important class of engineered nanomaterials with a broad application in many industrials. Concerns over potential metal oxide nanoparticle-induced toxicity have emerged, particularly due to their ability to induce oxygen radicals and oxidative stress. Results obtained from this study will lead to development of methods for early detection and interventions of CoO and La2O3 -induced pulmonary diseases, particularly fibrosis, in humans.
Systematic assessment of multiwalled carbon nanotubes in pulmonary disease Study Scientist: Qian	To detect and identify novel biomarkers and molecular mechanisms of multiwalled carbon nanotube-induced pulmonary diseases, including fibrosis and cancer, for early detection and treatment interventions. Concerns over potential adverse pulmonary effects of airborne

	exposure to multiwalled carbon nanotubes have been raised due to their high aspect ratio (length and diameter), nanoscale diameter, fiber like-shape, durability, and biopersistence. Increasing evidence has indicated potential pulmonary health hazards associated with pulmonary exposure to multiwalled carbon nanotubes, including inflammation, damage, fibrosis, and potential carcinogenesis. The mechanisms underlying these adverse multiwalled carbon nanotube-induced pulmonary responses are not well understood. Currently, there is no available noninvasive screening test for early detection of lung fibrosis.
Industry-wide studies of workers exposed to carbon nanotubes and nanofibers Study Scientist: Schubauer-Berigan	To collect exposure data from participating pilot-scale or full-scale manufacturers or users of single-walled or multiwalled carbon nanotubes and carbon nanofibers. A study of biomarkers for early pulmonary, cardiovascular, and carcinogenic effect will be carried out among workers at these facilities.
Mortality, cancer incidence, and biomarker studies Study Scientist: Ruder	To elucidate exposure-outcome associations, especially dose-response relationships, for risk assessment and to examine relationships between biomarkers of exposure, susceptibility, and oncogene expression and determine health effects.

Environmental Monitoring

Project & Study Scientist	Project Summary
Analytical research and development infrastructure Study Scientist: Streicher	To provide for 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. Development, evaluation, validation, and use of methods for chemicals such as bisphenol A (BPA), manganese speciation, and flame retardants are part of the NIOSH/NTP exposure assessment interagency agreement. In FY 2015, a method developed for BPA was used to analyze field samples. The manganese speciation method used to evaluate field samples has undergone review for formal

inclusion in the NIOSH Manual of Analytical Methods. Additionally, sampling and analysis methods for flame retardants were investigated in support of field surveys.

Diacetyl exposure assessment

Study Scientist: Streicher

To develop and evaluate sampling and analytical methods for diacetyl and other higher molecular weight alpha dicarbonyl flavoring compounds and 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. One method measures alpha dicarbonyl compounds present as vapor and the other measures these compounds in airborne particles and bulk powders.

Nanoaerosol monitoring methods

Study Scientist: Birch

To develop and apply measurement methods for hazardous aerosols. Globally, exposure to hazardous aerosols remains a serious health concern, with growing attention on fine, ultrafine, and nanomaterial aerosols. New nanomaterials are being developed and used in multiple commercial products, but there is relatively little knowledge regarding their health and environmental impacts. Because the properties most responsible for nanoaerosol toxicity are unclear, and exposures are often to complex mixtures, multiple analytical tools are being applied. This research is providing critical exposure data and information on the widely differing physical and chemical properties of nanoscale aerosols and materials. These properties may have influence on particle toxicity. These methods have general application to exposure monitoring and control studies. In FY 2015, 15 bulk carbon nanomaterials were analyzed including endotoxins, specific surface area, and Raman analyses. Metal contents were determined by inductively coupled plasma atomic emission spectroscopy (ICP-AES) after microwave digestion in concentrated nitric acid. In addition, all materials were analyzed by thermogravimetric analysis, which gives the onset of oxidation, a measure related to stability, and residual ash content, a measure of purity. High iron content was found

	in most of the samples, and the residual ash contents of the materials ranged from about 1-10%. In FY 2016, polycyclic aromatic hydrocarbons (PAH) and transmission electron microscopy (TEM) analyses will be completed.

Exposure Assessment

Project & Study Scientist	Project Summary
Exposure assessment for toxicologically important chemicals Study Scientist: Curwin	To characterize workplace exposures to chemicals of toxicological concern as identified by NTP and NIOSH. Current studies include (1) welding fumes with emphasis on manganese, (2) occupational exposure to bisphenol A (BPA), (3) occupational exposure to carbon nanotubes and nanofibers, (4) flame retardants, and (5) polycyclic aromatic hydrocarbons (PAH's) in coal tar sealants. Goals of these studies include identifying industries, workplaces, uses, and users; determining occupational health relevance; estimating number of workers exposed; and conducting exposure sampling.
Industry-Wide Studies Branch research, development, and planning Study Scientist: Whelan	To support strategic planning and feasibility studies of high priority and emerging problems in occupational health.
Nanotechnology field evaluations Study Scientist: Geraci	To obtain information from as many different facilities in the field as possible, regarding the nature of engineered nanomaterials, the processes involved in their manufacture and use, potential worker exposures, and work practices and control procedures where nanomaterials are produced or used. As toxicology studies identify the biologic hazards of nanomaterials, it is important to gain a better understanding of actual workplace exposures.
Dermal permeation of benzene from gasoline and crude oil: current and historical issues Study Scientist: Frasch	To generate and interpret data on the dermal absorption potential of benzene from gasoline. Specifically, (1) to quantify benzene in a sample of gasoline to be used for dermal absorption rate testing. (2) To quantify the dermal absorption rate of benzene in gasoline. Both steady state fluxes from "infinite" dose application, and non-steady state absorption profiles from finite dose applications will

	be determined. (3) To repeat dermal absorption rates using gasoline fortified with benzene to mimic historically high levels, and undiluted or neat benzene. (4) To measure the thermodynamic activity of benzene in gasoline. This research will be used in the dermal risk assessment of current and historical benzene exposures.

Immunotoxicity and Immunology

Project & Study Scientist	Project Summary
Immunotoxicological evaluation of occupational chemicals Study Scientist: Anderson	To identify occupational and environmental chemical hazards and evaluate immune function and mechanisms associated with exposure. This research will contribute to better risk assessment and increased identification of immunological hazards encountered in the workplace, which will ultimately establish occupational exposure limits.
Identification of occupational allergens Study Scientist: Noti	(1) 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. (2) To develop improved techniques for the detection of such immune reactions before adverse clinical outcomes occur. (3) To develop improved techniques for the detection and identification of inciting occupational agents. This 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.
Characterization of in vivo protein haptenation following exposure to aerosolized 4,4'-methylene diphenyl diisocyanate Study Scientist: Hettick	To determine the molecular targets of inhaled diisocyanate particulates and better understand the pathogenic mechanism of isocyanate-induced allergic disease. The project will enhance the overall understanding of the fate of diisocyanate in vivo following occupational exposure by increasing our understanding of disease and identifying potential biomarkers of exposure.

Exosomes as biomarkers and immune modulators of diisocyanate asthma Study Scientist: Hettick	To define mechanisms underlying methylene diphenyldiisocyantate (MDI) associated occupational asthma (OA) by identifying biomarkers of MDI exposure and immune regulatory factors that influence the progression and severity of MDI-OA. Exposure to MDI, which is used in the manufacturing of glues and polyurethanes, results in OA in approximately 5-15% of workers. Currently, sensitive and reliable markers for MDI exposure and sensitization do not exist, partially due to the lack of specificity of markers commonly associated with asthma. Furthermore, the factors influencing susceptibility and severity of MDI-OA have not been elucidated. This project will identify response and legacy biomarkers found in exosomes secreted into the bloodstream that would indicate isocyanate exposure and sensitization. Attempts will be made to distinguish chemical induced biomarkers from high molecular weight allergen induced markers, and determine how exosome genetic content can influence asthma progression. The biomarkers identified in this study can be incorporated into a human exposome database and used in future studies to distinguish MDI-OA from general environmental asthmas.

Genetics

Project & Study Scientist	Project Summary
Immunotoxicity of subchronic fungal exposures Study Scientist: Nayak	To determine the pulmonary immunopathological outcomes of subchronic exposures to fungal spores in mice. The study will focus on fungal species of interest to NTP and determine the health effects associated with their long-term exposures. This research will aim to identify and characterize the underlying immunological mechanisms of allergic fungal diseases in lungs. We have completed subchronic exposure studies with *Aspegillurs fumigatus*. Two manuscripts are in preparation to disseminate the findings. Subchronic exposures of mice to *Stachybotrys chartarum* will conclude in November 2015. Proposed studies will help to identify biomarkers and specific targets for diagnostics, prevention, and

	therapeutic intervention of occupational-related pulmonary fungal diseases.
Immunomodulatory effects of triclosan on effector CD4 T cell development Study Scientist: Marshall	To identify the cellular and molecular mechanisms behind the immune-modulating effects of the antibacterial chemical triclosan. This information will provide the basis for evaluating other nonsensitizing antimicrobial chemicals and help identify potentially conserved mechanisms that contribute to allergic disease. This will help determine the need for evaluating these types of workplace chemicals, leading to better risk assessment and establishment of occupational exposure limits.
Highly sensitive and practical biomarkers for nanotoxicity Study Scientist: Joseph	To develop, validate, and test, in a rat model, highly sensitive and minimally invasive biomarkers for early detection of pulmonary toxicity potentially associated with exposure to toxic nanomaterials. Techniques will be employed to develop transcriptomic signatures in blood as surrogate biomarkers for the pulmonary toxicity induced by inhalation exposure to specific nanomaterials. Bioinformatic analysis of the global transcriptomics data will be conducted to gain insights into the molecular mechanisms underlying the pulmonary toxicity of nanomaterials. Determining the molecular mechanisms of pulmonary toxicity and developing highly sensitive and minimally invasive biomarkers for nanotoxicity have implications in monitoring workers for their risk of developing adverse health effects potentially associated with exposure to toxic nanomaterials.
Toxicological investigations of nitrogen-doped multiwalled carbon nanotubes Study Scientist: Porter	To examine the potential effect of altering the chemical composition of multiwalled carbon nanotubes on their bioactivity in vivo. Knowledge of doping modification may allow for the development and use of less bioactive multiwalled carbon nanotubes, which may reduce the hazard from workplace exposures. In the future, such information may allow material scientists to incorporate a prevention-through-design philosophy into the development of new nanoparticle-based technologies, using nanomaterials that pose lower risks to human health. These data will also contribute to NIOSH’s effort

to develop and implement an evidence-based strategy for recommending occupational exposure limits (OELs) or occupational exposure bands (OEBs) for carbon nanotubes. These studies will support these efforts by comparing two multiwalled carbon nanotubes with different chemical composition, such as multiwalled carbon nanotubes and nitrogen-doped multiwalled carbon nanotubes. These studies should increase our understanding of the toxicological mechanisms responsible for multiwalled carbon nanotube-induced pathologies, and may also identify extra-pulmonary sites of toxicity resulting from systemic transport of multiwalled carbon nanotubes after pulmonary exposure.

Toxicological evaluation of pulmonary exposure to graphenes

Study Scientist: Roberts

(1) To characterize the pulmonary, cardiovascular, and neurological toxicity that may be associated with respiratory exposure to graphenes, using an in vivo, tiered toxicity testing approach that incorporates a dose-response, time-course model with aspiration of nanomaterials as the route of exposure. This will be followed by an inhalation study with a specific particle and dose identified in the first tier of studies. (2) To determine potential mechanisms of pathology, when applicable, and address whether respiratory exposure to graphene nanomaterials, which differ in size and oxidative form, pose a risk for work-related illness. This project is from the Nanotechnology Research Center at NIOSH.

Neurological risks associated with workplace chemicals and nanomaterials

Study Scientist: Sriram

To evaluate potential neurotoxicological effects associated with exposure to chemical agents, incidental nanoparticles, and engineered nanomaterials in a laboratory-based animal model. This includes neurological hazard identification and risk characterization, evaluating molecular mechanisms of neurotoxicity, and identifying potential biomarkers of neurotoxicity. This project will attempt to identify brain electroencephalographic changes by telemetry and determine correlations with early stages of neuronal injury in an effort to establish real-time biomonitoring programs. Findings from this study may contribute toward

developing (1) novel biomarkers for monitoring exposures, including real-time biomonitoring technologies; (2) prejob planning protocols, and hazard and risk assessment paradigms; and (3) occupational safety standards for neurotoxic exposures to chemical agents, incidental nanoparticles, and engineered nanomaterials.

Mechanism of carbon nanotube (CNT)-induced carcinogenesis and aneuploidy

Study Scientist: Sargent

In vitro exposure of human cells to 1-4 nanometer diameter single-walled carbon nanotubes (SWCNT) disrupts the mitotic apparatus resulting in errors of chromosome number. Data comparison with 10-20 nanometer diameter multiwalled carbon nanotubes (MWCNT) suggests that the diameter of the nanotube is important in the genotoxic response, and that CNTs are potentially carcinogenic. Utilizing a two-stage initiation and promotion mouse model, inhaled MWCNTs demonstrated that they are strong promoters of lung adenocarcinoma. Currently, we are conducting studies to (1) examine the dose response of CNT-induced tumor promotion and (2) further examine the role of CNT physical properties and diameter in the genotoxic effect. Human cells are being exposed to well-characterized 49 nanometer native Mitsui-7 MWCNT, heat-treated Mitsui-7 MWCNT, and nitrogen-doped MWCNT. Data suggest that all carbon nanotubes induce predominately monopolar mitosis and cause disruption of the cell cycle, errors in chromosome number, centrosome fragmentation, and fragmentation of the chromosome center or centromere, with Mitsui-7 MWCNT being the most cytotoxic. These data suggest that nanotube diameter is the driving force in genotoxicity. Preliminary data from our ongoing dose-response study of tumor promotion indicate a dose-related, increased incidence of lung tumors and tumor number per mouse.

Epigenetic changes in response to nanoparticle exposure

Study Scientist: Ding

To investigate potential pulmonary carcinogenesis in response to tungsten carbide-cobalt (WC-Co) particle exposure using cell culture and animal models. Occupational exposure to hard metal dust is associated with an increased risk of lung cancer. Tungsten heavy

alloys are used broadly for radiation shielding in both medical equipment and oil well drilling industries, weights and counterbalances, boring bars and grinding quills, and tooling for die cast manufacturing. Nanograined WC-Co composites are exceptional surfacing materials used for hard coatings, decarburization, and metal spraying. Exposure to WC-Co has been shown to cause pulmonary disease and induce lung cancer. Our previous studies indicate that WC-Co nanoparticles generate more reactive oxygen species (ROS) than fine particles when incubated with cells. Both fine and nanoparticles of WC-Co stimulate ROS generation and MAPKs AP-1 cascade. The underlining mechanisms of WC-Co-induced carcinogenesis have not been investigated. Mechanistic investigations, including gene mutation, activation of transcription factors, and ROS generation, will be conducted to explain the events of WC-Co-induced tumor initiation, promotion, and progression. Determining the mechanisms involved in WC-Co-induced carcinogenesis and elucidating target-signaling pathways could provide insights for the development of biomarkers and possible prevention strategies for WC-Co-induced diseases.

Assessment of specific carbon nanotube-induced lung carcinogenesis

Study Scientist: Rojanasakul

Carbon nanotubes (CNTs) exhibit a fibrous morphology and biopersistence similar to asbestos, a known human carcinogen. Pulmonary exposure to CNTs results in disposition into alveolar and pleural areas, raising a major concern about human lung cancer and mesothelioma risks associated with long-term CNT exposure. The objective of this project is to test the hypothesis that pulmonary exposure to CNTs targets susceptible lung cells, such as epithelial and mesothelial cells, and induces neoplastic transformation of the cells, leading to carcinogenesis. This project addresses several critical needs and challenges associated with the poorly known cancer hazard potential of nanomaterial exposure. The specific aims are to (1) develop in vitro chronic exposure models, evaluate the carcinogenic potential of CNTs and determine the effects of dose, exposure time, and physicochemical properties of CNTs on their

carcinogenicity; (2) assess the tumorigenic potential of CNT-transformed cells in vivo; and (3) identify molecular signatures and gene targets of CNT-induced cell transformation as potential biomarkers, to predict CNT-induced lung cancer and mesothelioma. This project is from the Nanotechnology Research Center at NIOSH.

Fracking: toxicological effects of silica and diesel exhaust exposure

Study Scientist: Fedan

The toxicities of inhaled fracking sand dust, alone and in combination with inhaled diesel exhaust that mimic worker exposures during fracking operations, are being studied. Effects on several organ systems are being investigated using a battery of in vivo and in vitro animal model tests. The first round of exposures to fracking sand dust, using two exposure doses, is nearly finished. Effects of exposure on the lung, cardiovascular system, immune systems, brain, skin, and blood have been examined. The second round of exposures will be to diesel exhaust, and organ effects will be investigated. A tier-2 diesel engine has been procured and is being fitted to the animal quarters for animal exposures. These exposures will commence in FY 2016.

Pulmonary function and nanoparticle inhalation: in vivo and in vitro effects

Study Scientist: Fedan

To characterize multiwalled carbon nanotube (MWCNT) effects on critical aspects of lung function in vivo and airway function in vitro, and provide metrics to enable risk assessment strategies. In vivo experiments have demonstrated changes in pulmonary function in animals exposed to MWCNTs.

Health effects of inhaled crude oil

Study Scientist: Fedan

To design and build an inhalation exposure system that delivers crude oil vapor to rats. This system will be used to study the effects of crude oil vapor inhalation on the lung, cardiovascular system, immune system, brain, skin, and blood. Surrogate oil from the Gulf of Mexico, and oil from the Macondo well, has been obtained. The exposure system for delivering oil vapor to rats is completed and awaits calibration gases before the exposures can begin.

NTP at NIOSH: Occupationally-Relevant Exposures

Comprehensive Assessment of Occupationally-Relevant Exposures

NIEHS is coordinating an NTP effort with NIOSH to better understand worker exposures, identify occupational health research gaps, and educate workers. The NIEHS and NIOSH interagency agreement supports these projects. FY 2015 efforts listed in the table below address worker exposures to welding fumes, nanosized materials, food flavorings, bisphenol A, indium compounds, and other industrial chemicals.

NIOSH mobile lab for field studies

Related NIOSH Research:

Assessing Exposure to Substances in the Workplace

Immunotoxicology Research

The table below lists NIEHS and NIOSH Interagency Agreement Projects on Occupationally Relevant Exposures in FY 2015.

View Research Areas in

Occupationally Relevant Exposures

Show All

Search Projects

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Occupationally Relevant Exposures

Project & Study Scientist	Project Summary
Administrative support Study Scientist: 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, North Carolina, and Washington, D.C.
Occupational exposure assessment of welding fume with emphasis on manganese compounds Study Scientist: Hanley	(1) To identify industries, such as construction, shipbuilding, railroad, manufacturing companies, and unions involved in welding operations for exposure assessments where the potential for substantial manganese exposure exists; (2) develop methods to identify manganese compounds and different valence states, based on selective solubility with various welding fumes matrices; and (3) characterize welding fume exposures based on welding-associated jobs, tasks, and processes.
Exposure assessment of engineered nanoparticles Study Scientist: Geraci	(1) To identify workplaces engaged in the synthesis, manufacture, and use of engineered nanomaterials; and (2) characterize workplace exposure to selected engineered nanoparticles.
Durability of nanoscale cellulose fibers in artificial human lung fluids Study Scientist: 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.
Occupational exposure to bisphenol A (BPA) in the U.S. Study Scientist: Hines	(1) To understand bisphenol A (BPA) use in industry, including processes, jobs, and tasks with potential BPA exposure; (2) develop air, hand wipe, and surface wipe sampling, and analytical methods for BPA, using liquid chromatography-tandem mass spectrometry and liquid chromatography with ultraviolet detection; and (3) assess exposure to BPA among workers through air, hand wipe, and urine sample collection.
Industry-wide exposure assessment study of workers exposed to carbon nanotubes and	(1) To establish sampling and analysis protocols for detection and quantification of carbon nanotubes and

nanofibers Study Scientist: Dahm	nanofibers; (2) recruit companies and conduct exposure assessments for carbon nanotubes and nanofibers in a representative sample of U.S. 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 (5) evaluate higher-flow, respirable cyclones to assess health-relevant exposures.
Assessment of occupational exposures to flame retardants. Study Scientist: Estill	To assess exposure to nine alternative flame retardants plus a panel of polybrominated diphenyl ethers (PBDEs). Exposure will be assessed among workers involved in the manufacture, installation, or use of goods containing these nine alternative flame retardants. Worksite categories included in the study are manufacture of products that use flexible polyurethane foams, plastics, or resins; fabrication and manufacture of rigid polystyrene foam; cutting, installing, or spraying polyurethane foam insulation at construction sites; using gymnasiums; manufacture of wire harnesses or printed circuit boards; and the fire service industry. This study will compare exposures among industries, processes, and tasks; determine the route of exposure; and make recommendations to reduce exposures. These data will be used to determine exposure levels of workers in different occupations and how they relate to the general population by comparison to the National Health and Nutrition Examination Survey (NHANES) data. The results will aid in the design of toxicological studies, understanding and use of toxicological studies, and risk assessment.
Assessment of occupational exposure to polycyclic aromatic hydrocarbons (PAHs) in coal tar sealant applications Study Scientist: Fleming	To evaluate the levels of occupational chemical exposure among workers who are using coal tar-based pavement sealants. Coal tar is sometimes used as a base material for blacktop pavement sealants, accounting for as much as 35% of the formulation in some of these products. Coal tar is a byproduct of the production of coke, which is needed for steel production. Coal tar pitch volatiles are a

mixture of chemicals that can evaporate into air from products containing coal tar, including coal tar pavement sealants. These coal tar pitch volatiles contain several chemicals known as polycyclic aromatic hydrocarbons (PAHs). The focus of this study is the assessment of occupational exposure to PAHs among coal tar sealant workers. This study will provide data regarding levels of exposure to airborne chemicals that will be compared to current NIOSH recommended exposure limits (RELs) for coal tar pitch volatiles, and will report results for specific PAH chemicals using NIOSH analytical methods. PAHs will be measured in dermal wipe samples, and PAH metabolites will be measured in biological samples collected from workers to characterize levels present in this workforce.

NTP at NIOSH: Immunotoxicology Research

Interagency Agreement on Immunotoxicology Research

The NIEHS and 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 the table below, evaluate unique cohorts of individuals from professions associated with immune-mediated occupational diseases.

Related NIOSH Research:
Assessing Exposure to Substances in the Workplace
Comprehensive Assessment of Occupationally-Relevant Exposures

The table below lists NIEHS and NIOSH Interagency Agreement on Immunotoxicology Studies in FY 2015.

View Research Areas in

Immunotoxicology Studies

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Immunotoxicology Studies

Project & Study Scientist	Project Summary
Identification and characterization of cross-reactive fungal biomarkers	To develop species-specific monoclonal antibodies to recombinant fungal biomarker antigens. The utility of

Study Scientist: Green	these antibodies will be important for the quantification of fungal biomarkers, particularly to those fungi that are being studied by NTP. In this project, *Aspergillus terreus* was initially used as a model fungal organism for the development of fungal-specific proteins using recombinant technologies. *Aspergillus terreus* hemolysin was produced by recombinant technology, and a panel of species-specific monoclonal antibodies was also produced. The same recombinant technologies were used to identify and characterize additional candidate fungal allergens. Recombinant *Chaetomium globosum* enolase (rec-CgEnol) has been cloned, expressed, purified, and confirmed using mass spectrometry. Three rec-CgEnol specific immunoglobulin G1 (IgG1) monoclonal antibodies have been produced and characterized. Several manuscripts have been published that report these findings. The development of a sensitive immunoassay that can be used in the serological detection of this biomarker is anticipated.
Toxicity of subchronic fungal exposures Study Scientist: Green	To characterize the toxicological and pulmonary immune responses associated with subchronic fungal exposures using a model that replicates human exposure. This model utilizes an acoustical generator system, and nose-only exposure chamber to characterize toxicological endpoints following subchronic dry fungal spore and particle exposures. Following completion of a related study in FY 2014, a secondary aim of this project is to characterize subchronic toxicity and pulmonary immune responses to fungal contaminants nominated to the NTP, including *Stachybotrys chartarum* both mycotoxin producing and nonproducing chemotypes, *Aspergillus versicolor*, and *Alternaria alternata*. In FY 2015, protocols were submitted to NTP for the evaluation of *Aspergillus versicolor* and a mycotoxin producing chemotype of *Stachybotrys chartarum*. *Alternaria alternata*, mixed fungal exposures, and other occupationally relevant fungi identified in concurrent NTP funded diversity studies will be evaluated in future fiscal years. These toxicological studies will provide novel datasets that will be used to

characterize the hazards that fungal exposure may represent to human health.

Identification and characterization of fungal exposures

Study Scientist: Green

To investigate and characterize the diversity of fungal bioaerosols in the indoor and occupational environments, using large-scale ribosomal RNA sequencing. In collaboration with Assured Bio Labs LLC, Columbia University, and NIOSH in FY 2015, our laboratory has evaluated indoor and occupational environments, using large-scale ribosomal RNA approaches from samples collected in contaminated and noncontaminated environments. In addition, fungal species identified in this analysis will be directly compared to commercially available methods of fungal analysis, including the Environmental Relative Mold Index.

Analysis of mycotoxins in dust samples from a water-damaged building

Study Scientist: Park

To examine potential roles of exposure to fungal toxins on occupants' health in water-damaged buildings. We plan to (1) develop a cost-effective and robust method, using an ultra-performance liquid chromatography-tandem mass spectrometry, for simultaneous analysis of multiple fungal toxins in environmental samples; (2) increase accuracy of the method by using isotopically labeled (C13) mycotoxin internal standards to compensate for extraction loss and matrix effects; (3) apply the method to examine stability of mycotoxins in floor dust stored in different temperature conditions for different lengths of time; and (4) quantify fungal toxins in floor dust samples that have been collected from a funded school study in FY 2015 and previous studies of water-damaged buildings. These studies also have other types of exposure data, including fungal biomass, bacterial biomass, and occupants' health, which can be adjusted for in statistical models to examine the effect of exposure to fungal toxins on occupants' health.

NTP at NCTR

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.

NCTR/NTP Staff

Related NCTR Research:

NCTR Interagency Agreement Projects List

These NCTR studies, funded by NCTR voluntary allocations, are listed in the table below.

View Research Areas in

Biochemical and Molecular Basis of Toxicology
Neurotoxicology
Nanotoxicology
Bioassay and Biomarker Development and Evaluation

Show All

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Biochemical and Molecular Basis of Toxicology

Project & Study Scientist	Project Summary
Physiologically based pharmacokinetic (PBPK) models for bisphenol A (BPA) Study Scientist: Fisher	(1) To create physiologically based pharmacokinetic (PBPK) models for bisphenol A (BPA) in mouse, rat, and rhesus monkey for multiple life stages: adult; neonate; pregnant, including both mother and fetus; and lactating, both mother and neonate. These PBPK models will be used to calculate internal measures of dose for both aglycone (i.e., active) and conjugated (i.e., inactive) forms of BPA. (2) Human PBPK models for BPA (adult, neonate, pregnant mother and fetus, and lactating mother and infant) will be created using information obtained from the monkey, mouse, and rat, and limited information from humans published in the literature. The human suite of PBPK models will be used to extrapolate the internal doses of BPA associated with toxicity in laboratory animals to humans, and to extrapolate dosimetry from regions of observation to low levels of exposure to BPA for which no experimental data exist. This simulation protocol will help reduce the uncertainty in the assessment of health risks posed by BPA to human populations.
An evaluation of the effect of vehicle cream on the photococarcinogenicity of retinyl palmitate in SKH-1 mice Study Scientist: Boudreau	(1) To determine the stability and homogeneity of retinyl palmitate in control cream. In the previous photococarcinogenicity study of retinyl palmitate, diisopropyl adipate was used as a carrier and filler for the retinoids. The stability and homogeneity of retinyl palmitate has not been determined for a base cream that does not contain diisopropyl adipate. (2) To evaluate the photococarcinogenicity of retinyl palmitate when incorporated into the control cream and applied to the skin of SKH-1 mice in the absence and presence of simulated solar light. (3) To determine the photococarcinogenicity of diisopropyl adipate as the filler ingredient in the control cream, in the absence and presence of simulated solar light. In the previous study on

retinoic acid and retinyl palmitate, the control cream induced skin tumors even in the absence of simulated solar light. The suspect ingredient in the control cream was diisopropyl adipate. Diisopropyl adipate appears as an ingredient in numerous topically applied skin products, including sunscreens.

Biologically based dose-response modeling for the thyroid axis in the fetus and neonate

Study Scientist: Fisher

(1) To create biologically based dose-response models for the hypothalamic-pituitary-thyroid axis in the developing rat and human as a function of iodide status; (2) interface the models with physiologically-based pharmacokinetic (PBPK) or toxicokinetic models for thyroid active chemicals to predicted conditions, such as iodide status and chemical exposure, for which brain thyroid hormone homeostasis cannot be maintained in the fetus and neonate; and (3) 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.

Relationship between liver epigenetic phenotype and susceptibility to nonalcoholic steatohepatitis-induced (NASH) hepatocarcinogenesis in mice

Study Scientist: Pogribny

(1) To determine the role of epigenetic dysregulation in the etiology and pathogenesis of dietary nonalcoholic steatohepatitis (NASH)-induced hepatocarcinogenesis in mice; (2) determine whether or not interstrain-specific susceptibility of mice to NASH-induced hepatocarcinogenesis is associated with differences in individual hepatic epigenetic phenotypes; (3) determine the role of epigenetic dysregulation in the etiology and pathogenesis of NASH-induced hepatocarcinogenesis in mice induced by tamoxifen administration; and (4) determine whether or not aberrant epigenetic markers can be used as targets for prevention of NASH-induced hepatocarcinogenesis in mice.

Sex differences in drug-induced QT prolongation and torsade de pointes: establishing an in vitro model for high throughput screening and risk assessment of torsadogenic drugs

Study Scientist: Pang

(1) To establish a model and positive control; and (2) evaluate the sensitivity and specificity of the model, and test the possibility of high throughput screening and ranking of QT-prolonging drugs for the risk of torsade de pointes.

	Mechanism of tumorigenic pyrrolizidine alkaloids and development of liquid chromatography-electrospray ionization/multistage mass spectrometry (LC-ES/MS/MS) methodology for detection and quantification of pyrrolizidine alkaloids Study Scientist: Fu
	(1) To validate the proposed mechanism by which pyrrolizidine alkaloids induce tumors in rodents; (2) develop an LC-ES/MS/MS method for detection and quantification of dehaloperoxidase-derived DNA adducts in rodents; (3) develop an LC-ES/MS/MS method for detection and quantification of genotoxic pyrrolizidine alkaloids in herbal plants and herbal dietary supplements; and (4) develop an LC-ES/MS/MS method for detection and quantification of dehaloperoxidase-derived hemoglobin adducts in rodents.
Epigenetics, DNA methylation, and obesity Study Scientist: Varma	To evaluate the effect of differences in DNA methylation and agouti signaling protein in the offspring of Avy/a dams crossed with a/a sires as a result of nutrient x gene interactions. These preliminary data will be used to select the appropriate diets for further studies on obesity and Type 2 diabetes.
Dose-response genotoxicity of ethylmethane sulfonate in mice using the phosphatidylinositol glycan complementation group A (Pig-a) and transgenic gpt delta assays Study Scientist: Cao	(1) To use sensitive genotoxicity endpoints with low background frequencies to increase the sensitivity of the assays for detecting low-dose effects; (2) measure genotoxicity using a design to detect the maximum responses; (3) measure the effects of ethylmethane sulfonate exposure in neonatal as well as adult animals; and (4) measure genotoxicity in the major target tissues for ethylmethane sulfonate carcinogenicity.
Development of a method to use in vivo mutagenicity data to address whether a specific chemical induces cancer via a mutagenic or a nonmutagenic mode of action (MOA) Study Scientist: Heflich	To develop, evaluate, and disseminate a new method that utilizes in vivo mutagenicity and other key event data to address whether a chemical induces cancer via a mutagenic or a nonmutagenic mode of action (MOA).

	Study of drug-induced liver toxicity using state-of-the-art in vitro liver models including primary rat and mouse hepatocytes and stem cells Study Scientist: Guo
	To use primary hepatocytes from male and female mice and rats, to determine signature gene and proteomic expression changes and patterns in response to toxic compound-induced changes in cell homeostasis.
Development of predictive mitochondrial biomarkers for drug-induced cardiotoxicity using a systems biology approach Study Scientist: Desai	To determine the response to doxorubicin-induced cardiotoxicity in mice including (1) kinetics of toxicity using plasma troponin-T, creatinine kinase MB, and cardiolipin; (2) morphological damage and changes in the left ventricle using electron microscopy; (3) the effects of doxorubicin on mitochondrial gene expression in heart tissue using MitoChip, 2-D high-performance liquid chromatography-tandem mass spectrometry (HPLC/MS/MS) and endogenous metabolites using nuclear magnetic resonance (NMR) and mass spectrometry (MS); (4) to measure plasma biomarkers using MitoChip to measure creatinine, creatine, lactate, Krebs cycle intermediates, and small ketones using metabolomics; and (5) to evaluate the most predictive biomarkers of doxorubicin cardiotoxicity.
Human biomonitoring for bisphenol A (BPA) Study Scientist: Doerge	(1) To develop and implement sensitive and selective analytical methodology to measure bisphenol A (BPA) in the blood and urine from humans; and (2) to integrate animal exposure data and human biomonitoring data into a physiologically-based pharmacokinetic model for BPA.
Role of peroxisome proliferator-activated receptor alpha (PPARa) and PPARa-mediated species differences in triclosan-induced liver toxicity Study Scientist: Wu	To examine the role of human and mouse peroxisome proliferator-activated receptor alpha (PPARa) in triclosan-induced liver toxicity in vivo.

Neurotoxicology

Project & Study Scientist	Project Summary

The use of computed tomography (CT) combined with positron emission tomography (microPET) to evaluate the neurotoxicity associated with pediatric exposures to the anesthetics sevoflurane and propofol Study Scientist: Wang	(1) To use computed tomography (CT) and positron emission tomography (microPET) to study neurotoxicity in vivo associated with the pediatric use of gaseous anesthetics sevoflurane and propofol; (2) develop procedures to localize in vivo specific brain areas and structures to evaluate their response to test compounds; (3) determine the utility of fluorine-18-labeled PET compounds to identify stem cells and apoptotic cells in brain in vivo; and (4) determine cytotoxicity of compounds, including gaseous anesthetics, using embryonic neural stem cells in vitro.
Assessment of gaseous anesthetics in the developing nonhuman primate Study Scientist: Wang	(1) To determine the dose-response effects of individual or combined gaseous anesthetics nitrous oxide and isoflurane on neuronal cell death in the developing nonhuman primate, using magnetic resonance imaging (MRI) and positron emission tomography (MicroPET); (2) determine the effect of dose and duration of gaseous anesthetics on nonhuman primate long-term behavior and pathology, using MRI and MicroPET; and (3) evaluate antioxidants in the amelioration of toxicity of gaseous anesthetics.
Developmental neurotoxicity assessment of N-methyl-D-aspartate (NMDA) receptor antagonists in zebrafish Study Scientist: Kanungo	(1) To study wildtype zebrafish embryos exposed to NMDA receptor antagonists (MK-801, dextromethorphan, ketamine and sevoflurane), in order to assess their effects on Rohon-Beard sensory neurons. The effects on the primary and secondary motor neurons and their axons will also be assessed using hb9:GFP transgenic embryos. Postexposure washout experiments will be pursed to determine the effects of these drugs on the nervous system. (2) Certain NMDA receptor antagonists, such as ketamine, are known to modulate hormone levels in mammals and zebrafish. Based on the importance of the neuroprotective nature of neurosteroids, the study will determine estradiol-17’ levels in control and treated embryos. Changes in gene expression for the two CYP aromatases/estrogen synthases (brain aromatase cyp19a1b and gonadal aromatase cyp19a1a) will be quantified using quantitative polymerase chain reaction

	(qPCR). (3) Phenotype-based cell signaling mechanisms, such as MAPK and neuron development-specific gene expression, will be assessed. (4) Reversal of noted adverse effects of these compounds on neurons will be attempted, particularly by treatment with acetyl L-carnitine.

Nanotoxicology

Project & Study Scientist	Project Summary
Does the durable nanoparticle bioaccumulation in macrophages increase susceptibility to bacterial infection? Study Scientist: Khan	To determine whether animals exposed to durable nanoparticles are more susceptible to *Listeria* infection, as measured by the severity of disease and the length of time needed to clear the infection.
Evaluation of the applicability of in vivo micronucleus assays for assessing genotoxicity of engineered nanomaterials Study Scientist: 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 FDA, *Salmonella* Ames test, mouse lymphoma assay, and in vivo mouse micronucleus assay; and (2) evaluate the possible mechanisms of nanomaterial-induced genotoxicity using a transgenic mutation system, comet assay, and genomic analysis.
Proteomic assessment of the cytotoxic effects of nanoparticles on the blood-brain barrier Study Scientist: Gu	To use proteomics approaches to quantify alterations in expression and phosphorylation of proteins involved in apoptosis, inflammation, oxidative stress, and tumorigenesis signaling pathways in blood-brain barrier cells following exposure to nanoparticles. The long-term goal is to establish proteomic parameters for toxicity of nanoparticles.
Assessment of iron oxide nanoparticle-induced neurotoxicity in cell cultures and whole animal models	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

Study Scientist: Binienda	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 and rat brains using in vivo microdialysis; (3) alterations in the brain free fatty acid levels; (4) alterations in lipid peroxidation or changes in antioxidant enzyme activity (catalase, superoxide dismutase, or glutathione peroxidase) and glutathione levels in mice and rat brains; and (5) selective patterns of deposition and damage in different regions of rat and mice brain, using in vivo magnetic resonance imaging.
Complement assays for the detection of immune-sensitizing activity of nanomaterials Study Scientist: Leakey	(1) To establish two complement assays for routine evaluation of immune-sensitizing activity of nanomaterials; (2) validate the assays using nanoparticles with known immunoreactivity; and (3) determine the immune-sensitizing activity of novel nanomaterials.
Physiologically based pharmacokinetic (PBPK) modeling of nanomedicine; building clinically relevant standards for FDA-regulated nanoparticulate drug products Study Scientist: Leakey	(1) To determine in vivo liposomal doxorubicin release kinetics in individual tissues and blood stream by physiologically based pharmacokinetic (PBPK) modeling; (2) establish quantitative physicochemical property (liposomal size and content of ammonium sulfate) biodistribution relationships of liposomal doxorubicin products by PBPK modeling; and (3) extrapolate the PBPK model to rats and humans. A whole-body PBPK model will be developed to describe and simulate the biodistribution of liposomal vesicles and doxorubicin.
Development and evaluation of exposure dosimetry methods to optimize the standard in vitro mammalian genotoxicity assays for assessing engineered nanomaterials Study Scientist: Chen	(1) To evaluate whether the in vitro mammalian genotoxicity assay is suitable for assessing the genotoxicity of nanomaterials; (2) explore the possible mechanisms underlying genotoxicity of engineered nanomaterials by conducting genomic analysis; (3) identify potential improvements to the assay and general strategies for evaluating nanomaterials; and (4) 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 in vivo micronucleus assay.
Assessment of size- and shape- dependent toxicity of silver nanoparticles as measured by changes in the permeability at the gastrointestinal surface Study Scientist: Khare	(1) 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 determining the effect of nanomaterials on the permeability of intestinal epithelial cells in vitro and ileal mucosa ex vivo; and (2) measure 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.
In vitro genotoxicity of graphene family nanomaterials using FDA recommended short-term genetic toxicity test battery Study Scientist: Mei	To determine (1) the genotoxicity of graphene and derivatives in standard regulatory test battery assays; (2) if any mutagenicity in mouse lymphoma cells is due to loss of heterozygosity in chromosome 11; (3) if genotoxic and mutagenic response is mediated through oxidative pathways; and (4) genotoxic and mutagenic mode of action using gene expression arrays.
Graphene induced toxicity on the population of intestinal microbiota and gut-associated immune response Study Scientist: Khare	To evaluate the effects of graphene on gastrointestinal homeostasis by determining graphene derivative effects on intestinal bacterial cultures, polarized intestinal epithelial cells, intestinal commensal bacteria in vivo, and gastrointestinal immune responses in vivo.
NCTR/Office of Regulatory Affairs (ORA) Nanotechnology Core Facility Study Scientist: Patri	The goals of the Nanotechnology Core Facility are to 1) provide the expertise and equipment for characterization of nanomaterials used in toxicology studies, (2) provide the expertise and equipment to detect nanomaterials in in vitro and in vivo derived samples, and (3) serve as a resource for U.S. agencies for the design of toxicology studies and generation of standards for analytical methods.

Bioassay and Biomarker Development and Evaluation

Project & Study Scientist	Project Summary
Biomarkers of liver toxicity Study Scientist: Mendrick	(1) To discover biomarkers of hepatotoxicity in preclinical studies, which are predictive of adverse effects in

	humans, for eventual evaluation of predictivity in rodent assays (preclinical studies); and (2) qualify the discovered biomarkers.
Development of cancer-relevant biomarkers for identification of potential carcinogens: research to understand the normal background frequencies in rats Study Scientist: McKinzie	(1) To understand the distribution and range of spontaneous oncogene mutant frequencies in the major organs of rats and mice; and (2) to provide important basic information for the validation of these oncogene mutant frequencies as biomarkers of chemically induced carcinogenesis.
Phosphatidylinositol glycan complementation group A (Pig-A) mutagenesis: an international validation study comparing Pig-A mutation in rats with other biomarkers of genetic toxicity Study Scientist: Heflich	(1) To generate data using a standardized protocol, which 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) compare the Pig-A assay results with the in vivo comet and micronucleus formation assays, and hypoxanthine-guanine phosphoribosyltransferase lymphocyte gene mutation assays.
Mechanistic study on the disruption of thyroid hormone homeostasis resulting from subchronic dermal exposure of triclosan to mice Study Scientist: Fang	To examine the mechanisms underlying the effects of triclosan on thyroid hormone homeostasis in female B6C3F1 mice.
Development of a high throughput assay for measuring in vivo mutation in an autosomal gene Study Scientist: Dobrovolsky	To develop a high throughput, in vivo mutation model that detects mutations induced by a range of mechanisms including gene mutation, large deletions, and loss of heterozygosity. The basic properties and sensitivity of the model will be evaluated in experiments employing well-characterized mutagens.
Modification of the comet assay for in vitro and in vivo assessment of global and gene-specific methylation status	To evaluate the inclusion of restriction enzymes used for evaluating the regional and global methylation status of

Study Scientist: Manjanatha	DNA in cells with the comet assay. This modification can allow restriction site analysis and gene specific methylation, thus providing robust hazard identification for chemicals that follow an epigenetic mode of action for toxicity and carcinogenicity.
Development and application of a mitochondria-specific gene array (Mitochip) for the investigation of preclinical and clinical predictive biomarkers of toxicity Study Scientist: Desai	(1) To develop a MitoChip for mammalian species, including rat, nonhuman 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.
Development of the mouse embryonic stem cell test Study Scientist: Hansen	To gain hands-on experience to characterize the test and indicate potentially beneficial modifications to the assay.
	Identification of protein biomarkers for neurotoxicity assessments using a high throughput antibody microarray approach Study Scientist: Gu
	(1) To examine proteomic changes at both the expression and phosphorylation levels using five established in vivo models of neurotoxicity; (2) identify common changes in protein expression and phosphorylation status in these animal model systems; (3) confirm the observed alterations in protein expression and phosphorylation status by means of other independent methods; and (4) apply the proteomic findings to a global ischemic animal model to further validate the utility of protein biomarkers for use in neurotoxicity assessments.
Development and validation of 3-D quantitative structure-activity relationship (QSAR) models for prediction of the binding affinity of chemicals from the ToxCast database to the estrogen receptor (ER) Study Scientist: Slavov	To develop and validate a 3-D quantitative structure-activity relationship (QSAR) model for estrogen receptor binding and provide estrogen binding affinity for chemicals; (2) identify structural binding elements; and (3) evaluate the available databases, including EPA EPcat

	and EPA Endocrine Disruptor Screening Program data for estrogen receptor binding activity.
Establishment of embryonic stem cells as an in vitro model to explore developmental toxicity Study Scientist: 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 responsible for embryotoxicity associated with selected known or suspect embryotoxins that affect differentiation into osteoblasts.
Validation of a newly developed transgenic, hairless, albino mice Study Scientist: Manjanatha	To evaluate a newly developed transgenic, hairless, albino mouse bearing a gpt-delta reporter construct (THA) for (1) responsiveness of the construct (gpt and spi-red/gam genes) to ultraviolet B radiation (UVB); and (2) examine kinetics of induction of UVB-induced mutations in a reporter construct in the dermis and epidermis, and correlate activity with UVB induction of skin tumors.

NTP at NCTR: Interagency Agreement Projects

FY 2015 projects that are funded through an NIEHS/NTP interagency agreement with FDA.

Related NCTR Research:
Additional Research in Partnership with NCTR

Interagency Agreement funded projects are listed below..

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Food Contaminants
Dermal Toxicology Program
Dietary Supplement Program
Nanoscale Material Program
Reproductive and Developmental Toxicology Program
Enhancing Toxicology Program

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Food Contaminants

Project & Study Scientist	Project Summary
Two-year chronic toxicology study of bisphenol A (BPA) administered by gavage to NCTR Sprague Dawley rats from gestational day 6 until birth and directly to pups from postnatal day 1; continuous and stop-dose exposures CASRN: 80-05-7	To characterize the long-term toxicity of orally administered bisphenol A (BPA), including developmental exposure, in NCTR Sprague Dawley rats 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

Study Scientist: Delclos	predictive of long-term toxic effects or reveal potential effects undetected by standard toxicological evaluations.
Evaluation of molecular, morphological, and functional endpoints in NCTR Sprague Dawley rats treated with bisphenol A (BPA) administered by gavage from gestational day 6 until birth and directly to F1 pups from postnatal day 1; continuous and stop-dose (postnatal day 21) exposures CASRN: 80-05-7 Study Scientist: Delclos	To evaluate a range of molecular, morphological, and functional endpoints in rats dosed orally with a wide range of bisphenol A (BPA) doses in a chronic toxicology study. The endpoints were selected based on reports from previous animal toxicology or human epidemiology studies, suggesting they are affected by BPA exposure. Assessments will be conducted at various ages (postnatal days 1, 21, and 90, as well as 6 and 12 months) to determine if any effects observed are predictive of long-term effects evaluated in the companion chronic toxicology study, or if they reveal potential effects undetected by standard toxicological evaluations.
Combined nephrotoxicity of melamine and cyanuric acid in rats – recovery study CASRN: 108-78-1, 108-80-5 Study Scientist: Gamboa	To assess the degree of functional and histological recovery after 30- and 90-day recovery periods in rats orally coexposed for 90 days to a mixture of melamine and cyanuric acid.
Role of perinatal development on toxicokinetics of inorganic arsenic CASRN: 7784-46-5 Study Scientist: Doerge	To determine serum pharmacokinetics and metabolism of inorganic arsenic at a low dose in adult female CD-1 mice, Sprague Dawley rats, and rhesus monkeys.
Two-year carcinogenicity bioassay of furan in Fischer 344 rats CASRN: 110-00-9 Study Scientist: Beland	To determine the dose-response relationship for the carcinogenicity of furan in F344/N (NCTR) male rats in a two-year bioassay.

Dermal Toxicology Program

Project & Study Scientist	Project Summary
Two-year dermal carcinogenicity of triclosan in B6C3F1 mice CASRN: 3380-34-5 Study Scientist: Fang	To determine the toxicity and carcinogenicity of topically applied triclosan in mice.

Dietary Supplement Program

Project & Study Scientist	Project Summary
Thirteen-week dosed water study to determine the potential toxicity of aloin in the cecum and large intestine of F344 rats CASRN: 1415-73-2 Study Scientist: Boudreau	To evaluate whether or not drinking water administration of aloin-A and aloin-B to F344 rats exerts similar effects in the rat large intestine when administered at concentrations similar to those in previous NCTR studies on Aloe vera whole leaf extract.

Nanoscale Material Program

Project & Study Scientist	Project Summary
Thirteen-week study to evaluate the toxicity of silver nanoparticles in Sprague Dawley rats CASRN: 744-22-4 Study Scientist: Boudreau	To determine the toxicity of nanoscale (10, 70, and 107 nanometers) silver particles in a 13-week toxicity bioassay.

Reproductive and Developmental Toxicology Program

Project & Study Scientist	Project Summary
Effect of oxybenzone on fertility and early embryonic development in Sprague Dawley rats (Segment I) CASRN: 131-57-7 Study Scientist: Inselman	(1) To examine the reproductive toxicity of oxybenzone in male and female rats, focusing 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 conducted simultaneously by NIEHS/NTP.
Effect of oxybenzone on embryo/fetal development in Sprague Dawley rats (Segment II) CASRN: 131-57-7 Study Scientist: Inselman	To determine the potential developmental toxicity of oxybenzone and compare the results of a typical Segment I, II, and III study design with results from a modified one-generation study conducted simultaneously by NIEHS/NTP.
Effect of oxybenzone on prenatal and postnatal development in Sprague Dawley rats (Segment III) CASRN: 131-57-7 Study Scientist: Inselman	(1) To determine the potential toxicity of oxybenzone on prenatal and early postnatal development in male and female rats; and (2) to compare the results of a typical Segment I, II, and III study design with results from a modified one-generation study conducted simultaneously by NIEHS/NTP.

Enhancing Toxicology Program

Project & Study Scientist	Project Summary

NTP capability building for microbiome assessment on toxicology studies: assessing the role that the microbiome may play in the toxicity of xenobiotics

Study Scientist: Cerniglia

To address critical knowledge gaps in the microbiome field by using the latest advances in microbiome analysis, using in vitro, in vivo, and ex vivo models in toxicity testing risk assessments.