Welcome to the 2018 Annual Report

"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, NIEHS and NTP Director

Read the 2018 Letter from the NIEHS and NTP Director.

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Director of Office of Liaison, Policy, and Review and Editor in Chief: Mary Wolfe | Managing Editor: Joshua Cleland (ICF)

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Letter from the NIEHS and NTP Director

In fiscal year (FY) 2018, NTP continued to advance toxicology and inform public health policy by providing information to decision makers and the public about substances in our environment. Numerous studies were published on substances of public health concern, such as flame retardants, cell phone radiofrequency radiation, and widely used industrial chemicals. Among these is the final report from the CLARITY-BPA core study and data sets from CLARITY-BPA grantee studies to evaluate the range of potential health effects from BPA in rats.

In addition, NTP engaged in several activities to advance alternatives to animal testing. Particularly noteworthy was publication of the *Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States*, a consensus perspective developed with input from many groups. The “Tox21” consortium met to discuss the new Toxicology in the 21st Century (Tox21) strategic plan that will continue to refine prediction of chemical toxicity to humans.

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.)

NTP continued its systemic review literature activities to identify potential hazards for human health. In partnership with the NIH Countermeasures Against Chemical Threats (CounterACT) Program, NTP conducted a systematic review to assess long-term neurological effects following acute exposure to the organophosphorus nerve agent sarin. Antimony trioxide and *Helicobacter pylori* were evaluated for possible listing in the congressionally mandated Report on Carcinogens.

I invite you to read this report to learn about our work and what we accomplished in FY 2018 toward advancing toxicology and safeguarding public health by generating and communicating trusted scientific information.

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

FY 2018 at a Glance

FY 2018 Timeline

Highlighted NTP activities in FY 2018.

Completed NTP Reports and Publications

NTP studies are published in various NTP report series after undergoing peer review. NTP reports published in FY 2018 or expected for peer review in FY 2019 are listed. Full citations for NTP reports, journal publications, and book chapters published during FY 2018 are provided as an appendix to this section.

NTP Public Health Impact

Federal and state regulatory agencies use NTP study data and recommendations when considering the need to test and regulate specific chemicals to protect human health.

Brian Berridge takes the Helm at the NTP

As NTP's new Associate Director, Brian Berridge, D.V.M., Ph.D., hopes to help NTP integrate cutting-edge toxicology methods, including animal studies, cell-based toxicity testing, and data intensive computer modeling.

Tox Challenge – Stage Two Winners Announced

NTP names five winners of stage two of the Transform Toxicity Testing Challenge for producing practical new rapid chemical testing technologies.

Roadmap to Guide Progress Toward Replacing Animal Use

The newly published *Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States* will guide progress toward replacing use of animals for safety testing of drugs and chemicals in the United States.

NTP Releases Findings from Two CLARITY-BPA Study Components

The newly released draft CLARITY-BPA report presents research from an initiative to studying the full range of potential health effects in rats from exposure to bisphenol A (BPA).

NTP Cell Phone Studies — Experts Recommend Elevated Conclusions

A panel of external scientific experts convened by NTP recommended that some conclusions be changed to indicate stronger evidence that cell phone radiofrequency radiation (RFR) caused tumors in rats.

Federal Partners Put Tox21 Plan into Action

The new Toxicology in the 21st Century (Tox21) strategic plan promotes an automated, high-throughput approach to rapidly measure the toxicity of chemicals.

NTP Framework for Innovation

Speaking to the Board of Scientific Counselors, NTP Associate Director Brian Berridge, D.V.M., Ph.D., introduced the NTP Translational Toxicology Pipeline Plan for strategic realignment.

ICCVAM Publishes 2016–2017 Biennial Report

The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Biennial Report summarizes activities of 16-member agencies that require, use, generate, or disseminate toxicological and safety testing information.

PFAS in the Spotlight across the Globe

NIEHS and NTP Director Linda Birnbaum, Ph.D., testifies at the U.S. Senate September 26 hearing titled “The Federal Role in the Toxic PFAS Chemical Crisis.”

Additional Activities

An overview of additional meetings with stakeholders and the scientific community in which NTP participated.

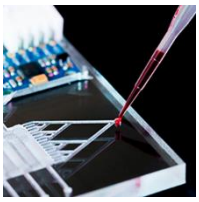
FY 2018 Timeline

October 2017

Peer Review of Draft NTP Approach to Genomic Dose-Response Modeling

An expert panel was convened October 23–25 to review and provide NTP scientific input on the elements of its proposed approach.

November 2017



Alternative Test Methods to Reduce Vertebrate Animal Testing Under TSCA

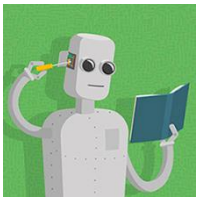
On November 2, EPA and NICEATM cosponsored a public meeting to obtain input toward development of an EPA strategic plan that promotes the development and implementation of alternative test methods and strategies.

December 2017

NTP Board of Scientific Counselors Meeting

At the December 7–8 meeting, the BSC heard about the U.S. Strategic Roadmap for establishing new approach methodologies and various programmatic NTP activities.

January 2018



ICCVAM Communities of Practice Webinar: Machine Learning in Toxicology

This January 23 webinar explored the fundamentals of machine-learning approaches and precautions that should be taken when evaluating their output.

January 2018

Peer Review of the Draft Report on Carcinogens Monograph on Antimony Trioxide

On January 24, an external panel peer reviewed the draft monograph and concurred with NTP's listing recommendation for antimony trioxide in the Report on Carcinogens.

January 2018

Publication of the *Strategic Roadmap* Guide.

The roadmap is a resource to guide U.S. federal agencies and stakeholders seeking to adopt new approaches that improve human relevance and replace or reduce the use of animals.

March 2018

Peer Review of Draft NTP Reports on Cell Phone Radiofrequency Radiation

An external panel was convened on March 26–28 to peer review two draft reports. The panel voted to accept most conclusions as written and recommended changes to some conclusions.

April 2018

Predictive Models for Acute Oral Systemic Toxicity Workshop

Scientists were invited to a workshop on April 11–12 to present their in silico models of acute oral systemic toxicity for five endpoints, which were developed in response to an ICCVAM-sponsored project.

April 2018

Peer Review of the Draft NTP Research Report on CLARITY-BPA Core Study

On April 26, an external panel was convened to review and evaluate the scientific and technical elements of the core study and its presentation.

May 2018

ICCVAM Public Forum

On May 24 in-person meeting attendees and webcast viewers heard presentations by ICCVAM members on current activities related to the development and validation of alternative test methods and approaches.

June 2018

NTP Board of Scientific Counselors Meeting

At its June 20 meeting, the board heard about a strategic realignment of NTP's research and current projects as examples of translational toxicology at NTP.

September 2018

Scientific Advisory Committee on Alternative Toxicological Methods Meeting

At the September 5-6 meeting, the committee heard presentations on the goals of the U.S. Strategic Roadmap for new approaches to safety and risk assessment.

September 2018

The Monocyte Activation Test for Pyrogen Testing of Medical Device Workshop

NICEATM and PETA International Science Consortium co-organized the September 18 workshop to foster discussion on in vitro approaches for medical device pyrogen testing.

Completed NTP Reports and Publications

The findings of NTP studies and research projects are published in four types of NTP reports.

- NTP technical reports document long-term toxicology and carcinogenicity studies, generally of 2 years' duration.
- NTP toxicity reports document shorter-term studies, generally up to 13 weeks' duration.
- NTP research reports provide the results of research studies, rapid communications, and literature surveys that do not fall under the scope of the first two report series.
- NTP Report on Carcinogens monographs are prepared for candidate substances selected for review. Each monograph consists of a cancer evaluation and substance profile to support NTP's policy decision to list the substance in the Report on Carcinogens.

All published NTP reports are peer reviewed by experts who are screened for conflicts of interest prior to their service. In 2018, NTP completed three technical reports, three toxicity reports, four research reports, and one Report on Carcinogens monograph. Full citations for these reports are provided in an Appendix, and all NTP reports completed in FY 2018, and in prior years, are available on the NTP website.

Publications during FY 2018

NTP scientists published more than 250 journal articles and book chapters during FY 2018. Citations for these publications are provided in an Appendix.

NTP Public Health Impact

Federal and state regulatory agencies use NTP study data and recommendations in considering the need to regulate and test specific chemicals for the protection of human health. The NTP data and recommendations used by other agencies in FY 2018 are listed below. A full listing is available on the NTP website.

Use of NTP Study Data or Recommendations by Federal and State Health Regulatory and Research Agencies in FY 2018

Notice	Summary of Notice	NTP Information Cited
Prohibition of Children's Toys and Child Care Articles Containing Specified Phthalates, Final Rule October 27, 2017 82 FR 49938	The U.S. Consumer Product Safety Commission issued a final rule prohibiting children's toys and child care articles that contain concentrations of more than 0.1% of diisononyl phthalate (DINP), diisobutyl phthalate (DIBP), di-n-pentyl phthalate (DPENP), di-n-hexyl phthalate (DHEXP), and dicyclohexyl phthalate (DCHP).	NTP (2015). Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. NTP (2016). 14th Report on Carcinogens.
NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings: Proposed Additions to the NIOSH Hazardous Drug List 2018, Notice of Draft Document Available for Public Comment January 14, 2018 83 FR 6563	The National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention announced the availability for public comment of proposed additions to the list of antineoplastic and other hazardous drugs in healthcare settings, as well as NIOSH Policy and Procedures for Developing the NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings.	NTP (2016). 14th Report on Carcinogens.
Notice of Proposed Rulemaking Title 27, California Code of Regulations Amendment to Section 25705 Specific Regulatory Levels Posing No Significant Risk: Bromodichloroacetic Acid January 26, 2018 Proposition 65	The California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) proposed to adopt a Proposition 65 No Significant Risk Level of 0.95 micrograms per day for bromodichloroacetic acid by amending Title 27, California Code of Regulations, section 25705(b).	NTP (2015). Toxicology Studies of Bromodichloroacetic Acid (CAS No. 71133-14-7) in F344/N Rats and B6C3F1/N Mice and Toxicology and Carcinogenesis Studies of Bromodichloroacetic Acid in F344/NTac Rats and B6C3F1/N Mice (Drinking Water Studies). TR 583.
Notice of Intent to List: TRIM VX January 26, 2018 Proposition 65	The California Environmental Protection Agency's OEHHA proposed to list TRIM VX as known to the state to cause cancer under the Safe Drinking Water and Toxic Enforcement Act of 1986.	NTP (2016). NTP Technical Report on the Toxicology and Carcinogenesis Studies of TRIM VX in Wistar Han [Crl:WI (Han)] Rats and B6C3F1/N Mice (Inhalation Studies). TR 591.
Announcement of Second Public Comment Period for the Draft Technical Support Document on the Proposed Updates of the Public Health	The California Environmental Protection Agency's OEHHA announced the availability of the revised draft technical support document for the proposed updates of the Public Health Goals for nitrate and nitrite in drinking water.	NTP (2001). NTP Technical Report on the Toxicology and Carcinogenesis Studies of Sodium Nitrite (CAS No. 7632-00-0) in F344/N Rats and B6C3F1 Mice. TR 495. NTP (2014). 13th Report on Carcinogens.

Notice	Summary of Notice	NTP Information Cited
Goals for Nitrate and Nitrite in Drinking Water February 09, 2018 Proposition 65		
Amendment to Section 25705 No Significant Risk Level – Glyphosate April 10, 2018 Proposition 65	On April 6, 2018, the California Office of Administrative Law approved an amendment of Title 27, California Code of Regulations, section 25705, that establishes a No Significant Risk Level of 1100 micrograms per day for glyphosate.	NTP (2015). Handbook for Preparing Report on Carcinogens Monographs.
Current Proposition 65 No Significant Risk Levels (NSRLs) Maximum Allowable Dose Levels (MADLs) April 17, 2018 Proposition 65	Under Proposition 65, California has established Safe Harbor levels, which include NSRLs for cancer-causing chemicals and MADLs for chemicals causing reproductive toxicity, for many listed chemicals. Exposure levels and discharges to drinking water sources that are below the safe harbor levels are exempt from the requirements of Proposition 65. In some instances, enforcement actions might have resulted in negotiated exposure levels relative to specific settlement agreements.	NTP (1987). Toxicology and Carcinogenesis Studies of Chlorendic Acid in F344 Rats and B6C3F1 Mice (Feed Studies). TR 304. NTP (1991). Chemical Status Report. NTP (1986). Toxicology and Carcinogenesis Studies of C.I. Basic Red 9 Monohydrochloride in F344/N Rats and B6C3F1 Mice (Feed Studies). TR 285. NTP (1982). Toxicology and Carcinogenesis Studies of D & C Red 9 in F344/N Rats and B6C3F1 Mice (Feed Study). TR 225. National Cancer Institute (NCI) (1980). Bioassay of 4,4'-Oxydianiline for Possible Carcinogenicity. TR 205. NTP (1986). Toxicology and Carcinogenesis Studies of Diglycidyl Resorcinol Ether in F344/N Rats and B6C3F1 Mice (Gavage Studies). TR 257. NTP (1986). Toxicology and Carcinogenesis Studies of Dimethylvinyl Chloride (1-chloro-2-methyl-propene) in F344/N Rats and B6C3F1 Mice (Gavage Studies). TR 316. NTP (1985). Toxicology and Carcinogenesis Studies of HC Blue 1 in F344/N Rats and B6C3F1 Mice (Feed Studies). TR 271. NTP (1989). Toxicology and Carcinogenesis Studies of Hexachloroethane in F344/N Rats (Gavage Studies). TR 361.
Notice of Amendment to Section 25705 No Significant Risk Level (NSRL) for Vinylidene Chloride	On May 9, 2018, the California Environmental Protection Agency's Office of Administrative Law approved an amendment of Title 27, California Code of Regulations, section 25705, which	NTP (2015). Toxicology and Carcinogenesis Studies of Vinylidene Chloride (CAS No. 75-35-4) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). TR 582.

Notice	Summary of Notice	NTP Information Cited
May 17, 2018 Proposition 65	establishes an NSRL for vinylidene chloride of 0.88 micrograms per day.	
Acrylamide Notice May 21, 2018 Proposition 65	The California OEHHA published a notice providing information on the existing Proposition 65 listing of Acrylamide.	NTP (2016). 14th Report on Carcinogens.
Chemical Listed Effective May 25, 2018 as Known to the State of California to Cause Cancer: TRIM® VX May 25, 2018 Proposition 65	The California Environmental Protection Agency's OEHHA added TRIM® VX to the list of chemicals known to the State of California to cause cancer for purposes of Proposition 65. The listing of TRIM® VX was based on formal identification by NTP that the chemical causes cancer.	NTP (2016). NTP Technical Report on the Toxicology and Carcinogenesis Studies of TRIM® VX in Wistar Han [Crl:WI (Han)] Rats and B6C3F1/N Mice (Inhalation Studies). TR 591.
Revised Draft Technical Support Document on the Proposed Updates of the Public Health Goals for Cis- and Trans-1,2-Dichloroethylene in Drinking Water June 01, 2018 Proposition 65	The California Environmental Protection Agency's OEHHA announced the availability for public comment of the (1) revised draft technical support document for the proposed updates of the Public Health Goals for cis- and trans-1,2-dichloroethylene in drinking water.	NTP (2002) NTP Technical Report on the Toxicity Studies of Trans-1,2-dichloroethylene (CAS No. 156-60-5) Administered in Microcapsules in Feed to F344/N Rats and B6C3F1 Mice. TOX 55.
Asbestos; Significant New Use Rule, Proposed Rule June 11, 2018 40 CFR Part 721	Under the Toxic Substances Control Act (TSCA), EPA proposed a significant new use rule for asbestos as defined under the Asbestos Hazard Emergency Response Act. The proposed significant new use of asbestos (including as part of an article) in manufacturing (including importing) or processing for certain uses identified by EPA as no longer ongoing.	NTP (2016). 14th Report on Carcinogens.
Authoritative Bodies Tracking Table, Notice June 13, 2018 Proposition 65	The California Environmental Protection Agency's OEHHA revised the table of chemicals considered for addition to the Proposition 65 list.	NTP (2014). Toxicology Studies of Cobalt Metal (CAS No. 7440-48-4) in F344/N Rats and B6C3F1/N Mice and Toxicology and Carcinogenesis Studies of Cobalt Metal in F344/NTac Rats and B6C3F1/N Mice (Inhalation Studies). TR 581. NTP (2016). NTP Technical Report on the Toxicology and Carcinogenesis Studies of Trim VX in Wistar Han [Crl:WI (Han)] Rats and B6C3F1/N Mice (Inhalation Studies) TR 591.
Review of the Dust-Lead Hazard Standards and the	As part of efforts to reduce childhood lead exposure, EPA evaluated the current dust-lead hazard standards (DLHS) and the definition of lead-based paint (LBP). Based	NTP (2012). Health Effects of Low-Level Lead. NTP Monograph.

Notice	Summary of Notice	NTP Information Cited
Definition of Lead-Based Paint, Proposed Rule July 02, 2018 83 FR 30889	on this evaluation, EPA proposed to lower the DLHS from 40 µg/ft^2 and 250 µg/ft^2 to 10 µg/ft^2 and 100 µg/ft^2 on floors and window sills, respectively. EPA proposed no changes to the current definition of LBP due to insufficient information to support such a change.	NTP (2012). NTP Monograph: Health Effects of Low-Level Lead.
The Safer Affordable Fuel-Efficient (SAFE) Vehicles Rule for Model Years 2021-2026 Passenger Cars and Light Trucks, Notice of Proposed Rulemaking August 24, 2018 83 FR 42986	The National Highway Traffic Safety Administration and EPA proposed the "Safer Affordable Fuel-Efficient Vehicles Rule for Model Years 2021-2026 Passenger Cars and Light Trucks" (SAFE Vehicles Rule). If finalized, the rule would amend certain existing vehicle emissions standards and establish new standards, all covering model years 2021 through 2026.	NTP (2014). 13th Report on Carcinogens.

*CASRN = Chemical Abstracts Service Registry Number

Brian Berridge Takes the Helm at the National Toxicology Program

NTP welcomed Brian Berridge, D.V.M., Ph.D., as its new associate director on January 7, 2018. He hopes to help NTP integrate cutting-edge toxicology methods, including animal studies, cell-based toxicity testing, and data intensive computer modeling.

As the former director of Worldwide Animal Research Strategy at GlaxoSmithKline (GSK), he led efforts to improve animal and non-animal methods for testing pharmaceuticals. He has contributed this expertise to the federal Scientific Advisory Committee on Alternative Toxicological Methods since 2015.

One part of Berridge's role at GSK was decreasing dependence on animal studies by exploring alternative ways to test drugs under development, such as by using cells or computer modeling. These alternative toxicological methods are a priority for NTP.

Berridge worked as a safety assessment pathologist at Eli Lilly and Company before moving to GSK, where he served first as a regulatory toxicologic pathologist. He is now looking forward to applying this experience to the NTP mission.

Berridge said that it has been satisfying to work in the pharmaceutical industry, developing drugs that help people live longer and feel better. "I'm interested in a bigger picture, particularly now that I have two granddaughters," he added. "The environmental public health mission of NTP is really appealing."

Berridge acknowledged that when environmental pollutants have long-term implications, for example, on aging or brain development, toxicology can become really challenging. "But it's a mission worth doing," he said. "It's not easy, but even incremental progress can have real impact on people."

NTP's mission is not just environmental, it includes pharmaceuticals, and part of what I'm interested in is how to leverage this full breadth of resources for toxicology," Berridge said. (Photo courtesy of Steve McCaw.)

Tox Challenge – Stage Two Winners Announced

Scientists are using high-speed, automated screening technologies, called high-throughput screening (HTS) assays, to expose living cells or isolated proteins to chemicals. Current HTS assays measure toxicity of the chemicals themselves, but do not test for metabolites, which are altered forms of chemicals produced as the body breaks down the original compound and are sometimes more toxic than the original chemical.

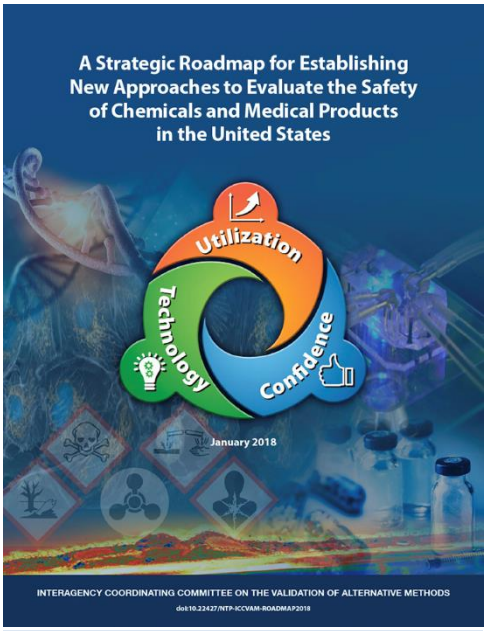
To help capture that missing information, NTP and partners launched the Transform Toxicity Testing Challenge in January 2016. The “Tox Test Challenge” asked teams of scientists to develop techniques to retrofit existing HTS assays to incorporate processes that reflect how the body metabolizes chemicals. After selecting semi-finalists in May 2017, the partners named the five stage two winners on November 1, 2017.

The winners produced practical designs for new technologies that can rapidly test whether some of the thousands of chemicals in use can harm human health:

- Brian Johnson, Ph.D., Onexio Biosystems, LLC. Johnson created a system that uses the natural metabolic activity of human liver cells to generate chemical metabolites and then deliver these metabolites to existing assays. This Metabolism Integrated Cell RepOrter MicroTiter plate (MICRO MT) system is technically simple and requires little additional equipment.
- Moo-Yeal Lee, Ph.D., Cleveland State University and Rayton Gerald, Solidus Biosciences. Lee and Gerald developed a 384-well plate that supports three-dimensional cell cultures. It includes an array of human liver cells for both gene expression and high-content toxicity screening.
- Albert Li, Ph.D., In Vitro ADMET Laboratories (IVAL), LLC. Li developed the MetMax Human Hepatocytes system to serve as an external liver metabolism system. The test chemical is added to allow metabolism by liver cells. Both the parent chemical and its metabolites then migrate across a semi-permeable membrane to interact with the target cells.
- Lawrence Vernetti, Ph.D., University of Pittsburgh Drug Discovery Institute. Vernetti developed a system to supply rodent or human liver cells for co-culture with a second cell or cell-free assay. It allows both test agents and metabolites to be transferred directly to the test plates.
- Hongbing Wang, Ph.D., University of Maryland School of Pharmacy. Wang developed a cell culture model that uses a type of cell called human primary hepatocyte. The platform can be scaled up to an HTS format that allows current cell culture-based assays to produce physiologically relevant metabolites.

New Roadmap Guides Progress toward Replacing Animal Use

The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), which includes representatives of 16 federal government agencies, published the *Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States* on January 30, 2018. The roadmap will guide the replacement of animal use in safety testing of drugs and chemicals in the United States.



The roadmap provides a conceptual framework for development, evaluation, and use of new approach methodologies. (Photo courtesy of NTP.)

Many accepted methods for chemical safety testing rely on laboratory animals. It has been demonstrated that non-animal testing approaches based on toxicity pathways could better predict effects in humans. However, acceptance of such approaches to date has been limited by a lack of communication and coordination among regulatory agencies, test method developers, and regulated industries.

The roadmap was developed to guide the application of new technologies to toxicity testing of chemicals and medical products. The roadmap describes three strategic goals required for progress.

(1) Connect new test method developers with end users.

(2) Promote flexible approaches for establishing confidence in new methods.

(3) Ensure that new methods will be used by federal agencies and regulated industries once validated.

The roadmap describes activities to achieve these goals that should be undertaken by regulatory agencies, test method developers, regulated industries, funding agencies, and other stakeholders.

The roadmap has been translated into Spanish Chinese, Japanese, Korean, and Portuguese. These are available on the NICEATM website.

At its September 5–6, 2018 meeting, members of the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) and other experts discussed these actions outlined in the roadmap and advised U.S. government scientists on issues that should be addressed to replace animal use for safety testing. This panel of experts was drawn from industry, academia, and animal welfare organizations and meets annually to advise ICCVAM, NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), and the NIEHS director on activities related to ICCVAM's mission.

NTP Releases Findings from Two CLARITY-BPA Study Components

NIEHS and the U.S. Food and Drug Administration (FDA) convened the Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA) to study the range of potential health effects from exposure to bisphenol A (BPA) in rats and provide data that can be used for regulatory decisions.

CLARITY-BPA united standard research practices used by regulators, called federal guideline studies, with innovative research conducted at universities through grants from NIEHS. One purpose of CLARITY-BPA was to assess whether these federal guideline studies are sensitive enough to detect health effects from low-dose, endocrine-disrupting chemicals.

CLARITY-BPA has two complementary components:

(1) Core Study: A two-year guideline-compliant study of potential BPA toxicity in rats conducted by FDA's National Center for Toxicological Research (NCTR) with guidance from a CLARITY-BPA steering committee. This portion of the project examined health endpoints typical of so-called guideline studies, such as animal weights, tissue changes, and developmental outcomes.

(2) Grantee Studies: Studies conducted by 14 university researchers that tested a range of additional endpoints, including genetic effects, cardiovascular disease, obesity, and behavior. These studies used control animals, BPA-exposed animals, and BPA-exposed tissues from animals handled identically to those in the core study, ensuring that animals used in both parts of the study were raised in the same conditions and exposed to the same doses of BPA.

BPA is a chemical produced in large quantities and is primarily used in the production of polycarbonate plastics, including water bottles and epoxy resins. BPA is also used in some dental sealants and composites.

NTP released for public comment a draft report of the core study on February 23, 2018. It was reviewed by a panel of external scientific experts at NIEHS on April 26, 2018, which agreed with NTP conclusions that there were minimal toxic effects of BPA exposure in rats for the range of doses studied in the core report. The panel, however, recommended revisions to several specific interpretations of the study findings, which were considered by NTP and FDA staff when they finalized the core study report.

On September 28, 2018, the CLARITY-BPA program released the final report from the CLARITY-BPA core study and the data sets from the CLARITY-BPA grantee studies.

A final integrated report from this collaboration between NIEHS, NTP, FDA, and academic researchers is expected in 2019.

NTP Cell Phone Studies – Experts Recommend Elevated Conclusions

A panel of external scientific experts met at NIEHS March 26–28, 2018, to review the conclusions of two draft NTP technical reports. The goal of the NTP studies was to establish the potential health hazard of exposure to cell phone radiofrequency radiation (RFR).

The $30 million studies took more than 10 years to complete and are the most comprehensive assessment to date of health effects in animals exposed to RFR with modulations used in 2G and 3G cell phones; 2G and 3G networks were standard when the studies were designed and are still used for calls and texting.

The expert panel agreed with NTP conclusions that there was little indication of RFR-related health problems in mice, but the panel recommended that some findings be changed to indicate stronger levels of evidence that RFR caused tumors in rats. Working with the NTP scale of clear evidence, some evidence, equivocal evidence, and no evidence, the panel made several recommendations:

- Tumors in tissues surrounding nerves in the hearts of male rats, called malignant schwannomas, should be reclassified from some evidence to clear evidence of carcinogenic activity.
- Malignant schwannomas in female rats should be reclassified from no evidence to equivocal evidence of carcinogenic activity.
- A type of brain tumor called malignant glioma and a tumor in the adrenal gland called pheochromocytoma should be reclassified as some evidence of carcinogenic activity in male rats.

The panel agreed there were unusual patterns of cardiomyopathy, or damage to heart tissue, in exposed male and female rats and that there were increases in damage to brain tissue in exposed male and female rats, which further supported the classifications of cancerous effects in the brain. For several other tissues, including the prostate and pituitary glands, the panel agreed that tissue changes were equivocal, meaning it was unclear if any of these tumor increases were related to RFR.

In the final reports, prepared for release in November 2018, NTP concluded there is clear evidence that male rats exposed to high levels of RFR developed cancerous heart tumors and that there is also some evidence of tumors in the brain and adrenal gland of exposed male rats. For female rats, and male and female mice, the evidence was equivocal as to whether cancers observed were associated with exposure to RFR.

The final reports represent the consensus of NTP and the panel of external scientific experts who reviewed the studies in March 2018.

To detect a potential effect in the studies, the rodents' whole bodies were exposed to levels equal to and higher than the highest level permitted for local tissue exposure in cell phone emissions today. More recent 4G, 4G-LTE, and 5G networks for streaming video and downloading attachments use different cell phone signal frequencies and modulations than NTP used in these studies.

Federal Partners Put Tox21 Plan into Action

Federal partners gathered at NIEHS May 15–16, 2018, to discuss the implementation of the new Toxicology in the 21st Century (Tox21) strategic plan.

For more than a decade, Tox21 has used automation and cell-based tests to rapidly measure the toxicity of chemicals with a mechanized, high-throughput approach.

Under the new strategic plan, NTP Tox21 activities will continue to refine prediction of chemical toxicity to humans:

- Enhanced methods for testing genetic toxicity will assess whether chemicals are toxic to thousands of genes in specific types of cells.
- Increased use of stem cells will support study of the effects of chemicals on developmental processes.
- New computational models will help to better predict the relationship between external chemical doses and resulting chemical concentrations in tissues.
- The Tox21 consortium will test toxicity in biological systems more complex than single cell types.
- Some testing will be done in alternative species like zebrafish.

Tox21 is exploring the use of 3-D cellular models or tissue chip systems that model the structure and function of different organs, or even how these organs interact. Such approaches will not be as fast as current Tox21 assays, so testing thousands of compounds will have to be carefully strategized.

The Tox21 consortium will continue to refine its high-throughput methods and is also developing performance standards to establish confidence in novel approaches.

NTP Framework for Innovation Rolled Out at Board Meeting

NTP Associate Director Brian Berridge, D.V.M., Ph.D., introduced an updated approach to the organization's mission at the June 20, 2018, Board of Scientific Counselors (BSC) meeting.

Berridge described the NTP Translational Toxicology Pipeline Plan as a strategic realignment and said the new approach aims to inform the present and innovate the future, using contemporary tools such as literature analysis, animal studies, in vitro systems, and in silico or computational analytics.

These tools and strategies will be used to advance public health and the discipline of toxicology in ways that are translatable, predictive, and timely.

"Our proposal is to innovate at a robust pace and for good cause," said Berridge. "By doing that, we're linking the innovations to real problems. So, we're building tools that we need to answer the problems we have today." Berridge aims to accelerate and improve how NTP processes inform public health decisions about chemicals.

The concepts driving the strategic realignment arose from the comprehensive review of NTP operations that Berridge undertook upon his arrival. He emphasized the complexity of NTP research and the breadth of the organization's scientific endeavors.

Much of the remainder of the BSC meeting was devoted to updates about NTP research on cell phone RFR, BPA and related chemicals, crumb rubber, and more. The scientists presenting the updates provided examples of the strategic realignment in action and NTP's long-standing willingness to tackle tough scientific problems.

ICCVAM Publishes 2016–2017 Biennial Report

ICCVAM published its 2016–2017 ICCVAM Biennial Report summarizing activities of member agencies in August 2018. ICCVAM is composed of representatives from 16 regulatory and research agencies, including NIEHS, that require, use, generate, or disseminate toxicological and safety testing information.

The report highlights member agency activities in 2016 and 2017 that supported toxicology innovation as well as regulatory agency initiatives to promote the 3Rs (replace, reduce, or refine animal use) and to provide information about the use of in vitro methods.

Compiled by NICEATM, the biennial report summarizes U.S. government activities to reduce and replace animal use for chemical safety testing. Key ICCVAM and NICEATM accomplishments summarized in the report include:

- Publication of the *Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States*
- Publication of guidance documents by EPA describing approaches to reduce animal use in the testing required for pesticide registration
- Publication of notices by the U.S. Department of Agriculture describing approaches to reduce animal use for vaccine testing
- Publication of the “Predictive Toxicology Roadmap” by FDA
- Development of a non-animal defined approach by NICEATM and EPA that can identify substances that might interact with the androgen receptor
- Development of a non-animal defined approach by NICEATM and ICCVAM to predict skin sensitization risk
- Development of a proposed method in collaboration with international partners to evaluate non-animal approaches to identify skin sensitizers
- Launch of the NICEATM Integrated Chemical Environment (ICE), an online e-resource that provides high-quality curated data and computational workflows for chemical safety assessment

PFAS in the Spotlight across the Globe

From the halls of the U.S. Congress to an international gathering in Zurich, policymakers, scientists, regulators, and others are responding to health concerns about a class of chemicals known by the acronym PFAS.

Per- and polyfluoroalkyl substances, or PFAS, possess a variety of useful qualities for industry and commerce. At the same time, they are highly persistent in the environment and are linked to effects on the immune system, hormone levels, neurodevelopment, pregnancy outcomes, cancer, and other health concerns, according to the U.S. Agency for Toxic Substances and Disease Registry.

After years of use as firefighting foam and in industrial processes, PFAS have been found in both surface and groundwater drinking sources, from which they can cause exposures through ingestion, inhalation during showering, and absorption through the skin.

NIEHS-supported research is contributing new insights into the ways PFAS might affect the health of individuals and communities. NIEHS representatives had opportunities to speak at various worldwide venues in 2018 at which they conveyed an urgency that we learn more about how these chemicals affect the body, and how contaminated water can best be treated:

NIEHS and NTP Director Linda Birnbaum, Ph.D., along with others from EPA, Department of Defense, and Government Accountability Office, testified at a hearing of the Senate Subcommittee on Federal Spending Oversight and Emergency Management titled "The Federal Role in the Toxic PFAS Chemical Crisis" on September 26, 2018.

Additional Activities

During FY 2018, NTP attended several meetings with stakeholders and the scientific community. At the 2018 annual meeting of the Society of Toxicology in San Antonio, Texas, staff from NTP and NIEHS participated in numerous workshops, symposia, platform sessions, education and information sessions, and poster sessions. The full program, including all NTP and NIEHS activities, can be found at the Society of Toxicology website. At this meeting, NTP Director Linda Birnbaum received the annual Arnold J. Lehman Award for exemplary scientific contributions to risk assessment and the regulation of chemical agents.

Birnbaum accepted the Arnold J. Lehman Award from SOT Vice President Leigh Ann Burns Naas, Ph.D.
(Photo courtesy of SOT.)

NTP regularly hosts symposia and workshops to discuss the state of the science or issues of public health concern. For example, NTP held “Pathology Potpourri,” an annual satellite symposium, in Indianapolis, Indiana, the day before the 2018 Society of Toxicologic Pathology meeting. The symposium’s goal was to present current diagnostic pathology or nomenclature issues to the toxicological pathology community. Proceedings were published in the journal, *Toxicologic Pathology*, including summaries of presentations and images of specific pathologies that were used for audience voting and discussion on specific diagnostic and nomenclature issues.

NTP also hosted two workshops in FY 2018 related to alternative methods development:

- Using the Monocyte Activation Test as a Standalone Release Test for Medical Devices
- Predictive Models for Acute Oral Systemic Toxicity

Learn About Us

About NTP

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: NIEHS, NIOSH, and FDA/NCTR.

Interagency Agreements

In FY 2018, NIEHS provided support for NTP activities through interagency agreements with other federal agencies.

Funding

NTP budget for FY 2018 and contracts that support NTP research.

Program Contact Information

General inquiries, websites, and staff directory information.

About NTP

The U.S. Department of Health, Education, and Welfare, now the U.S. Department of Health and Human Services, established NTP in 1978 in response to concerns about the potential human health effects of chemicals in our environment. NTP goals are 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 MISSION:

To evaluate agents of public health concern by developing and applying the tools of modern toxicology and molecular biology

NTP provides scientific data to regulatory agencies and other health-related research groups and interpretation and guidance in their appropriate use. The American people and government agencies, at state and federal levels, rely on NTP to provide a strong scientific basis for decisions aimed at protecting public health. In the past 40 years, NTP has studied and shared information on the health effects of more than 2,800 substances, including dietary supplements, industrial chemicals, consumer products, and complex mixtures.

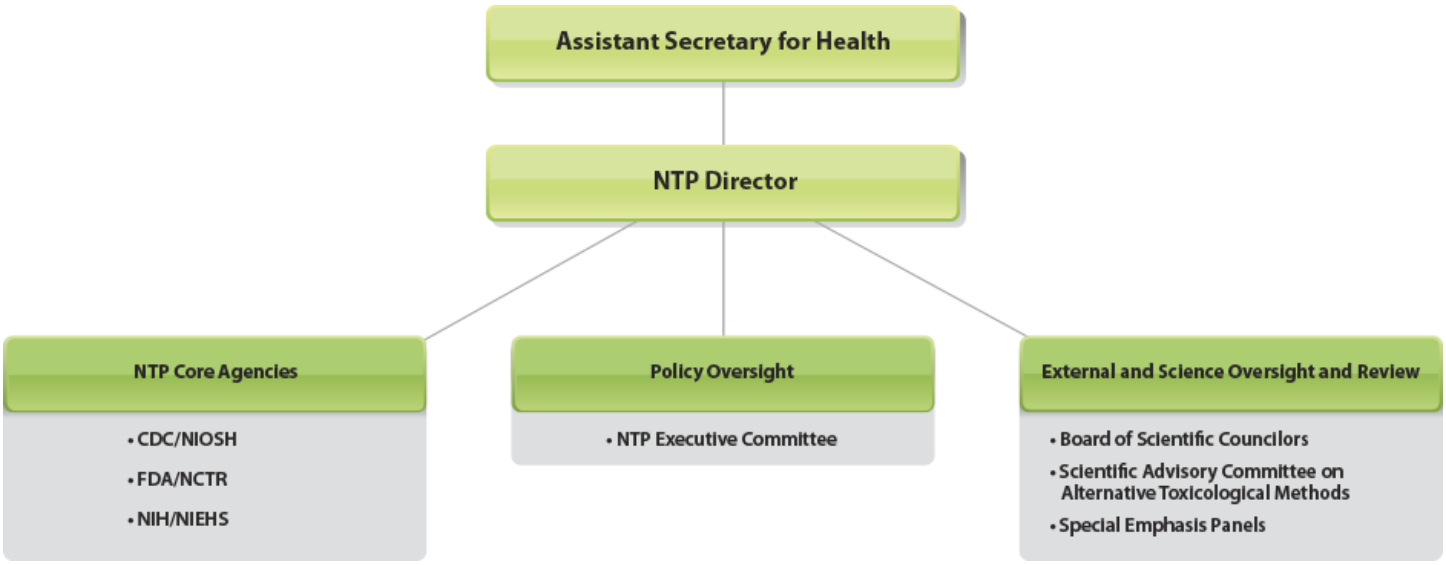
In following government-wide efforts to increase access to the results of federally funded scientific research, NTP maintains open communication and dialogue with the public, federal and state agencies, industry, nongovernmental organizations, and academic institutions. The NTP website provides the public with a variety of information, including Federal Register notices, status of and data from NTP studies, access to NTP reports and journal publications, notifications through media releases, a calendar of upcoming events, and a newsletter, the *NTP Update*.

The public and other interested parties can stay abreast of NTP activities and events by subscribing to receive emails of news. In addition, requests for information can be made through the Central Data Management office (984-287-3211 or cdm@niehs.nih.gov) and an online contact form.

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 (984-287-3209 or the online contact form).

Organizational Structure and Oversight

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



NTP is located administratively at NIEHS, and Linda Birnbaum, Ph.D., is director of both NIEHS and NTP. Beginning January 7, 2018, Brian Berridge, D.V.M., Ph.D., serves as NTP Associate Director and director of the NTP Division at NIEHS, herein referred to as NIEHS/NTP, which is a focal point for many NTP activities. NIEHS and NTP espouse 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. Staff from two NIOSH divisions participate in NTP activities. Elizabeth Whelan, Ph.D., chief of the Industry-wide Studies Branch, and Cheryl Estill, Ph.D., supervisor of Industrial Hygiene, manage NTP activities within the Division of Surveillance, Hazard Evaluations, and Field Studies. Donald Beezhold, Ph.D., is the principal investigator for the "Immunotoxicity of Workplace Xenobiotics" project through a NIOSH-NIEHS interagency agreement.

NIOSH's participation in NTP is consistent with its mandate to protect worker health and safety under the Occupational Safety and Health Act and the Federal Mine Safety and Health Act.

William Slikker Jr., Ph.D., director of FDA/NCTR, provides management oversight and coordination of NTP activities within NCTR. Their scientists partner with other researchers in FDA, other government agencies, academia, and industry to 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.

Interagency Agreements

In FY 2018, NIEHS provided support for NTP activities through interagency agreements with other federal agencies.

FDA/NCTR

Under an interagency agreement, NIEHS provided resources to FDA to conduct toxicology studies on FDA-regulated agents and on issues of mutual interest to NIEHS and FDA at the National Center for Toxicological Research. Gonçalo Gamboa da Costa, Ph.D., Division of Biochemical Toxicology, is FDA project officer of the NCTR-NIEHS interagency agreement and provides oversight and coordination of NCTR activities funded under the interagency agreement with NIEHS. 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. The interagency agreement supports studies on endocrine-active agents, dietary supplements, food additives and contaminants, therapeutics and medicines, cosmetic ingredients, nanoscale materials and development of novel toxicological approaches. Studies in these areas have produced 18 published NTP technical reports and more than 250 peer-reviewed journal publications. The studies have led to an increased understanding of the pharmacokinetics, mode-of-action, and dose-response relationships of the substances and to refinements of risk assessment models. Further information about NTP at the National Center for Toxicological Research and current research can be found in the Partner Agency Research section of this annual report.

CDC/NIOSH

NIEHS/NTP provides support to the National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention (CDC) through two interagency agreements. Studies under the interagency agreement on “Immunotoxicity of Workplace Xenobiotics” have assessed the potential toxicity of exposures to substances such as fungi, mycotoxins, volatile organic compounds, lead, latex, nickel, isocyanates, nanomaterials, and beryllium in occupationally exposed populations such as miners, farmers, health care workers, autoworkers, and firefighters. The second interagency agreement supports the development of methods to assess complex mixtures, such as asphalt fumes, welding fumes, and tungsten fibers, and to conduct occupational exposure assessments to identify toxicologically relevant exposures. Research under these agreements in FY 2018 evaluated occupational exposure to bisphenol A, alternative flame retardants, and polycyclic aromatic hydrocarbons in coal tar sealants. For more information, see the Partner Agency Research section of the Annual Report.

NIH/NCATS/DPI

This interagency agreement supports ongoing and anticipated studies conducted at the National Center for Advancing Translational Sciences/Division of Pre-Clinical Innovation to evaluate high-throughput and high-content screening assays in support of Tox21. Tox21 is a collaboration among federal agencies to characterize the potential toxicity of chemicals by using cells and isolated molecular targets instead of laboratory animals. This interagency agreement between NIEHS/NTP and the division produces data for information-poor substances to help prioritize them for further studies, including toxicological evaluation, mechanisms of action investigation, and development of predictive modeling for biological response.

DOE/ORNL

Under this interagency agreement, NTP is working with DOE's Oak Ridge National Laboratory to develop tools important to evaluating the use and impact of its work. For example, publication mining tools help to evaluate NTP's impact across the agencies and with stakeholders to whom the work is disseminated and to extract and organize data (e.g., potential outcomes and impacts) from NTP's large inventory of documents (e.g., publications and progress reports).

EPA/NCCT

With projects under this interagency agreement, EPA's National Center for Computational Toxicology works to accelerate the development and use of advanced methods and models for quantitative and qualitative risk assessments of environmental chemicals. Specifically, research in FY 2018 used non-targeted approaches to characterize chemicals present in feminine hygiene products.

EPA/NCEA

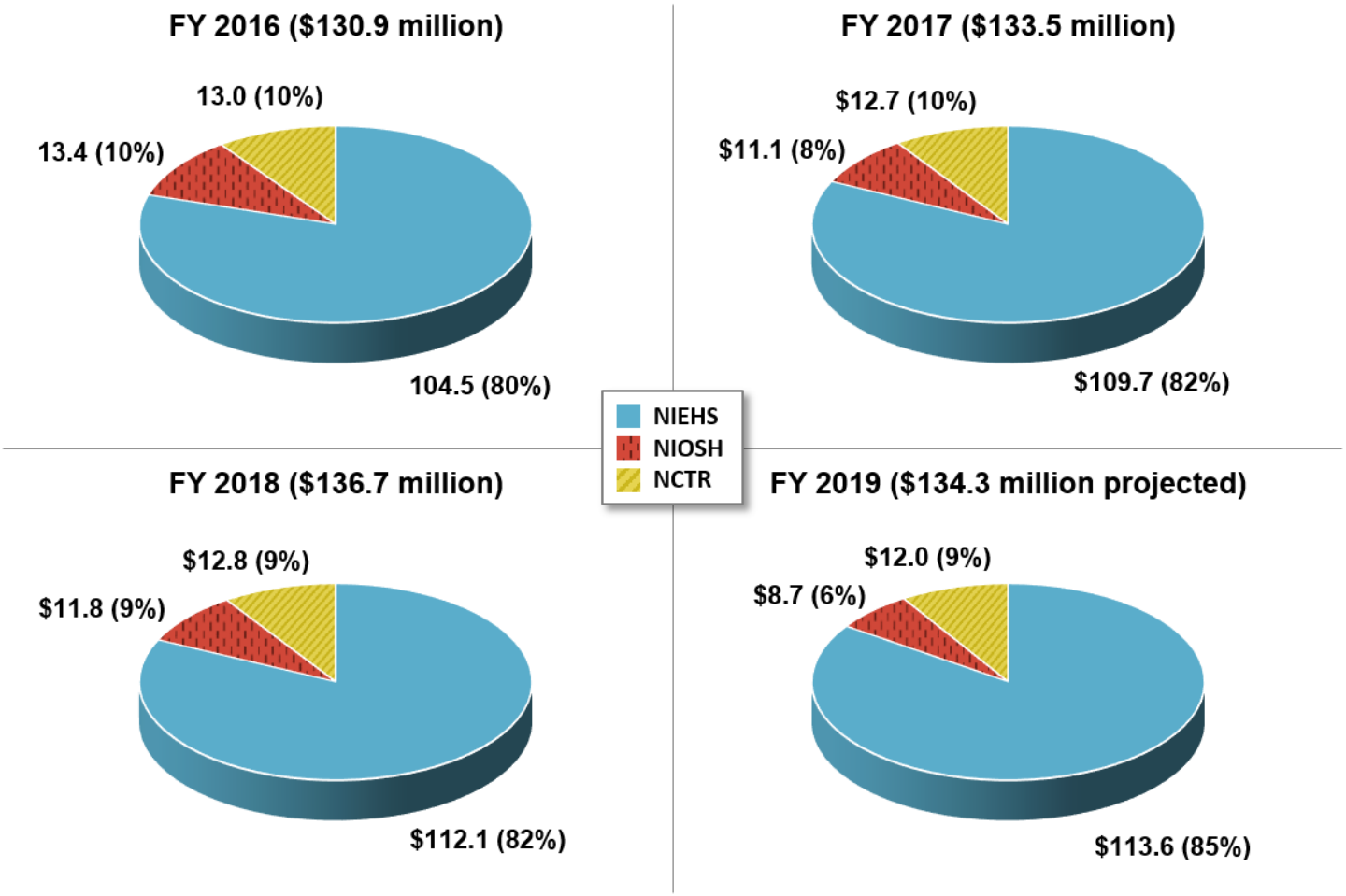
This IAA between NTP and EPA' National Center for Environmental Assessment facilitates communication and coordination to foster common practices in human health assessments and to minimize the differences in hazard assessment methodologies. Through exchange of scientific expertise and peer review of work products, the agencies increase the quality and integrity of toxicological assessments while ensuring efficient use of federal resources and avoiding duplicative effort.

NIST

Through an IAA to support the experimental study of cell phone radiofrequency radiation exposure, NIEHS/NTP and the National Institute of Standards and Technology collaborated under this interagency agreement to develop a new exposure system that addresses the limitation in existing systems. In a separate agreement, the NIST Text Analysis Conference, NIST assisted NTP with development of automated systematic review methods.

Funding

NTP relies on voluntary allocations from the three core agencies—NIEHS, FDA/NCTR, and CDC/NIOSH—to support its activities. These allocations are specified after annual appropriations have been determined. The total NTP budget for FY 2018 was $136.7 million.



NTP conducts its research through in-house studies at the three core agencies or through contract laboratories or interagency agreements with other agencies. In FY 2018, NIEHS funded 30 contracts, listed below, held two workshops, three peer-review meetings, two Board of Scientific Counselors meetings, and one scientific advisory meeting. CDC and FDA could have additional contracts that support some of their voluntary NTP efforts.

NIEHS Contracts That Supported NTP Activities in FY 2018

Description	Contractor
Analytical Chemistry Services	Battelle Memorial Midwest Research Institute Research Triangle Institute
Archives and Specimen Repository	Experimental Pathology Laboratories
Bioinformatics Methylation Project	Laboratory Corp of America

Description	Contractor
Bioinformatics Support	SCIOME, LLC.
Collaborative Work with Ramazzini	DOE/ORISE
Evaluation of Alternative Toxicological Methods	Integrated Laboratory Systems
Evaluation of Toxicity Following Early Life Exposure	Southern Research Institute
Evaluation of the Toxicity of Selected Chemicals	Battelle Memorial
Genetic Toxicity Testing Support Services	Integrated Laboratory Systems
Immunotoxicity	Burleson Research Technologies
In-Life Data Collection and Management System	INSTEM, LSS
Kelly Scientific Government Services	Kelly Scientific
NTP Information Systems Support	Signature Consulting Group, LLC
NTP Technical Reports Preparation Support Services	Biotechnical Sciences, Inc.
Pathology Support	Experimental Pathology Laboratories Integrated Laboratory Systems PAI/Charles River Laboratories
Production of B6C3F$_1$ Mice	Taconic Biosciences, Inc.
Provision for Animals and Specialized Services	Charles River Laboratories The Jackson Labs Taconic Biosciences
Quality Assessment Support/Audits & Inspections	CSS-Dynamac Corporation
Reproductive Assessments by Continuous Breeding	Research Triangle Institute
Scientific Information Management and Literature-Based Evaluations for the NTP	ICF
Statistical Support	Social and Scientific Systems
Support for Toxicological Data	Vistronix, LLC
Support Services for Clinical Research Studies	Social and Scientific Systems
Toxicological and Carcinogenic Potential of Chemicals	Battelle Memorial

Program Contact Information

For general inquiries, contact:

Central Data Management
P.O. Box 12233, MD K2-05
Research Triangle Park, NC 27709
984-287-3211
cdm@niehs.nih.gov (or use contact form)

A Staff Directory is available.

Scientific and Public Input Opportunities

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.

Scientific Advisory Committee on Alternative Toxicological Methods

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

Scientific 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.

Training Opportunities

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

NTP Board of Scientific Counselors

The NTP Board of Scientific Counselors (BSC), a federally chartered advisory group whose members are appointed by the Secretary of Health and Human Services, oversees the scientific merit of NTP programs and activities. The BSC includes scientists, primarily from the public and private sectors, with expertise relevant to NTP activities. The current roster and meeting minutes are available on the NTP website. In FY 2018, Mary Wolfe, Ph.D., served as the designated federal officer for the BSC. A list of FY 2018 members follows.

The Board met twice in FY 2018: December 7–8, 2017 and June 20, 2018. Materials and highlights from each meeting can be accessed on the Past NTP Board of Scientific Counselors Meetings web page. The June meeting was Dr. Brian Berridge's first meeting as new NTP Associate Director. At that meeting, Dr. Berridge introduced an updated approach to the organization's mission and also described the NTP Translational Toxicology Pipeline Plan as a strategic realignment aimed to inform the present and innovate the future using contemporary tools such as literature analysis, animal studies, in vitro systems, and in silico or computations analytics. These tools and strategies would yield fit-for-purpose products that advance public health and the discipline of toxicology in ways that are translatable, predictive, and timely.

NTP Board of Scientific Counselors members and NTP staff at the June 2017 BSC meeting

NTP Board of Scientific Counselors Membership Roster FY 2018

Name and Title	Affiliation	Term End Date
Cynthia Afshari, Ph.D. Scientific Executive Director	Amgen, Inc. Thousand Oaks, California	6/30/19
Norman J. Barlow, D.V.M., Ph.D. Head of Nonclinical Sciences	Seatte Genetics Bothell, Washington	6/30/19
Paul Brandt-Rauf, Dr.P.H., M.D., Sc.D. Office of the Dean	Drexel University Philadelphia, Pennsylvania	6/30/20
Myrtle Davis, D.V.M., Ph.D. Executive Director, Discovery Toxicology, Pharmaceutical Candidate Optimization	Bristol-Myers Squibb Princeton, New Jersey	6/30/20
Daniel Kass, M.S.P.H. Senior Vice President, Environmental Health	Vital Strategies New York, New York	6/30/19
Kenneth McMartin, Ph.D. Board Chair Professor, Pharmacology, Toxicology, and Neuroscience	Louisiana State University Health Science Center Shreveport, Louisiana	6/30/19
Kenneth Ramos, M.D., Ph.D. Associate Vice President, Precision Health Sciences Center	Arizona Health Sciences Center Tucson, Arizona	6/30/19
Jennifer Sass, Ph.D. Senior Scientist	Natural Resources Defense Council Washington, District of Columbia	6/30/20
James Stevens, Ph.D. President	Paradox Found Consulting Services, LLC Apex, North Carolina	6/30/19
Donald G. Stump, Ph.D., D.A.B.T. Vice President, Nonclinical Safety Science	WIL Research Ashland, Ohio	6/30/20
Katrina Waters, Ph.D. Deputy Director, Biological Sciences Division	Pacific Northwest National Laboratory Richland, Washington	6/30/19

SACATM

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) is a federally chartered advisory committee established on January 9, 2002, in response to the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Authorization Act of 2000 (42 U.S.C. 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, and the roster for FY 2018 is listed below. SACATM typically meets once a year and members serve rotating terms of up to 4 years. Elizabeth Maull, Ph.D., served as the FY 2018 designated federal officer and manager of SACATM.

SACATM met on September 5–6, 2018, at the NIEHS Rodbell Auditorium in Research Triangle Park, North Carolina. In January 2018, ICCVAM published the *Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States*. The SACATM meeting focused on implementation efforts for the three strategic goals required for its progress:

- Connect new test method developers with end users.
- Promote flexible approaches for establishing confidence in new methods.
- Ensure that new methods will be used by federal agencies and regulated industries once validated.

Members of SACATM and ICCVAM and staff from NIEHS and NTP at the September 2018 SACATM meeting

SACATM Membership Roster FY 2018

Name and Title	Affiliation	Term End Date
Michael B. Bolger, Ph.D. Chief Scientist	Simulations Plus, Inc. Lancaster, California	11/30/20
Kelly P. Coleman, Ph.D., D.A.B.T., R.A.C. Distinguished Scientist and Technical Fellow	Medtronic PLC Minneapolis, Minnesota	11/30/20
Hisham K. Hamadeh, Ph.D., D.A.B.T., M.B.A. Director, Comparative Biology and Safety Sciences	Amgen, Inc. Thousand Oaks, California	11/30/19
William P. Janzen Executive Director of Lead Discovery	Epizyme, Inc. Cambridge, Massachusetts	11/20/18
Lawrence M. Milchak, Ph.D., D.A.B.T. Senior Manager, Toxicology and Strategic Services	3M St. Paul, Minnesota	11/30/19
Pamela J. Spencer, Ph.D., D.A.B.T. Committee Chair Director of Regulatory and Product Stewardship	ANGUS Chemical Company Buffalo Grove, Illinois	11/30/19
ClarLynda Williams-Devane, Ph.D. Director, Bioinformatics, Genomics, and Computational Chemistry Biotechnology Biomedical Research Institute	North Carolina Central University Durham, North Carolina	11/30/20
Wei Xu, Ph.D. Associate Professor, Department of Oncology McArdle Laboratory for Cancer Research	University of Wisconsin at Madison Madison, Wisconsin	11/30/18
Hao Zhu, Ph.D. Assistant Professor, Department of Chemistry	Rutgers University Camden, New Jersey	11/30/19

Scientific Panels

NTP convenes 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 others. All panel reviews provide the opportunity for public comment. These panels help ensure that NTP receives transparent, unbiased, and scientifically rigorous input for its use in making credible decisions about human health hazards, setting research and testing priorities, and evaluating test methods for toxicity screening.

NTP Technical Reports Peer Reviewed in FY 2018

NTP technical reports are published results of long-term studies, generally 2-year rodent toxicology and carcinogenesis studies. For each technical report, the panel is charged with reviewing the scientific and technical elements and presentation of the study and determining whether the study's experimental design and conduct support NTP conclusions regarding the carcinogenic activity of the substance tested.

The draft technical reports, listed below, underwent peer review in FY 2018. Additional information about past technical reports' peer-review meetings can be found on the NTP Technical Reports Peer-Review Panels web page.

Topic	Technical Report Number	Use	Peer Review Information
Studies in Rats Exposed to Whole-body Radio Frequency Radiation at a Frequency (900 MHz) Used by Cell Phones	TR-595	Utilized in cell phones to transmit between the devices and the network.	Actions Peer-Review Report
Studies in Mice Exposed to Whole-body Radio Frequency Radiation at a Frequency (1,900 MHz) Used by Cell Phones	TR-596	Utilized in cell phones to transmit between the devices and the network.	Actions Peer-Review Report

NTP Research Reports Peer Reviewed in FY 2018

Research report peer-review panels are technical, scientific advisory bodies established on an as-needed basis to review drafts reports.

The draft research reports, listed below, underwent peer review in FY 2018. Additional information about past research reports' peer-review meetings can be found on the NTP Research Reports Peer-Review Panels web page.

Topic	Research Report Number	Aim	Peer Review Information
National Toxicology Program Approach to Genomic Dose-Response Modeling	RR-05	With expert input, outline NTP's approach for in vivo and in vitro genomic dose-response studies.	Actions Peer-Review Report
The CLARITY-BPA Core Study: A Perinatal and Chronic Extended-Dose-Range Study of Bisphenol A in Rats	RR-09	Characterize the toxicological potential of bisphenol A (BPA) following perinatal-only or a chronic exposure in rats exposed to BPA.	Peer-Review Report

NTP Report on Carcinogens Monographs Peer-Reviewed in FY 2018

The Report on Carcinogens monographs are prepared for each candidate substance selected for review and consist of a cancer evaluation component and a substance profile. For each monograph, the panel is 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, the panel is charged with commenting on whether the scientific justification presented supports the preliminary NTP policy decision on the Report on Carcinogens listing status.

The draft Report on Carcinogens monographs, listed below, underwent peer review in FY 2018. Additional information about past Report on Carcinogens monographs' peer-review meetings can be found on the NTP Report on Carcinogens Monographs Peer-Review Panels web page.

Chemical/Topic	CASRN*	Use/Aim	Peer Review Information
Antimony Trioxide	1309-64-4	Used as a flame retardant in canvas, textiles, paper, and plastics; also used in batteries, enamels, paint pigment, ceramics, and fiberglass.	Actions Peer-Review Report
Night Shift Work and Light at Night	—	Evaluate potential carcinogenic hazard from working night shifts and being exposed to aberrant lighting conditions at night.	Actions Peer-Review Report

*CASRN = Chemical Abstracts Service Registry Number

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. In FY 2018, NIEHS/NTP staff mentored 20 postdoctoral fellows at NIEHS in six focal areas (below). Full details on opportunities, benefits, and the application process can be found on the NIEHS training website. The training program has six focal areas:

(1) Applied Toxicology and Carcinogenesis

(2) Biomolecular Screening and Computational Toxicology; Alternative Methods

(3) Health Assessment and Translation

(4) Laboratory Animal Medicine

(5) Systems and Mechanistic Toxicology

(6) Toxicological Pathology

NIEHS/NTP Training Program Postdoctoral Fellows in FY 2018

Training Program	Fellow
Applied Toxicology and Carcinogenesis	Anika Dzierlenga Kelly Shipkowski Madelyn (Mimi) Huang Troy Hubbart AtLee Watson
Biomolecular Screening and Computational Toxicology	Sreenivasa Ramaiahgari Katelyn Lavrich Alex Borrel
Health Assessment and Translation	none
Laboratory Animal Medicine	Manushree Bharadwaj David Crizer Jingli Liu Tony Luz Xian Wu
Systems and Mechanistic Toxicology	Gopi Gadupudi Miaofel Xu Janice Harvey Donna Webb-Wright
Toxicological Pathology	Daven Jackson-Humbles Gregory Krane Eui Jae Sung

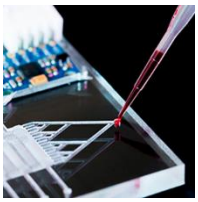
Research and Testing

Tox21

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

Testing and Toxicology Studies

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



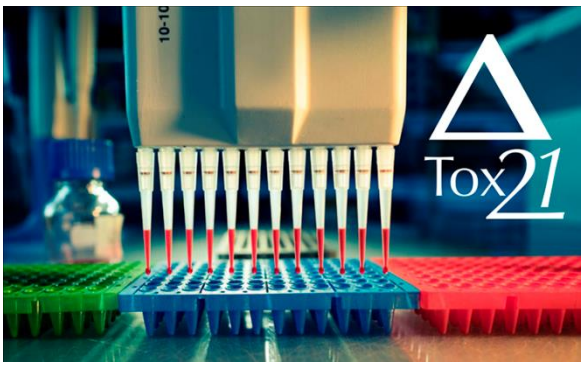
NICEATM

The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) 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 at NIEHS.

Tox21



Toxicology in the 21st Century (Tox21) is a unique federal collaboration among the National Institutes of Health (NIH), including the National Toxicology Program (NTP) at the National Institute of Environmental Health Sciences (NIEHS) and the National Center for Advancing Translational Sciences (NCATS), Environmental Protection Agency (EPA), and U.S. Food and Drug Administration (FDA). Its purpose is to develop new methods to rapidly test whether chemicals adversely affect human health. Tox21 uses robotic, high-throughput screening methods and other testing approaches to evaluate large numbers of chemicals quickly and efficiently to provide insight into potential human health effects. Bioinformatics and computational toxicology support for Tox21 is provided by Tox21 members, including members of the Biomolecular Screening Branch and the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods.

NTP Tox21 projects in FY 2018 were carried out by the NIEHS/NTP staff listed below.

Assay Development

Project Study Scientist	Project Summary
Development of a stable cell line to screen compounds that affect the estrogen-related receptor alpha/peroxisome proliferator-activated receptor coactivator pathway Alex Merrick, Tina Teng, Kristine Witt	This project focuses on the development of an assay to detect compounds that interfere with a critical pathway for metabolic homeostasis. Stable human cell lines expressing the appropriate reporter construct were successfully generated. Quantitative high-throughput screening efforts, including the full Tox21 10K library, were the subject of two peer-reviewed manuscripts published in FY 2017 and FY 2018. Another manuscript, “High-Throughput Screening," which describes the receptor antagonism results, is in preparation for submission in early 2019 to a special issue of the journal *Molecules*.
Use of HepaRG cells for high-content screening Stephen Ferguson, Sreenivasa Ramaiahgari	This study examines the establishment of metabolically functional human HepaRG liver cells (derived from a human hepatic progenitor cell line) for completing multiplex, high-content screening assays. Studies to characterize the metabolism of xenobiotic compounds in these cells began in FY 2016 and research continuing into FY 2018 examined the metabolic function of these HepaRG liver cells in response to 24 reference compounds with known effects on human liver. High-throughput transcriptomics were incorporated in these studies to help characterize liver-like responses of these cultures. A manuscript is currently under review for publication in 2019.
Testing of gene signatures and profiles in NTP archival tissues Alex Merrick, Julie Foley	This study is determining whether RNA and DNA extracted from fixed tissue and frozen tissue blocks can be used to measure gene signatures and mutational profiles based on studies of chemical exposure to toxic compounds. The goal is to measure molecular changes caused by chemical exposures in rat and mouse organs. A study investigating mutational signatures utilizing a newly developed rat exome-sequencing platform was published in FY 2018.

Project Study Scientist	Project Summary
Screening of chemical toxicity in stem cells Stephen Ferguson, Fred Parham, Jui-Hua Hsieh, Mamta Behl	This study screened for chemical toxicity in human or mouse stem cell lines (undifferentiated or differentiated) by using quantitative high-throughput screening or lower throughput assays. Data were generated on a library of 80+ predominantly developmental neurotoxicants evaluated for (1) effects on neurite outgrowth in a human stem cell-derived neural cell population, (2) cytotoxicity in different neural populations derived from human stem cells, and (3) effects on the beating of human stem cell-derived cardiomyocytes. Dose-response analyses have been completed on the data from these assays. Two manuscripts were published in FY 2017 and two in FY 2018.
High-throughput assays and computational models to replace current EPA Endocrine Disruptor Screening Program Tier 1 tests Warren Casey, Nicole Kleinstreuer	This project entails developing an approach for using validated ToxCast and 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. The method has been described in several publications. In FY 2017, a similar computational model was developed for androgenic activity. In FY 2018, the androgen computational model was evaluated against the rodent Hershberger and other in vivo tests with androgen-responsive endpoints.
Liquid biopsy: Circulating cell-free DNA as a predictor of chemical toxicity Julie Foley, Alex Merrick	Methods were developed for extracting circulating cell-free DNA (ccfDNA) from human, rat, and mouse plasma. ccfDNA changes can serve as a liquid biopsy and might help predict or better describe toxicity in affected tissues during chemical exposure. The amounts and sequence changes of ccfDNA are being investigated as new biomarkers for chemical toxicity and disease as part of this project. An NIEHS ccfDNA workshop was held in FY 2018. NTP studies are underway to assess ccfDNA changes after chemical exposure in mice and rats.
Liquid biopsy: miRNA as a tissue and cell-specific biomarker of underlying organ injury Alison Harrill	Prior experiments indicated that kidney injury biomarkers are leaked into the urine following kidney injury, including proteins and miRNA derived from kidney cells that can serve as sensitive injury biomarkers. This project is using RNA-seq to identify cell-type specific miRNA abundance in the kidney to identify biomarkers of specific underlying pathology. The project, focused on miRNA specific to the glomerulus, proximal tubule, loop of Henle, and collecting duct, is a collaboration through the Health and Environment Sciences Institute with Bristol-Myers Squibb, Sanofi, Bayer, Abcam, and EPA. In a parallel effort, the project team is currently writing a review article on technical challenges of miRNA biofluid measurements.
Tox21 Cross-Partner Project: In vitro pipeline to assess population toxicodynamic variability for chemicals suspected to cause developmental neurotoxicity Alison Harrill, Richard Paules, Kristine Witt	This project encompasses the development of a computational and cellular testing framework for assessing genetic susceptibility to chemical agents suspected of causing developmental neurotoxicity. A Tox21 Cross-Partner Project, it is a collaboration with FDA and EPA in which ~200 Diversity Outbred mouse neural progenitor cell lines will be exposed to a chemical test battery. Cellular effect potency will be assessed using high-content imaging techniques. In FY 2018, a Bayesian statistical framework was developed and implemented to quantify inter-individual variability and cytotoxicity data were analyzed.
Tox21 Cross-Partner Project: Retrofitting existing Tox21 HTS assays with metabolic capability	This project aims to refine existing methods to (1) imbue Tox21 assays with metabolic capability, (2) screen the Tox21 10K compound collection using these new methods to identify chemicals that are either bioactivated or

Project Study Scientist	Project Summary
Kristine Witt	detoxified by liver cytochrome P450s and cofactors, and (3) identify the particular CYPs responsible for observable shifts in bioactivity. The p53RE-bla assay will be used initially to test this approach. Subsequently, metabolism will be incorporated into high-throughput screens by running the Real Time Cell Viability assay and the material-mediated pyrogens assay, which have a profile of CYP enzymes similar to that of primary human hepatocytes.

Data Analysis

Project Study Scientist	Project Summary
Analysis of Tox21 quantitative high-throughput screening assay data Jui-Hua Hsieh	Data analysis pipelines are being developed for Tox21 Phase II quantitative high-throughput screening data to determine the activity of compounds in assays. The developed ranking, or calling procedure, accounts for compound potency, efficacy, and data reproducibility. A manuscript describing this pipeline was published, and computational tools to analyze Tox21 data have been made publicly available through the Tox21 Toolbox on the NTP public website.
Prioritization of Tox21 compounds for genotoxicity Jui-Hua Hsieh, Kristine Witt, Stephanie Smith-Roe, Scott Auerbach, Alex Merrick	A prioritization approach is being developed that includes compounds showing clear evidence of activity in the quantitative high-throughput screening genotoxicity assays and compounds that are weakly active based on chemical structure-activity relationship analysis. A manuscript using this approach as part of the analysis of the Tox21 quantitative high-throughput screening p53 activation assay was published in FY 2017. In FY 2018, a more extensive modeling exercise was completed using data from all Tox21 quantitative high-throughput screening assays.
Design of Tox21 data exploration graphical user interface Jui-Hua Hsieh	This project entails the development of two graphical user interfaces for viewing Tox21 data. One graphical user interface is used to explore the concentration-response data in a line chart, and the second is used to explore compound similarity relationships in terms of their chemical structures and activities in Tox21 quantitative high-throughput screening assays. Prototype graphical user interfaces were first developed during FY 2013 and made public in FY 2015. In FY 2018, these computational tools to analyze Tox21 data were developed further and expanded and made publicly available through the Tox21 Toolbox on the NTP public website.
Unsupervised, data-driven analysis of Tox21 assay data project Scott Auerbach, Nicole Kleinstreuer	This unsupervised data analysis is focusing on 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 assays used to screen the 10K library. The results are being used to help prioritize compounds for more extensive toxicological testing. An updated web interface for multiple integrated tools

Project Study Scientist	Project Summary
	was made public in FY 2018, along with a supporting manuscript, and further updates were begun for release in FY 2019. Basic machine learning workflows using the Tox21 data for model building and data exploration are available on ICE.
High-throughput in vitro-in vivo extrapolation (IVIVE) using Tox21 data Nisha Sipes, Warren Casey, Nicole Kleinstreuer	This project entails the development and refinement of ways to extrapolate all Tox21 chemical-concentration effect data to estimated human equivalent exposure doses. The effort builds on previous efforts (outside of NTP) using high-throughput toxicokinetics models and combines them with in silico-estimated parameters. A publicly available web application based on these methods is available through the Tox21 Toolbox on the NTP public website, and refinement and use of the models in a research and prioritization context continued throughout FY 2018. Additionally, a simple IVIVE workflow allowing users to select Tox21 assays and chemicals and extrapolate to estimated exposures is available on ICE.
Cell line selection for Tox21 Phase III Nisha Sipes	This established Tox21 cross-partner project is developing and using a data-driven approach to choose cells to maximize biological diversity. A content maximization approach, along with programmatic interest, were used to pick a diverse set of 30+ cells based on publicly available gene expression data. Baseline gene expression profiling is planned in these cells using the appropriate technology platform, which will allow harmonization across projects. In vitro chemical testing will commence subsequently.
Aggregated hit-call of Tox21 data Nisha Sipes	This project involves the comparison of Tox21 data analysis methods, identification of higher-confidence chemical-assay actives, and development of a website for public access to the data and visualizations. A web interface with the aggregated hit-call function was developed during FY 2018 for an anticipated in FY 2019.
Next-generation sequencing in toxicology Alex Merrick, Kristine Witt, Stephanie Smith-Roe	Under this project, bioinformatics pipelines are being developed 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. The effort was recently expanded to evaluate gene expression changes in frozen tissue samples from brain subregions obtained from genetic toxicity studies conducted as part of the NTP Cell Phone Radio Frequency Radiation study. In addition, new informatic tools have been developed to better identify long noncoding RNAs.
Development of a reference database for estrogenic activity Warren Casey, Nicole Kleinstreuer	This project is supporting 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 more than 2,660 distinct combinations of chemicals, studies, and protocols. These data have potential utility for developing adverse outcome pathways or models of estrogenic activity, prioritizing chemicals for further testing, or evaluating species-specific responses to chemicals.

Project Study Scientist	Project Summary
	The database is described in a manuscript published in FY 2016. This activity is complete, but the database is being used as a training set for the automation of systematic reviews.
Optimization of approaches for in vitro-in vivo extrapolation using Tox21 data Warren Casey, Nicole Kleinstreuer	NICEATM developed and applied one-compartment or physiologically based pharmacokinetic models to data from validated in vitro (EPA ToxCast estrogen receptor pathway model) and in vivo (uterotrophic) methods to correlate in vitro and in vivo dosimetry quantitatively for estrogen receptor reference chemicals. This approach highlighted the importance of pharmacokinetic considerations in assessing and ranking endocrine-active chemicals based on in vitro, high-throughput screening assays. Subsequent work has focused on understanding the effect of various parameters, such as using free plasma concentration as a surrogate for total plasma concentration and comparing multiple modeling approaches and was published in FY 2018.
Evaluation of Tox21 data for predicting acute oral toxicity Warren Casey, Nicole Kleinstreuer	This project is determining 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 LD_{50} data to determine which tests or combinations of tests best characterize the rat oral toxicity data. The analysis 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. A global collaboration to use quantitative structure-activity relationships, Tox21, and other alternative sources to predict acute oral toxicity has been initiated. Consensus models have been built as a result of the collaboration and a manuscript is being drafted.
Evaluation and qualification of in silico methods for predicting metabolism Stephen Ferguson	This evaluation of various in silico methods for predicting the extent of xenobiotic metabolism is also identifying metabolites and for prioritizing chemicals in the Tox21 10K library. Computational methods are used to partition the 10K library and develop subsets of chemicals that are likely to be metabolized appreciably in humans.
Selection of a target set of genes for use in a high-throughput transcriptomics screen Richard Paules, Scott Auerbach, Elizabeth Maull, Alex Merrick, Nisha Sipes	This project includes identifying patterns of exposure-induced biological responses to characterize toxicity and disease pathways and facilitate extrapolation of findings from model species to humans. Criteria were developed for selecting the best target set of genes representing humans, rats, mice, and zebrafish. A manuscript describing this work was published in FY 2018. A manuscript describing the gene selection process for the creation of a zebrafish S1500+ gene set is in preparation for submission in early 2019.
Development of a computational model for androgen receptor pathway activity Warren Casey, Nicole Kleinstreuer	This integration of data from nine Tox21 and ToxCast assays into a computational model will be used to predict agonist and antagonist activity against the androgen receptor pathway. A manuscript describing this work was published in FY 2017. A follow-up manuscript comparing the results of the computational model against

Project Study Scientist	Project Summary
	reference chemicals derived from an in vivo database was published in FY 2018.
Development of quantitative structure-activity relationship (QSAR) models to predict nuclear receptor-mediated endocrine activity Warren Casey, Nicole Kleinstreuer	Using the computational model of the androgen receptor pathway, NICEATM developed QSAR models to predict androgen receptor binding and activity. These QSAR models are currently being refined, with a goal of using them to predict androgen receptor pathway activity of chemicals in the EPA Endocrine Disruptor Screening Program. A manuscript is expected to be submitted in late 2018 or early 2019.
Development of reference databases for androgen receptor activity Warren Casey, Nicole Kleinstreuer	To develop a reference chemical list for in vitro androgen receptor binding and transactivation assay activity, NICEATM conducted 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 was made available to the public on the NTP website and manuscript describing this work was published, both in FY 2017. A parallel data curation effort with OECD and EPA partners focused on in vivo androgen activity data. These data will be used for evaluating high-throughput screening approaches, testing strategies, and further development of alternative test methods. A manuscript describing this work was published in FY 2018.
Tox21 assay target mapping and Bayesian network modeling Warren Casey, Nicole Kleinstreuer	NICEATM is mapping Tox21/ToxCast assay targets to known modes of action for developmental toxicity, acute toxicity, and carcinogenicity. Carcinogenicity assay target mapping is informed by the key characteristics of carcinogens and the hallmarks of cancer. Mapped assays are being combined with in silico features to build Bayesian network models to provide probabilistic predictions of chemical hazard. A manuscript describing this approach is being drafted.
Curation of high-throughput screening data Warren Casey, Nicole Kleinstreuer	NICEATM has curated high-throughput screening data from Tox21 and EPA ToxCast HTS program to identify and exclude low-confidence activity calls. Factors considered in the curation include chemical stability and purity information, robustness of concentration-response curve fits, and contextualization of active concentrations relative to testing range. These data are available through the NICEATM ICE database. ICE, launched in 2017, provides high-quality, curated data from NICEATM and its partners as well as other data resources and tools to support development of new approaches for assessing chemical safety.
Evaluation of FXR-active chemicals identified from Tox21 screening Elizabeth Maull	To better characterize chemicals identified in Tox21 quantitative HTS assays as having farnesoid X receptor alpha agonist or antagonist activity, NICEATM and collaborators evaluated them using four experimental approaches. Experiments generally confirmed the Tox21 results, provided orthogonal data on protein-to-protein interactions and receptor docking, and translated those results to an *in vivo* system (larval medaka assay). The study, presented at the 2018 SOT meeting, demonstrated an approach to targeted evaluation of putative bioactivity derived from HTS data.

Project Study Scientist	Project Summary
Development of software and methods for performing genomic dose-response analysis Scott Auerbach	Methods and software were developed for performing genomic dose-response analysis to identify sensitive, screening-level potency estimates. An expert panel meeting to discuss the proposed method was held and software released in FY 2017. A manuscript describing NTP's method and approach, along with a manuscript describing the software, were published in FY 2018.
Evaluation of the in vivo genomic dose-response approach for identifying biological effect points of departure Mike DeVito, Will Gwinn, Scott Auerbach, Fred Parham	This evaluation focused on determining if dose-response modeling of toxicogenomics data from short-term, in vivo studies can be used to identify biological effect points of departure that are comparable in potency to those derived from long-term toxicity studies. A manuscript describing the findings from these studies will be published in FY 2019.
Tox21 Cross-Partner Project: Performance-Based Validation of Tox21 Assays Nicole Kleinstreuer	The goal of this project was to develop semi-automated approaches to identify reference chemicals for Tox21/ToxCast assay targets with EPA. A manuscript on "RefChemDB" was submitted in FY 2018. A manuscript is being drafted with NCATS and EPA co-authors on the analysis of Tox21 assays designed to measure luciferase inhibition and autofluorescence to identify interference reference chemicals and build structure-based models to predict assay interference; publication is expected in FY 2019.

Testing Projects

Project Study Scientist	Project Summary
Epigenetic changes in chemical toxicity Alex Merrick	This project is focused on determining methylation patterns on a genome-wide basis and validation of selected CpG sites (regions of DNA where a cytosine nucleotide occurs next to a guanine nucleotide) altered by chemical exposure. Methylation of CpG sites can turn a gene off, while demethylation can cause transcriptional activation. A generalized approach for methylated DNA enrichment has been developed and a manuscript describing this work is in press for publication in FY 2018.
Polycyclic aromatic hydrocarbons (PAHs) Stephen Ferguson	Studies are in progress evaluating approximately 20 PAHs considered relevant to human exposure in metabolism-competent HepaRG cells using multiplexed high-content screening assays and gene expression platforms.
Tox21 Cross-Partner Project: Predictive Modeling of Developmental Toxicity with Human Pluripotent Stem Cells Nicole Kleinstreuer	In this evaluation of approximately 80 chemicals in a metabolomic biomarker-based assay using human pluripotent stem cells, chemicals were selected based on ICH guidance, reference NTP in vivo studies, and relevance to the program. Testing has been completed and data analysis is underway. Data will be combined with EPA ToxCast results and IVIVE to build predictive models for developmental toxicity.
Genotoxicity testing projects	This evaluation of the genotoxicity of 19 test articles included in NTP's glyphosate toxicity study (formulations and neat compounds present as

Project Study Scientist	Project Summary
Kristine Witt, Stephanie Smith-Roe	active ingredients in the formulations) is using bacterial reverse mutation and in vitro mammalian cell micronucleus assays, as well as in vitro comet assays and the in vitro MultiFlow DNA Damage Assay to provide information on mode of action for compounds shown to have genotoxic activity. Efforts to further characterize the genotoxicity profile for several members of the cohosh family of botanical supplements continue, with in vitro comet assays planned. Results of the in vitro micronucleus studies conducted on 13 cohosh samples were published in 2018. A set of eight flame retardants of interest to the NTP is being evaluated for genotoxicity using the bacterial reverse mutation, in vitro micronucleus, and in vitro comet assays. Continued evaluation of tissue samples obtained from radiofrequency radiation-exposed rats to assess gene expression changes.
Tox21 Cross-Partner Project: Development of a common reference chemical data set for interpretation of high-throughput transcriptomic screening data Stephen Ferguson, Richard Paules, Suramya Waidyanatha	Reference chemicals with a rich legacy of molecular target interaction knowledge (e.g., IC_{50}, K_i, K_D, EC_{50}) are being leveraged to create a contextualized biological-response space in MCF-7 cells and 3D HepaRG spheroid culture models as a framework for the interpretation of future transcriptomic screening studies.

NTP WormTox Laboratory Projects

Project Study Scientist	Project Summary
Mitochondrial toxicants Windy Boyd, Mamta Behl, Jui-Hua Hsieh	This project determined 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 two manuscripts reporting the findings were published, the first in 2016 and the second in 2018.

Testing and Toxicology Studies

About Testing and Toxicology Studies

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

Disposition, Metabolism, and Toxicokinetic Studies

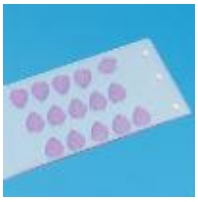
A list of substances evaluated through disposition, metabolism, and toxicokinetic studies.

Genetic Toxicity Studies

A list of substances tested for genetic toxicity.

Organ System Toxicity Studies

A list of substances tested for toxicity in organ systems.

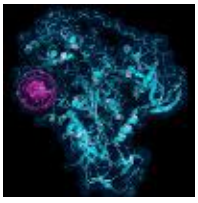


Modified One-Generation Reproduction Studies

A list of planned or ongoing modified one-generation studies in FY 2018.

Toxicology and Carcinogenicity Studies

A list of prechronic and chronic toxicity and carcinogenicity studies that were initiated, ongoing, or completed during FY 2018.



Toxicogenomic Studies

A list of planned or ongoing toxicogenomic studies in FY 2018.

About Testing and Toxicology Studies

The NTP testing program evaluates substances for a variety of health-related effects, generally using rodent models. For each test article, a study team develops an appropriate testing strategy to address the identified research needs, 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 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.

Studies initiated, ongoing, or completed in 2018 are listed in this section.

Related Links:

Disposition, Metabolism, and Toxicokinetic Studies

Genetic Toxicity Studies

Organ System Toxicity Studies

Modified One-Generation Reproduction Studies

Toxicology and Carcinogenicity Studies

Toxicogenomic Studies

Disposition, Metabolism, and Toxicokinetic Studies

Complete dosimetry of a chemical or physical agent describes its absorption, distribution, metabolism, and excretion in the body of both humans and test animals at differing levels of exposure, of all ages, via several routes of exposure, and under varying genetic backgrounds. Substances evaluated during FY 2018 are listed below.

Disposition, Metabolism, and Toxicokinetics Studies during FY 2018

Test Article	CASRN*	Species	Route	Status	Study Scientist
2-Ethylhexyl p-methoxycinnamate	5466-77-3	Rats	Dosed-feed, gavage, intravenous	Ongoing	Barry McIntyre
2-((1-(4-Phenoxyphenoxy)propan-2-yl)oxy)pyridine	95737-68-1	Rats, Rabbit	Gavage	Ongoing	Barry McIntyre
Bisphenol AF	1478-61-1	Mice, Rats	Gavage, intravenous	Ongoing	Veronica Godfrey Robinson
Efavirenz	154598-52-4	Mice	Gavage	Completed	Barry McIntyre
Emtricitabine	143491-57-0	Mice	Gavage	Completed	Barry McIntyre
Phenolic benzotriazoles (2-(2H-benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl)phenol)	70321-86-7	Rats	Gavage, intravenous	Ongoing	Chad Blystone
Phenolic benzotriazoles (2-(2H-benzotriazol-2-yl)-4-tert-butylphenol)	3147-76-0	Rats	Gavage, intravenous	Ongoing	Chad Blystone
Phenolic benzotriazoles (2-(2H-Benzotriazol-2-yl)phenol)	10096-91-0	Rats	Gavage, intravenous	Ongoing	Chad Blystone
Phenolic benzotriazoles (2-(5-Chloro-2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)phenol)	3864-99-1	Rats	Gavage, intravenous	Ongoing	Chad Blystone
Phenolic benzotriazoles (3-(2H-Benzotriazol-2-yl)-5-(1,1-dimethylethyl)-4-hydroxybenzenepropanoic acid, octyl ester)	84268-23-5	Rats	Gavage, intravenous	Ongoing	Chad Blystone
Phenolic benzotriazoles (Bumetrizole)	3896-11-5	Rats	Gavage, intravenous	Ongoing	Chad Blystone
Phenolic benzotriazoles (Drometrizole)	2440-22-4	Rats	Gavage, intravenous	Ongoing	Chad Blystone
Polyethylene glycol monomethyl ether	N/A	Rats	Subcutaneous injection	Ongoing	Nigel Walker

Test Article	CASRN*	Species	Route	Status	Study Scientist
Sulfolane	126-33-0	Mice, Rats	Gavage, intravenous	Ongoing	Chad Blystone
Tenofovir Disoproxil Fumarate (TDF)	202138-50-9	Mice	Gavage	Completed	Barry McIntyre
Tricombination FTC:TDF:EFV (1:1.5:3)	N/A	Mice	Gavage, intravenous	Completed	Barry McIntyre
Tris(chloropropyl)phosphate	13674-84-5	Mice, Rats	Gavage, intravenous	Completed	Kristen Ryan
Vinpocetine	42971-09-5	Rats	Gavage	Completed	Natasha Catlin

*CASRN = Chemical Abstracts Service Registry Number

Related Links:

Genetic Toxicity Studies

Organ System Toxicity Studies

Modified One-Generation Reproduction Studies

Toxicology and Carcinogenicity Studies

Toxicogenomic Studies

Genetic Toxicity Studies

Genetic toxicity test results are used to help interpret general toxicity, carcinogenicity, or other in vivo test results and to provide a database for use in structure-activity relationship analysis. Substances evaluated during FY 2018 are listed below.

Genetic Toxicity Studies in FY 2018

Test Article	CASRN*	Species/ Cell Line	Testing Battery	Status	Study Scientist
1,2,4-Trimethylbenzene	95-63-6	Mice	Micronucleus in vivo	Ongoing	Kristine Witt
1,2,4-Trimethylbenzene	95-63-6	Rats	Micronucleus in vivo	Ongoing	Kristine Witt
1020 Long multiwalled carbon nanotube	N/A	Mice	Micronucleus in vivo	Ongoing	Kristine Witt
1020 Long multiwalled carbon nanotube	N/A	Rats	Micronucleus in vivo	Ongoing	Kristine Witt
1H-Isoindole-1,3(2H)-diimine	3468-11-9	TK6 cells	Micronucleus in vitro	Planned	Kristine Witt
1H-Isoindole-1,3(2H)-diimine	3468-11-9	Salmonella	Salmonella	Ongoing	Kristine Witt
2-(Thiocyanomethylthio)benzothiazole	21564-17-0	TK6 cells	Micronucleus in vitro	Planned	Kristine Witt
2-(Thiocyanomethylthio)benzothiazole	21564-17-0	Salmonella	Salmonella	Ongoing	Kristine Witt
2,2'-Dimorpholinodiethyl ether	6425-39-4	Salmonella	Salmonella	Completed	Kristine Witt
2,2'-Dimorpholinodiethyl ether	6425-39-4	Mice	Micronucleus in vivo	Ongoing	Kristine Witt
2,2'-Dimorpholinodiethyl ether	6425-39-4	Rats	Micronucleus in vivo	Ongoing	Kristine Witt
2-Acetylaminofluorene	53-96-3	Rats	Comet assay	Completed	Kristine Witt
2-Chloro-N-(2-methyl-4-bromophenyl)acetamide	96686-51-0	Salmonella	Salmonella	Ongoing	Kristine Witt
2-Chloro-N-(2-methyl-4-bromophenyl)acetamide	96686-51-0	TK6 cells	Micronucleus in vitro	Planned	Kristine Witt
2-Hydroxy-4-methoxybenzophenone	131-57-7	Salmonella	Salmonella	Completed	Kristine Witt
4-(Hexyloxy)phenol	18979-55-0	TK6 cells	Micronucleus in vitro	Planned	Kristine Witt
4-(Hexyloxy)phenol	18979-55-0	Salmonella	Salmonella	Ongoing	Kristine Witt

Test Article	CASRN*	Species/ Cell Line	Testing Battery	Status	Study Scientist
Acrylamide	79-06-1	Mice	Comet assay	Completed	Kristine Witt
Bisphenol S	80-09-1	Rats (female dams)	Micronucleus in vivo	Planned	Kristine Witt
Bisphenol S	80-09-1	Rats (PND28 pups)	Micronucleus in vivo	Planned	Kristine Witt
Black cohosh	84776-26-1	Salmonella	Salmonella	Completed	Kristine Witt
Cell phone radiation: CDMA	N/A	Mice	Comet assay	Completed	Kristine Witt
Cell phone radiation: CDMA	N/A	Rats	Comet assay	Completed	Kristine Witt
Cell phone radiation: GSM	N/A	Mice	Comet assay	Completed	Kristine Witt
Cell phone radiation: GSM	N/A	Rats	Comet assay	Completed	Kristine Witt
Deoxynivalenol	51481-10-8	Rats	Micronucleus in vivo	Ongoing	Kristine Witt
Dipentaerythritol pentaacrylate	60506-81-2	TK6 cells	Micronucleus in vitro	Planned	Kristine Witt
Dipentaerythritol pentaacrylate	60506-81-2	Salmonella	Salmonella	Ongoing	Kristine Witt
Dipyrithione	3696-28-4	TK6 cells	Micronucleus in vitro	Planned	Kristine Witt
Dipyrithione	3696-28-4	Salmonella	Salmonella	Ongoing	Kristine Witt
Echinacea purpurea root extract	90028-20-9	Rats (female dams)	Micronucleus in vivo	Planned	Kristine Witt
Echinacea purpurea root extract	90028-20-9	Rats (PND28 pups)	Micronucleus in vivo	Planned	Kristine Witt
Echinacea purpurea root extract	90028-20-9	Rats (90 day)	Micronucleus in vivo	Planned	Kristine Witt
Emtricitabine (FTC)	143491-57-0	Mice	Comet assay	Completed	Kristine Witt
Indium trichloride	10025-82-8	TK6 cells	Micronucleus in vitro	Completed	Kristine Witt
N-Butylbenzenesulfonamide	3622-84-2	Mice	Micronucleus in vivo	Ongoing	Kristine Witt

Test Article	CASRN*	Species/ Cell Line	Testing Battery	Status	Study Scientist
N-Butylbenzenesulfonamide	3622-84-2	Rats	Micronucleus in vivo	Ongoing	Kristine Witt
N-Nitrosodimethylamine	62-75-9	Rats	Comet assay	Planned	Kristine Witt
p-Chloro-a,a,a-trifluorotoluene	98-56-6	Salmonella	Salmonella	Completed	Kristine Witt
Phenolic benzotriazoles (2-(2H-benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl)phenol)	70321-86-7	Rats	Micronucleus in vivo	Ongoing	Kristine Witt
Phenolic benzotriazoles (2-(2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylpropyl)phenol)	25973-55-1	Rats	Micronucleus in vivo	Ongoing	Kristine Witt
Phenolic benzotriazoles (2-(2H-Benzotriazol-2-yl)-4-tert-butylphenol)	3147-76-0	Rats	Micronucleus in vivo	Ongoing	Kristine Witt
Phenolic benzotriazoles (2-(2H-Benzotriazol-2-yl)phenol)	10096-91-0	Rats	Micronucleus in vivo	Ongoing	Kristine Witt
Phenolic benzotriazoles (2-(5-Chloro-2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)phenol)	3864-99-1	Rats	Micronucleus in vivo	Ongoing	Kristine Witt
Phenolic benzotriazoles (3-(2H-Benzotriazol-2-yl)-5-(1,1-dimethylethyl)-4-hydroxybenzenepropanoic acid, octyl ester)	84268-23-5	Rats	Micronucleus in vivo	Completed	Kristine Witt
Phenolic benzotriazoles (Bumetrizole)	3896-11-5	Rats	Micronucleus in vivo	Ongoing	Kristine Witt
Phenolic benzotriazoles (Drometrizole)	2440-22-4	Rats	Micronucleus in vivo	Ongoing	Kristine Witt
Phenolic benzotriazoles (Octrizole)	3147-75-9	Rats	Micronucleus in vivo	Ongoing	Kristine Witt
Potassium dicyanoaurate	13967-50-5	TK6 cells	Micronucleus in vitro	Planned	Kristine Witt
Potassium dicyanoaurate	13967-50-5	Salmonella	Salmonella	Ongoing	Kristine Witt
Pubertal vinclozolin study	50471-44-8	Mice	Comet assay	Completed	Kristine Witt
Sodium metavanadate	13718-26-8	Mice	Micronucleus in vivo	Ongoing	Kristine Witt
Sodium metavanadate	13718-26-8	Rats	Micronucleus in vivo	Ongoing	Kristine Witt
Sodium tungstate dihydrate	10213-10-2	Mice	Comet assay	Completed	Kristine Witt

Test Article	CASRN*	Species/ Cell Line	Testing Battery	Status	Study Scientist
Sodium tungstate dihydrate	10213-10-2	Rats	Comet assay	Completed	Kristine Witt
Stachybotrys chartarum	67892-26-6	Mice	Micronucleus in vivo	Ongoing	Kristine Witt
Sulfolane	126-33-0	Mice	Micronucleus in vivo	Completed	Kristine Witt
Sulfolane	126-33-0	Rats	Micronucleus in vivo	Completed	Kristine Witt
Triclosan	3380-34-5	Rats (female dams)	Micronucleus in vivo	Planned	Kristine Witt
Tris(4-chlorophenyl)methane	27575-78-6	Rats	Micronucleus in vivo	Ongoing	Kristine Witt
Vanadyl sulfate	27774-13-6	Mice	Micronucleus in vivo	Ongoing	Kristine Witt
Vanadyl sulfate	27774-13-6	Rats	Micronucleus in vivo	Ongoing	Kristine Witt
Vincristine sulfate salt	2068-78-2	Rats	Comet assay	Completed	Kristine Witt
Vinpocetine	42971-09-5	Mice	Micronucleus in vivo	Completed	Kristine Witt
Vinpocetine	42971-09-5	TK6 cells	Micronucleus in vitro	Completed	Kristine Witt
Vinpocetine	42971-09-5	Mice	Comet assay	Completed	Kristine Witt

*CASRN = Chemical Abstracts Service Registry Number

Related Links:

Disposition, Metabolism, and Toxicokinetic Studies

Organ System Toxicity

Modified One-Generation Reproduction Studies

Toxicology and Carcinogenicity Studies

Toxicogenomic Studies

Organ System Toxicity Studies

NTP studies toxicity of environmental substances on development, reproduction, and on the nervous and immune systems. Organ systems toxicity studies conducted during FY 2018 are listed below.

Neurotoxicity, Developmental Toxicity, and Reproductive Toxicity Studies during FY 2018

Test Article	CASRN*	Species	Testing Battery	Length	Route	Status	Study Scientist
2-((1-(4-Phenoxyphenoxy)propan-2-yl)oxy)pyridine	95737-68-1	Rabbit	Teratology pilot	GD 7-28	Gavage	Initiated	Vicki Sutherland
2-((1-(4-Phenoxyphenoxy)propan-2-yl)oxy)pyridine	95737-68-1	Rabbit	Conventional teratology	GD 7-28	Gavage	Initiated	Vicki Sutherland
3,3',4,4'-Tetrachloroazobenzene	14047-09-7	Rats	Immunotoxicity	28 days	Gavage	Ongoing	Mamta Behl
2,3-Butanedione	431-03-8	Mice	Immunotoxicity	28 days	Inhalation	Ongoing	Dan Morgan
Benz(j)aceanthrylene	202-33-5	Mice	Immunotoxicity	28 days	Gavage	Initiated	Cynthia Rider
Dibenz(a,h)anthracene	53-70-3	Mice	Immunotoxicity	28 days	Gavage	Ongoing	Cynthia Rider
Dibenz(a,h)anthracene	53-70-3	Mice	Immunotoxicity	28 days	Subcutaneous injection	Ongoing	Cynthia Rider
Dibenzo(a,l)pyrene	191-30-0	Mice	Immunotoxicity	28 days	Gavage	Ongoing	Cynthia Rider
Dibenzothiophene	132-65-0	Mice	Immunotoxicity	28 days	Gavage	Ongoing	Cynthia Rider
Perfluorodecanoic acid	335-76-2	Rats	Immunotoxicity	28 days	Gavage	Ongoing	Chad Blystone
Vinclozolin	50471-44-8	Rats	Continuous breeding	9 months	Gavage	Ongoing	Barry McIntyre
Tenofovir disoproxil fumarate (TDF)	202138-50-9	Mice	Teratology pilot	GD 5 - PND 21	Gavage	Ongoing	Anika Dzierlenga
dibenzo(a,l)pyrene	191-30-0	Mice	Immunotoxicity	28 days	Gavage	Ongoing	Cynthia Rider
Dibenzothiophene	132-65-0	Mice	Immunotoxicity	28 days	Gavage	Ongoing	Cynthia Rider
Perfluorodecanoic acid	335-76-2	Rats	Immunotoxicity	28 days	Gavage	Ongoing	Chad Blystone

Test Article	CASRN*	Species	Testing Battery	Length	Route	Status	Study Scientist
1020 Long multiwalled carbon nanotube	N/A	Rats	Immunotoxicity	30 days	Inhalation	Ongoing	Dan Morgan
1020 Long multiwalled carbon nanotube	N/A	Mice	Immunotoxicity	30 days	Inhalation	Ongoing	Dan Morgan
1020 Long multiwalled carbon nanotube	N/A	Mice	Immunotoxicity	90 days	Inhalation	Ongoing	Dan Morgan
2-((1-(4-Phenoxyphenoxy)propan-2-yl)oxy)pyridine	95737-68-1	Rats	Conventional teratology	GD 6-21	Gavage	Ongoing	Vicki Sutherland
2-((1-(4-Phenoxyphenoxy)propan-2-yl)oxy)pyridine	95737-68-1	Rabbit	Conventional teratology	GD 7-28	Gavage	Ongoing	Vicki Sutherland
2-((1-(4-Phenoxyphenoxy)propan-2-yl)oxy)pyridine	95737-68-1	Rats	Immunotoxicity	28 days	Gavage	Ongoing	Vicki Sutherland, Barry McIntyre
2-Hydroxy-4-methoxybenzophenone	131-57-7	Rats	Developmental toxicity	GD 6 to PND 21	Dosed-feed	Ongoing	Dr. D. Hansen
4-Methylcyclohexanemethanol	34885-03-5	Mice	Immunotoxicity	7 days	Topical application	Ongoing	Scott Auerbach
4-Methylimidazole	822-36-6	Rats	Continuous breeding	Continuous	Dosed-feed	Ongoing	Mamta Behl
Acenaphthenequinone	82-86-0	Mice	Immunotoxicity	28 days	Gavage	Ongoing	Cynthia Rider
Arsenic	7440-38-2	Rats	Developmental toxicity	Pregnant dams through PND21	Gavage & dosed-water	Completed	Nigel Walker
Benzo(a)pyrene	50-32-8	Mice	Immunotoxicity	28 days	Gavage	Ongoing	Cynthia Rider
Benzo(b)fluoranthene	205-99-2	Mice	Immunotoxicity	28 days	Gavage	Initiated	Cynthia Rider
Benzo(c)fluorene	205-12-9	Mice	Immunotoxicity	28 days	Gavage	Initiated	Cynthia Rider
Benzo(k)fluoranthene	207-08-9	Mice	Immunotoxicity	28 days	Gavage	Initiated	Cynthia Rider
Bisphenol AF	1478-61-1	Rats	Immunotoxicity	GD 6 - PND 96	Dosed-feed	Ongoing	Vicki Sutherland

Test Article	CASRN*	Species	Testing Battery	Length	Route	Status	Study Scientist
Chrysene	218-01-9	Mice	Immunotoxicity	28 days	Gavage	Ongoing	Cynthia Rider
Crude 4-Methylcyclohexanemethanol	N/A	Mice	Immunotoxicity	7 days	Topical application	Ongoing	Scott Auerbach
Diisobutyl phthalate	84-69-5	Rats	Continuous breeding	Continuous	Dosed-feed	Ongoing	Chad Blystone
Echinacea purpurea root extract	90028-20-9	Rats	Immunotoxicity	28 days	Gavage	Planned	Kristen Ryan
Gum guggul extract	N/A	Mice	Immunotoxicity	28 days	Gavage	Ongoing	Dori Germolec
Indeno(1,2,3-cd)pyrene	193-39-5	Mice	Immunotoxicity	28 days	Gavage	Initiated	Cynthia Rider
Lovastatin	75330-75-5	Mice	Immunotoxicity	28 days	Gavage	Ongoing	Dori Germolec
N-Butylbenzenesulfonamide	3622-84-2	Rats	Immunotoxicity	GD 6 - PND 42	Dosed-feed	Ongoing	Cynthia Rider
Nelfinavir mesylate	159989-65-8	Mice	Immunotoxicity	28 days	Gavage	Ongoing	Dori Germolec
Phenanthrene	85-01-8	Mice	Immunotoxicity	28 days	Gavage	Ongoing	Cynthia Rider
Pyrene	129-00-0	Mice	Immunotoxicity	28 days	Gavage	Ongoing	Cynthia Rider
Sodium metavanadate	13718-26-8	Mice	Immunotoxicity	28 days	Dosed-water	Ongoing	Georgia Roberts
Sulfolane	126-33-0	Mice	Immunotoxicity	13 weeks	Gavage	Ongoing	Chad Blystone
Sulfolane	126-33-0	Rats	Immunotoxicity	13 weeks	Gavage	Ongoing	Chad Blystone
Tricombination FTC:TDF:EFV (1:1.5:3)	N/A	Mice	Teratology pilot	GD 5-18, GD 5-15	Gavage	Ongoing	Barry McIntyre
Tricresyl phosphate	1330-78-5	Rats	Immunotoxicity	21 days	Dosed-feed	Planned	Mamta Behl
Tris(Chloropropyl)phosphate	13674-84-5	Rats	Immunotoxicity	GD 6 - PND 127	Dosed-feed	Ongoing	Kristen Ryan

*CASRN = Chemical Abstracts Service Registry Number

Related Links:

Disposition, Metabolism, and Toxicokinetic Studies

Genetic Toxicity Studies

Modified One-Generation Reproduction Studies

Toxicology and Carcinogenicity Studies

Toxicogenomic Studies

Modified One-Generation Reproduction Studies

NTP modified one-generation study design emphasizes a full evaluation of the first-generation offspring of 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. Planned or ongoing modified one-generation studies are listed below.

Modified One-Generation Studies in FY 2018

Test Article	CASRN*	Species	Testing Battery	Status	Study Scientist
Bisphenol AF	1478-61-1	Rats	Dose range finding	Ongoing	Vicki Sutherland
Echinacea purpurea root extract	90028-20-9	Rats	Conventional teratology	Ongoing	Kristen Ryan
Echinacea purpurea root extract	90028-20-9	Rats	Fertility assessment	Ongoing	Kristen Ryan
Echinacea purpurea root extract	90028-20-9	Rats	Subchronic	Ongoing	Kristen Ryan
Resveratrol	501-36-0	Rats	Developmental toxicity, F0 generation, fertility assessment	Ongoing	Anika Dzierlenga
2,2'-Dimorpholinodiethyl ether	6425-39-4	Rats	Repeated dose	Ongoing	Georgia Roberts
2-Ethylhexyl p-methoxycinnamate	5466-77-3	Rats	Subchronic	Ongoing	Barry McIntyre
2-Hydroxy-4-methoxybenzophenone	131-57-7	Rats	Developmental toxicity	Ongoing	Barry McIntyre
Bisphenol S	80-09-1	Rats	Dose range finding	Ongoing	Vicki Sutherland
Bisphenol S	80-09-1	Rats	F0 Generation	Planned	Vicki Sutherland
Boric acid	10043-35-3	Rats	Dose range finding	Ongoing	AtLee Watson
Deoxynivalenol	51481-10-8	Rats	Dose range finding	Ongoing	Dori Germolec
Echinacea purpurea root extract	90028-20-9	Rats	Dose range finding	Ongoing	Kristen Ryan
Ethylene glycol 2-ethylhexyl ether	1559-35-9	Rats	Dose range finding	Ongoing	Chad Blystone
Hydroquinone	123-31-9	Rats	Dose range finding	Planned	Vicki Sutherland

Test Article	CASRN*	Species	Testing Battery	Status	Study Scientist
N-Butylbenzenesulfonamide	3622-84-2	Rats	F0 generation	Ongoing	Cynthia Rider
N-Butylbenzenesulfonamide	3622-84-2	Rats	Maternal transfer	Ongoing	Cynthia Rider
N-Butylbenzenesulfonamide	3622-84-2	Rats	Developmental toxicity	Ongoing	Cynthia Rider
N-Butylbenzenesulfonamide	3622-84-2	Rats	Neurotoxicology assessment	Ongoing	Cynthia Rider
N-Butylbenzenesulfonamide	3622-84-2	Rats	Subchronic	Ongoing	Cynthia Rider
Simvastatin	79902-63-9	Rats	Dose range finding	Ongoing	Barry McIntyre
Triclosan	3380-34-5	Rats	Dose range finding	Ongoing	Vicki Sutherland
Tricombination FTC:TDF:EFV (1:1.5:3)	N/A	Mice	F0 generation	Initiated	Anika Dzierlenga
Tricombination FTC:TDF:EFV (1:1.5:3)	N/A	Mice	Subchronic	Planned	Anika Dzierlenga
Tricombination ABC:DTG:3TC	N/A	Rats	Dose range finding	Planned	Kristen Ryan
Tris(4-chlorophenyl)methane	27575-78-6	Rats	Dose range finding	Ongoing	Troy Hubbard
Valerian (Valeriana officinalis L.) root extract	8057-49-6	Rats	Dose range finding	Ongoing	Georgia Roberts

*CASRN = Chemical Abstracts Service Registry Number

Related Links:

Disposition, Metabolism, and Toxicokinetic Studies

Genetic Toxicity Studies

Organ System Toxicity Studies

Toxicology and Carcinogenicity Studies

Toxicogenomic Studies

Toxicology and Carcinogenicity Studies

NTP performs toxicity studies to provide dose-setting information for chronic studies and to address specific deficiencies in the toxicology database for the chemical. Toxicology and carcinogenicity studies fall into two categories: prechronic toxicity studies and chronic 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 Reproductive and Developmental Toxicity of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP) (May 2011). Prechronic and chronic toxicity studies and carcinogenicity studies, that were initiated, ongoing, or completed during FY 2018, are listed below.

Prechronic Toxicology and Carcinogenicity Studies FY 2018

Test Article	CASRN*	Species	Length	Route	Status	Study Scientist
1,2,4-Trimethylbenzene	95-63-6	Mice, rats	13 weeks	Inhalation	Ongoing	Dan Morgan
1,2-Bis(2,4,6-tribromophenoxy)ethane	37853-59-1	Rats	5 days	Gavage	Ongoing	June Dunnick
1,2-bis(pentabromophenyl)ethane	84852-53-9	Rats	5 days	Gavage	Completed	June Dunnick
1,3,5,7,9,11-Hexabromocyclododecane	25637-99-4	Rats	5 days	Gavage	Completed	June Dunnick
1020 Long multiwalled carbon nanotube	N/A	Mice, rats	30 days	Inhalation	Ongoing	Dan Morgan
1020 Long multiwalled carbon nanotube	N/A	Mice, rats	2 years	Inhalation	Ongoing	Dan Morgan
2,2',4,4'-Tetrabromodiphenyl ether	5436-43-1	Rats	5 days	Gavage	Completed	June Dunnick
2,2'-Dimorpholinodiethyl ether	6425-39-4	Mice	28 days	Gavage	Ongoing	Troy Hubbard
2,3-Butanedione	431-03-8	Mice, rats	2 years	Inhalation	Completed	Dan Morgan
2-ethylhexyl-2,3,4,5-tetrabromobenzoate	183658-27-7	Rats	5 days	Gavage	Completed	June Dunnick
2-ethyltoluene	611-14-3	Mice, rats	2 weeks, 90 days	Inhalation	Initiated	Dan Morgan
2-Hydroxy-4-methoxybenzophenone	131-57-7	Mice, rats	2 years	Dosed-feed	Ongoing	Barry McIntyre
3,3',4,4'-Tetrachloroazobenzene	14047-09-7	Rats	5 days	Gavage	Ongoing	Mamta Behl
Acetaminophen (4-hydroxyacetanilide)	103-90-2	Rats	90 days	Gavage	Initiated	Vicki Sutherland
Acrylamide	79-06-1	Rats	5 days	Gavage	Ongoing	William Gwinn
Aging cohort study: 12951/SvlmJ mouse	N/A	Mice	2 years	Not applicable	Ongoing	June Dunnick

Test Article	CASRN*	Species	Length	Route	Status	Study Scientist
Aging cohort study: A/J mouse	N/A	Mice	2 years	Not applicable	Ongoing	June Dunnick
Aging cohort study: B6C3F1J mouse	N/A	Mice	2 years	Not applicable	Ongoing	June Dunnick
Aging cohort study: C3H/HeJ mouse	N/A	Mice	2 years	Not applicable	Ongoing	June Dunnick
Aging cohort study: C57/BL/6J mouse	N/A	Mice	2 years	Not applicable	Ongoing	June Dunnick
Aging cohort study: CAST/EiJ mouse	N/A	Mice	2 years	Not applicable	Ongoing	June Dunnick
Aging cohort study: NOD. B10Sn-H2(b)/J	N/A	Mice	2 years	Not applicable	Ongoing	June Dunnick
Aging cohort study: NZO/HiLtJ mouse	N/A	Mice	2 years	Not applicable	Ongoing	June Dunnick
Aging cohort study: PWK/PhJ mouse	N/A	Mice	2 years	Not applicable	Ongoing	June Dunnick
Aging cohort study: WSB/EIJ mouse	N/A	Mice	2 years	Not applicable	Ongoing	June Dunnick
Aloin	1415-73-2	Rats	13 weeks	Dosed-water	Completed	Alex Boudreau
alpha/beta Thujone mixture	76231-76-0	Rats	5 days	Gavage	Ongoing	William Gwinn
alpha-Pinene	80-56-8	Mice, rats	2 years	Inhalation	Ongoing	Cynthia Rider
Antimony trioxide	1309-64-4	Mice, rats	2 years	Inhalation	Completed	Matt Stout
Arsenic	7440-38-2	Mice, rats	acute	Gavage & dosed-water	Ongoing	Nigel Walker
Arsenic	7440-38-2	Monkey	acute	Gavage	Ongoing	Nigel Walker
Aspergillus fumigatus mold	N/A	Mice	13 weeks	Inhalation	Ongoing	Dori Germolec
Bis(2-ethylhexyl) tetrabromophthalate	26040-51-7	Rats	5 days	Gavage	Completed	June Dunnick
Bisphenol A	80-05-7	Rats	2 years	Gavage	Completed	Barry Delclos
Bisphenol AF	1478-61-1	Rats	5 days	Gavage	Ongoing	Vicki Sutherland
Bisphenol S	80-09-1	Mice	14 days	Dosed-feed	Ongoing	Vicki Sutherland
Black cohosh	84776-26-1	Mice, rats	2 years	Gavage	Ongoing	Chad Blystone

Test Article	CASRN*	Species	Length	Route	Status	Study Scientist
Brominated vegetable oil	8016-94-2	Rats	90 days	Dosed-feed	Ongoing	Nigel Walker
Cell phone radiation: CDMA	N/A	Mice, rats	2 years	Whole body exposure	Completed	Michael Wyde
Cell phone radiation: GSM	N/A	Mice, rats	2 years	Whole body exposure	Completed	Michael Wyde
Coumarin	91-64-5	Rats	5 days	Gavage	Ongoing	June Dunnick
Crumb rubber various	N/A	Mice	14 days	N/A	Completed	Georgia Roberts
Damp building mold mixture	N/A	Mice	90 days	Inhalation	Planned	Dori Germolec
Decabromodiphenyl ether	1163-19-5	Rats	5 days	Gavage	Completed	June Dunnick
Di(2-ethylhexyl) phthalate	117-81-7	Rats	5 days	Gavage	Ongoing	Troy Hubbard
Di(2-ethylhexyl) phthalate	117-81-7	Rats	Perinatal + 2 years, 2 years	Dosed-feed	Ongoing	Paul Foster
Dibutyl Phthalate	84-74-2	Mice, rats	2 years	Dosed-feed	Ongoing	Chad Blystone
Dimethylamine borane	74-94-2	Mice	2 weeks	Dermal	Completed	AtLee Watson
Ethinyl estradiol	57-63-6	Rats	5 days	Gavage	Ongoing	William Gwinn
Fenofibrate	49562-28-9	Rats	5 days	Gavage	Ongoing	Barry McIntyre
Furan	110-00-9	Rats	5 days	Gavage	Ongoing	William Gwinn
Garcinia cambogia extract	90045-23-1	Mice, rats	14 days	Dosed-feed	Ongoing	Cynthia Rider
Ginkgo biloba extract	90045-36-6	Rats	5 days	Gavage	Completed	Cynthia Rider
Ginseng	50647-08-0	Rats	5 days	Gavage	Ongoing	Po Chan
Goldenseal extract	84603-60-1	Rats	5 days	Gavage	Completed	Cynthia Rider
Green tea extract	N/A	Rats	5 days	Gavage	Completed	Cynthia Rider
Hexachlorobenzene	118-74-1	Rats	5 days	Gavage	Ongoing	Mike Devito
Hexachlorobenzene	118-74-1	Rats	90 days	Gavage	Ongoing	Mike Devito
Hexachlorocyclopentadienyl-dibromocyclooctane	51936-55-1	Rats	5 days	Gavage	Completed	June Dunnick

Test Article	CASRN*	Species	Length	Route	Status	Study Scientist
Insertional mutagenesis – definitive vector study	N/A	Mice	14 months	Intravenous	Completed	Dori Germolec
Ionic liquid: 1-Butyl-1-methylpyrrolidinium Chloride	479500-35-1	Mice, rats	90 days	Dosed-water	Ongoing	Kristen Ryan
Ionic liquid: 1-Butyl-3-methylimidazolium Chloride	79917-90-1	Mice, rats	90 days	Dosed-water	Ongoing	Kristen Ryan
Ionic liquid: 1-Ethyl-3-methylimidazolium Chloride	65039-09-0	Mice, rats	90 days	Dosed-water	Ongoing	Kristen Ryan
Ionic liquid: N-Butylpyridinium Chloride	1124-64-7	Mice, rats	90 days	Dosed-water	Ongoing	Kristen Ryan
Isopropylated phenol phosphate	68937-41-7	Mice	2 weeks	Dosed-feed	Ongoing	Mamta Behl
Libby amphibole 2007	N/A	Rats	30 days	Inhalation	Planned	Matt Stout
Melamine + cyanuric acid combination	N/A	Rats	90 days	Gavage	Ongoing	Gonçalo Gamboa da Costa
Melamine + cyanuric acid combination	N/A	Not Applicable	N/A	Not Applicable	Ongoing	Nigel Walker
Melamine + cyanuric acid combination	N/A	Rats	90 days + recovery	Gavage	Ongoing	Gonçalo Gamboa da Costa
Methyleugenol	93-15-2	Rats	5 days	Gavage	Ongoing	William Gwinn
Microbiome	N/A	Not Applicable	N/A	Not Applicable	Ongoing	Carl Cerniglia
Microcystin LR	101043-37-2	Mice	Gestation day 6 to postnatal day 35	Gavage	Planned	Vicki Sutherland
Milk thistle extract	84604-20-6	Rats	5 days	Gavage	Ongoing	June Dunnick
Mixed xylenes	N/A	Mice, rats	30 days	Inhalation	Planned	Dan Morgan
N-Butylbenzenesulfonamide	3622-84-2	Mice, rats	14 days, 13 weeks	Dosed-feed	Completed	Cynthia Rider
p-Chloro-a,a,a-trifluorotoluene	98-56-6	Mice, rats	90 days	Inhalation	Completed	Matt Stout
PCN 66/67 comparison study	N/A	Rats	2 weeks	Gavage	Ongoing	Mike Devito
PCN 66/67 comparison study	N/A	Rats	13 weeks	Gavage	Ongoing	Mike Devito
Pentabromodiphenyl ether mixture [DE-71 (technical grade)]	32534-81-9	Rats	5 days	Gavage	Ongoing	June Dunnick
Perfluorohexanoic acid (PFHXA)	307-24-4	Rats	28 days	Gavage	Ongoing	Chad Blystone
Perfluorooctanoic acid	335-67-1	Rats	2 years	Dosed-feed	Ongoing	Chad Blystone

Test Article	CASRN*	Species	Length	Route	Status	Study Scientist
Perfluorooctanoic acid	335-67-1	Rats	5 days, 28 days	Gavage	Ongoing	Chad Blystone
Phenolic benzotriazoles (2-(2H-benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl)phenol)	70321-86-7	Rats	14 days	Gavage	Ongoing	Chad Blystone
Phenolic benzotriazoles (2-(2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylpropyl)phenol)	25973-55-1	Rats	14 days	Gavage	Ongoing	Chad Blystone
Phenolic benzotriazoles (2-(2H-Benzotriazol-2-yl)-4-tert-butylphenol)	3147-76-0	Rats	14 days	Gavage	Ongoing	Chad Blystone
Phenolic benzotriazoles (2-(2H-Benzotriazol-2-yl)phenol)	10096-91-0	Rats	14 days	Gavage	Ongoing	Chad Blystone
Phenolic benzotriazoles (2-(5-Chloro-2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)phenol)	3864-99-1	Rats	14 days	Gavage	Ongoing	Chad Blystone
Phenolic benzotriazoles (3-(2H-Benzotriazol-2-yl)-5-(1,1-dimethylethyl)-4-hydroxybenzenepropanoic acid, octyl ester)	84268-23-5	Rats	14 days	Gavage	Ongoing	Chad Blystone
Phenolic benzotriazoles (Bumetrizole)	3896-11-5	Rats	14 days	Gavage	Ongoing	Chad Blystone
Phenolic benzotriazoles (Drometrizole)	2440-22-4	Rats	14 days	Gavage	Ongoing	Chad Blystone
Phenolic benzotriazoles (Octrizole)	3147-75-9	Rats	14 days	Gavage	Ongoing	Chad Blystone
Pulegone	89-82-7	Rats	5 days	Gavage	Ongoing	Scott Auerbach
Resveratrol	501-36-0	Mice, rats	2 years	Gavage	Ongoing	Anika Dzierlenga
Sodium metavanadate	13718-26-8	Mice, rats	90 days	Dosed-water	Ongoing	Georgia Roberts
Sodium tungstate dihydrate	10213-10-2	Mice, rats	2 years	Dosed-water	Ongoing	Mamta Behl
Stachybotrys chartarum strain 1 mold (macrocyclic trichothecene chemotype)	N/A	Mice	90 days	Inhalation	Planned	Dori Germolec
Stachybotrys chartarum strain 2 mold (atranone chemotype)	N/A	Mice	90 days	Inhalation	Planned	Dori Germolec
Sulfolane	126-33-0	Guinea pigs, mice, rats	28 days	Gavage	Ongoing	Chad Blystone
Sulfolane	126-33-0	Mice, rats	2 years	Dosed-water	Ongoing	Chad Blystone

Test Article	CASRN*	Species	Length	Route	Status	Study Scientist
Tetrabromobisphenol A	79-94-7	Rats	5 days	Gavage	Ongoing	June Dunnick
Tetrabromobisphenol A-bis(2,3-dibromopropyl ether)	21850-44-2	Rats	90 days	Gavage	Completed	June Dunnick
Thallium (I) sulfate	7446-18-6	Mice	2 weeks	Dosed-water	Initiated	Troy Hubbard
Thallium (I) sulfate	7446-18-6	Rats	Gestation day 6 to postnatal day 28	Dosed-water	Initiated	Troy Hubbard
Triclosan	3380-34-5	Rats	5 days	Gavage	Ongoing	Vicki Sutherland
Triclosan	3380-34-5	Mice	2 years	Dermal	Ongoing	Jia-Long Fang
Trimethylsilyldiazomethane (TMSD)	18107-18-1	Mice, rats	10 days	Inhalation	Ongoing	William Gwinn
Triphenyl phosphate	115-86-6	Mice	2 weeks	Dosed-feed	Ongoing	Mamta Behl
Tris(chloropropyl)phosphate	13674-84-5	Rats	5 days	Gavage	Ongoing	Kristen Ryan
Tris(chloropropyl)phosphate	13674-84-5	Mice, rats	90 days	Dosed-feed	Ongoing	Kristen Ryan
Tris(chloropropyl)phosphate	13674-84-5	Mice, rats	2 years	Dosed-feed	Ongoing	Kristen Ryan
Valerian (Valeriana officinalis L.) root extract	8057-49-6	Mice	90 days	Gavage	Ongoing	Troy Hubbard
Vanadyl sulfate	27774-13-6	Mice, rats	90 days	Dosed-water	Ongoing	Georgia Roberts
Water damaged building mold mixture	N/A	Mice, rats	90 days	Inhalation	Planned	Dori Germolec
Water disinfection byproducts (Bromodichloroacetic acid)	71133-14-7	Rats	5 days	Gavage	Ongoing	Mike Devito
Zinc carbonate, basic	5263-02-5	Rats	2 years	Dosed-feed	Ongoing	Natasha Catlin

*CASRN = Chemical Abstracts Service Registry Number

Related Links:

Disposition, Metabolism, and Toxicokinetic Studies

Genetic Toxicity Studies

Organ System Toxicity Studies

Modified One-Generation Reproduction Studies

Toxicogenomic Studies

Toxicogenomic Studies

NTP is incorporating the latest toxicogenomic technologies into its testing program to gain further insights into the toxicity of environmental substances. Toxicogenomics examines how the entire genetic structure, or genome, influences an organism's response to environmental toxicants. Microarray, proteomic, metabolomics analyses, and next-generation (NextGen) sequencing are among the advanced technologies that NTP is using to study how chemical exposures change the expression of genes, proteins, and metabolites in targeted cells and tissues.

Measuring genome-wide changes in affected tissues could be useful for identifying disease biomarkers, detecting exposure to toxic substances, and understanding individual genetic susceptibilities. Once validated, biomarkers can be repeatedly sampled during long-term NTP studies to determine if chemical exposures can be detected or if developing diseases (e.g., cancer) provide a genetic signature.

NTP is investigating whether pattern analysis of gene expression can provide toxicity indicators at (1) earlier time points and (2) lower doses than are possible using traditional toxicological parameters. Evaluating patterns of gene expression is expected to provide insight into the pathogenesis of disease and how different rodent models respond to toxicants. In addition, metabolomics provides an opportunity to elucidate how chemicals affect metabolism within cells relative to changes in gene expression. Expression signatures linked to chemical exposures and apical measures are intended to contribute to NTP's efforts in predictive toxicology.

Several FY 2018 toxicogenomic studies used NextGen sequencing technologies, which improves gene expression analysis, including base pair-level resolution of accuracy and increased sensitivity compared to microarray platforms. Although microarray analysis is a stable and well-understood technology for assaying gene expression, NextGen sequencing methods like RNA-seq likely will become more common as sequencing costs decline and bioinformatic analyses become standardized and integrated with genomic sequencing.

One promising research area is the application of exome sequencing (Exome-Seq) to either frozen or formalin-fixed, paraffin-embedded 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 mutation insertions or deletions and other genetic abnormalities associated with disease. An additional area of development is the isolation of circulating, cell-free DNA (ccfDNA). DNA released from apoptosis or cell turnover normally appears in plasma, but chemical exposure can increase levels of ccfDNA due to toxicity, inflammation, or tumor development. The NTP is investigating the use and sequencing of ccfDNA in toxicology studies to determine its use as a new marker of chemical exposure.

Several NTP studies are using Exome-Seq for profiling mutations on a genome-wide scale to understand differences between spontaneous and chemically induced tumors. Another promising NextGen sequencing-related area in toxicogenomics is the S1500+ platform. This platform provides a way to use high-throughput transcriptomic screening for thousands of genes per sample and can be applied to both in vitro chemical toxicity screening and in vivo screening of RNA extracted from animal tissues.

NTP is evaluating study conditions that could 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 are underway to optimize methods for DNA and RNA extraction from archival tissues for molecular analysis. Planned or ongoing NTP toxicogenomic studies from FY 2018 are listed below.

Toxicogenomic Studies Planned or Ongoing in FY 2018

Chemical (CASRN*)	Species/Cell Line	Route	Duration	Test Type (Platform)	Study Scientist
Arsenite (7784-46-5)	Human prostate cell line	In vitro	30 weeks	NextGen sequencing Exome-Seq (Illumina)	Alex Merrick
2,3-Butanedione (diacetyl) (431-03-8) 2,3-Hexanedione (3848-24-6)	Human airway epithelium cell line	In vitro	4 days	High-throughput transcriptomic screening	William Gwinn
Bisphenol A and analogues (80-05-7)	Human hepatocyte cell line	In vitro	2 days	High-throughput transcriptomic screening	Mike DeVito
Bisphenol AF (1478-61-1) Tetrabromobisphenol A (79-94-7)	Rat	Gavage	5 days	S1500+ NextGen sequencing	Sue Fenton
Bromodichloroacetic acid (5589-96-8) Methyleugenol (93-15-2)	Mouse	Gavage	2 years	NextGen sequencing Exome-Seq (Illumina)	Arun Pandiri
Dieldrin (60-57-1) Ethinyl estradiol (57-63-6) Methyl mercury (115-09-3) Rotenone (83-79-4) Phenol (68937-41-7) Isopropylated phosphate (3:1) (60348-60-9) Pentabromodiphenyl ether (60348-60-9)	Mouse	In vitro	1 day	S1500+, NextGen sequencing	Alison Harrill
Phosphate flame retardants: tert-Butylphenyl diphenyl phosphate (56803-37-3) 2-Ethylhexyl diphenyl phosphate (1241-94-7) Isodecyl diphenyl phosphate (29761-21-5) Isopropylated phenol phosphate (68937-41-7)	Rat	Gavage	5 days	Microarray (Affymetrix) Metabolomics	Scott Auerbach
Ginkgo biloba extract (90045-36-6)	Rat	Gavage	5 days	Microarray (Affymetrix)	Cynthia Rider, Scott Auerbach
Induced pluripotent stem cells Embryoid bodies Embryonic stem cells	Human stem cell	N/A	N/A	High-throughput transcriptomic screening	Erik Tokar, Mike DeVito

Chemical (CASRN*)	Species/Cell Line	Route	Duration	Test Type (Platform)	Study Scientist
PCB-11 (2050-67-1)	Rat Human hepatocyte cell line	In vitro	1 day	S1500+ NextGen sequencing	Mike DeVito
PBDE-47 (32534-81-9)	Rat	Gavage	21 days	Microarray	June Dunnick
Polycyclic aromatic compounds: Acenaphthenequinone (82-86-0) Benzo[b]fluoranthene (205-99-2) Benzo(a)pyrene (50-32-8) Dibenz[a,h]anthracene (53-70-3) 9-Methylanthracene (779-02-2) 1-Methylfluorene (1730-37-6) Perinaphthenone (548-39-0) Phenanthrene (85-01-8) Pyrene (129-00-0)	Human hepatocyte cell line	In vitro	2 days	Cytotoxicity and gene expression by quantitative polymerase chain reaction	Cynthia Rider, Erik Tokar
Tetrabromobisphenol A (79-94-7) Pentabromodiphenyl oxide-technical (DE-71) (32534-81-9) Triclosan (3380-34-5) alpha, beta-Thujone (76231-76-0)	Rat	Gavage	5 days	High-throughput transcriptomic screening	Mike DeVito, William Gwinn
112-chemical compound test set (pharmaceuticals and environmental compounds)	Human hepatocyte cell line-HepaRG	In vitro	2 days	High-throughput transcriptomic screening	Stephen Ferguson, Sreenivasa Ramaiahgari
20-chemical compound test set (environmental compounds)	Primary rat hepatocytes Human HepaRG cells	In vitro	3 days	S1500+ NextGen sequencing	William Gwinn, Mike DeVito
N/A	Human mRNA Reference Isolation	In vitro	N/A	S1500+ NexGen Sequencing	Richard Paules
Carcinogens (HCC100)	Mouse	In vivo	2 years	HCC RNA-seq, CNV array	Miaofei Xu, Arun Pandiri

*Chemical Abstracts Service Registry Number

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

Related Links:

Disposition, Metabolism, and Toxicokinetic Studies

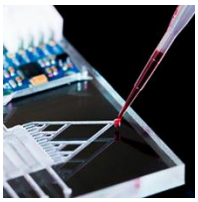
Genetic Toxicity Studies

Organ System Toxicity Studies

Modified One-Generation Reproduction Studies

Toxicology and Carcinogenicity Studies

NICEATM

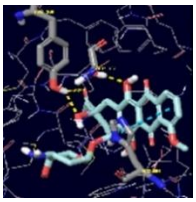


About NICEATM

The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) 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 Webinars and Workshops

A summary of webinars and workshops held or supported by NICEATM in FY 2018.



NICEATM Support of Tox21

A description of Tox21 projects NICEATM supported in FY 2018.

Additional NICEATM Activities

A summary of other activities NICEATM has conducted and participated in during FY 2018.

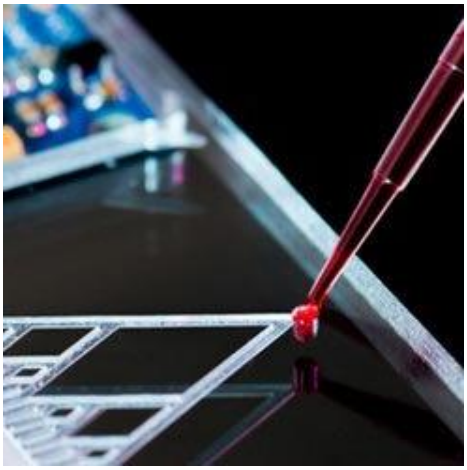
About NICEATM

The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) focuses on the development and evaluation of alternatives to animal use for chemical safety testing.

NICEATM activities include:

- 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 its website and other communications and by organizing workshops and symposia
- Coordinating and providing scientific and operational support for the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) 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 2018 NICEATM Webinars and Workshops

NICEATM Support of Tox21

Additional NICEATM Activities

NICEATM Webinars and Workshops

Workshop: Predictive Models for Acute Oral Systemic Toxicity

In coordination with the ICCVAM Acute Toxicity Workgroup, NICEATM organized a global project to develop in silico models of acute oral systemic toxicity that predict five specific endpoints identified by ICCVAM regulatory agencies. These endpoints included identification of:

- "Very toxic" chemicals (LD_{50} less than 50 mg/kg)
- "Nontoxic" chemicals (LD_{50} greater than or equal to 2,000 mg/kg)
- Point estimates for LD_{50}s
- Categorization of toxicity hazard using the EPA classification scheme
- Categorization of toxicity hazard using the United Nations Globally Harmonized System of Classification and Labelling classification scheme

The project was sponsored by the ICCVAM Acute Toxicity Workgroup.

NICEATM invited scientists to develop and submit in silico models that predicted any or all of these endpoints. This workshop, convened in April, provided an opportunity for project participants to present their submitted models. NICEATM scientists also presented an evaluation of the rat acute oral systemic toxicity test reproducibility as well as the development of a consensus model that integrates submitted models to generate consensus predictions for acute oral systemic toxicity. Workshop participants also discussed next steps needed to encourage appropriate use of predictive models in regulatory contexts.

Information about the workshop and follow-up project activities is available on the NTP website.

Workshop on the Monocyte Activation Test for Pyrogen Testing of Medical Devices

Pyrogens are substances that can produce fever when present as contaminants in a drug or medical device. Most pyrogens are biological substances derived from bacteria, fungi, and viruses; material-mediated pyrogens (MMPs), while less common, might also be present. Drugs for injection and medical device products for implantation or other systemic exposure should meet pyrogen limit specifications before they are marketed. Animal-based pyrogen tests are often conducted to investigate the presence of pyrogens. Non-animal monocyte activation tests (MATs) are widely available but infrequently used for pyrogen testing.

To review the MAT and discuss ongoing challenges to its widespread implementation for medical device testing, NICEATM and the PETA International Science Consortium (PISC) co-organized a September workshop. Meeting participants explored how the FDA Medical Device Development Tools Program could be used to qualify the use of the MAT as a standalone pyrogen test for specific medical device contexts of use. Participants generally agreed that the MAT could be qualified as acceptable for batch-release testing for microbial-based pyrogens; however, additional studies were recommended to demonstrate its ability to detect known MMPs. This testing would determine whether the assay can be used for both biocompatibility and sterility or if other information on MMPs would be needed to address biocompatibility. Participants also discussed information gaps on MMPs, potential test controls, and other challenges and opportunities for implementing the use of the MAT as a comprehensive pyrogen test.

More information about the workshop is available on the PISC website.

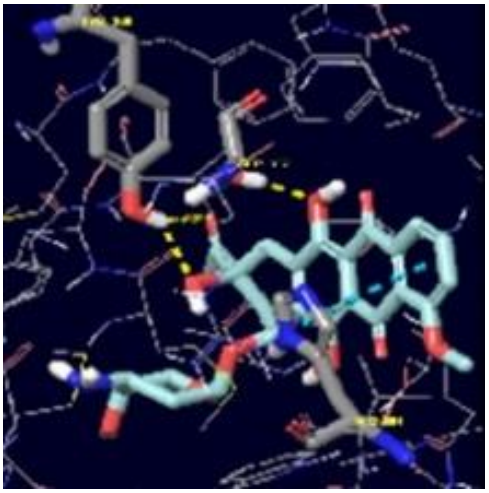
Related Annual Report Pages:

About NICEATM

NICEATM Support of Tox21

Additional NICEATM Activities

NICEATM Support of Tox21



The Tox21 research initiative aims to improve regulatory hazard assessment of substances potentially harmful to humans and the environment. Tox21 uses in vitro high-throughput screening assays to evaluate the biological activity of compounds in a 10,000-compound library and to relate observed activities to toxicological endpoints.

NICEATM provides support to the Tox21 effort primarily through its computational toxicology group. Specific NICEATM projects in support of Tox21 are included in the Tox21 Projects section.

Related Annual Report Pages:

About NICEATM

FY 2018 NICEATM Webinars and Workshops

Additional NICEATM Activities

Additional NICEATM Activities

Integrated Chemical Environment

Successful computational toxicology projects depend on freely available, high-quality data that are formatted for use in computational workflows. The NICEATM Integrated Chemical Environment (ICE) resource, launched in 2017, provides data from NICEATM and its partners as well as other resources and tools in an environment designed to support chemical safety assessment and new method development.

Updates to ICE in FY 2018 included:

- Adding formulation data and the ability for users to compare labeling categories from EPA "six-pack" studies with the performance of the formulation's active ingredients in non-animal methods
- Expanding physicochemical property predictions to include over 720,000 chemicals using an updated set of predictive models (Mansouri et al. 2018)
- Improving filtering on assay endpoints to allow more user control
- Adding androgen and estrogen pathway model predictions and rat acute oral LD_{50} data from a NICEATM predictive modeling project
- Providing a workflow to enable in vitro-to-in vivo extrapolation (Casey et al. 2018)

Updates in early FY 2019 will add two more workflows. The Machine Learning Workflow will provide five different machine learning algorithms to let users develop simple predictive models for a subset of endpoints using ICE data. The Chemical List Characterization Workflow will use physicochemical properties to provide property-based comparison of the chemicals.

ICE 2.0, to be launched later in FY 2019, will include a refresh to the user interface; data selections aimed to guide users less familiar with the assay; and more seamless movement between ICE tools, the Integrator, and external resources.

Acute Systemic Toxicity

Models developed for the acute oral systemic toxicity project (culminating in the April 2018 workshop) that met qualitative and quantitative review criteria were used by NICEATM to generate consensus predictions for the acute oral toxicity endpoints of interest. The consensus predictions generated for the project will be available in ICE, the EPA's CompTox Dashboard, and OPERA software. The consensus models will be made available and described in a manuscript to be submitted for publication in FY 2019.

NICEATM and NCCT are evaluating the potential of using ToxCast and Tox21 assay data for predicting acute oral toxicity; preliminary results suggest this approach could distinguish "toxic" from "nontoxic" chemicals. A manuscript describing the evaluation is planned for submission in early 2019.

Botulinum Neurotoxin Testing

Tests to detect and measure botulinum neurotoxin (BoNT) are required by multiple federal agencies for regulatory and other decision contexts. Currently, the standard test for these endpoints is a mouse lethality assay that can use large numbers of animals. To support evaluation and promotion of alternative test methods, NICEATM published a Federal Register notice in June requesting available data and information on approaches and/or technologies currently used to detect and measure BoNT. Information submitted in response to the request is being used to assess the state of the science and

determine technical needs for non-animal test methods used to detect the presence of BoNT and measure potency of BoNT preparations.

Cardiotoxicity

An initiative is underway to design, build, and test new non-animal approaches to assess cardiotoxicity hazard. The goal is to develop human cell- and protein-based assays to more efficiently screen drugs and chemicals for their potential to be toxic to the heart or circulatory system. The initiative is supported jointly by NTP (NIEHS/NTP Biomolecular Screening Branch and NICEATM), the FDA Center for Drug Evaluation and Research, and the Health and Environment Sciences Institute (HESI). Two NTP projects within this initiative focus on in silico screening approaches for assessing cardiovascular safety. This NICEATM project will mine public data sources to compile a structured cardiotoxicity database and human-relevant data will help build and test the capabilities of models and integrated testing strategies for cardiovascular hazards.

Developmental Toxicity

Developmental toxicity tests evaluate the extent to which exposure to a substance can interfere with normal development. This testing is required by multiple regulatory agencies and uses large numbers of animals. NICEATM supports efforts to develop, validate, and implement alternative approaches to identify potential developmental toxicants. To this end, NICEATM published a Federal Register notice in May requesting available data and information on approaches and/or technologies currently used to identify potential developmental toxicants. Submitted information will help assess the state of the science for these approaches and technologies and determine technical needs for approaches to assess developmental toxicity endpoints.

NICEATM continues to support the NTP Systematic Evaluation of the Application of Zebrafish in Toxicology program. A summary of current zebrafish husbandry and toxicology study practices will be published in Alternatives to Animal Experimentation in early FY 2019. An interlaboratory study to examine effects of key protocol elements will be initiated later in FY 2019.

Endocrine Disruptors

NICEATM compiled high-quality data from in vivo testing of chemicals for potential endocrine disruptor activity. These data have potential use for developing adverse outcome pathways or models of estrogenic activity, prioritizing chemicals for further testing, and evaluating species-specific responses to chemicals. Most recently, NICEATM collaborated with Organisation for Economic Co-operation and Development (OECD) and EPA scientists to develop a reference database and evaluate an in vitro model to identify chemicals with the potential to interact with the androgen receptor (AR). The AR model is potentially a rapid, cost-effective replacement for the in vivo Hershberger assay. Two recent papers describe data and methods used for this effort.

- Browne et al. 2018, describes assembly and curation of a data set of results for the Hershberger and other in vivo assays for AR activity. Ultimately, 49 chemicals were identified with reproducible AR pathway responses confirmed in at least two in vivo rodent studies. These 49 chemicals could be considered reference chemicals useful for validating alternative methods.
- Kleinstreuer et al. 2018, describes use of the reference chemicals identified through the data curation effort to interrogate the performance of a ToxCast/Tox21 AR model based on 11 high-throughput assays. The AR model had 100% positive predictive value for the in vivo response, where chemicals with conclusive AR model results were consistently positive in vivo.

NICEATM is collaborating with test method developer CertiChem, Inc., to validate an in vitro test method that uses MDA-Kb2 human breast cancer cells to measure AR agonist and antagonist

activity. Specifically, NICEATM provided guidance on incorporating a cytotoxicity assay into the test method protocol. Testing of 67 coded reference chemicals in agonist and antagonist modes to characterize method reliability and relevance is complete, and a report summarizing these results is being prepared.

Skin Sensitization

The DNTP Toxicology Branch is testing over 200 chemicals nominated by ICCVAM agencies using three in vitro test methods to expand the applicability domain of a defined approach for identifying skin sensitizers. Mouse local lymph node assay data are available for the nominated chemicals, which include pesticides, formulations, industrial chemicals, and other chemicals of interest to ICCVAM agencies. The three in vitro test methods are the LuSens method, the direct peptide reactivity assay, and the human cell line activation test. NICEATM is coordinating the testing, which began in 2017 and is scheduled for completion in early 2019. The study data will enable NICEATM and ICCVAM to evaluate the appropriateness of a defined approach using these three in vitro methods for various regulatory applications.

NICEATM collaborated with the Cosmetics Europe Skin Tolerance Task Force to evaluate integrated testing and assessment approaches for skin sensitization submitted to OECD. NICEATM evaluated six defined approaches with a set of previously untested chemicals having in vitro and in silico data provided by Cosmetics Europe. Descriptions of the data sets (Hoffman et al. 2018) and the outcome of the analyses (Kleinstreuer et al. 2018) were published in 2018 and demonstrated that many of these approaches perform as well or better than animal methods to predict human skin sensitization hazards.

Ocular Irritation

NICEATM, the PETA International Science Consortium, EPA, and CropLife America member companies are collaborating to develop an in vitro-defined approach for hazard classification of eye irritation potential of agrochemical formulations.

- NICEATM analyzed data from four in vitro assays paired with in vivo rabbit eye test data to determine if a defined approach using a combination of these assays could be used to assess eye irritation potential. While the results of this analysis indicated that developing such a defined approach was feasible, it was determined that the evaluated data sets were limited in size. Therefore, additional prospective testing was proposed.
- A two-phased prospective evaluation was designed to (1) assess the applicability of seven *in vitro* eye irritation/corrosion methods to agrochemical formulations and (2) develop a defined approach for agrochemical formulations testing for prediction of U.S. and international irritancy classifications. In Phase 1, completed in FY 2018, six formulations were tested in seven eye irritation test methods. All seven methods will be included in Phase 2A, which will evaluate 10 formulations that represent a range of eye irritancy classifications. Phase 2B will evaluate an additional 30 formulations with a range of eye irritancy potential, and methods to be included will be based on Phase 2A results. The study is expected to be completed in FY 2019 and will suggest assays that can form the basis of a defined approach for agrochemical formulations testing for eye irritation/corrosion potential.

Related Annual Report Pages:

About NICEATM

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NICEATM Support of Tox21

ICCVAM

About ICCVAM

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

A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States

ICCVAM is coordinating the development of a strategic roadmap to adopt new approaches to safety and risk assessment of chemicals and medical products that improve human relevance and replace or reduce the use of animals.

ICCVAM Meetings

A description of meetings held by ICCVAM in FY 2018.

ICCVAM Test Method Evaluation Activities

A list of NICEATM and ICCVAM test method evaluation activities in FY 2018.

ICCVAM International Validation Activities

A description and list of NICEATM and ICCVAM international validation activities in FY 2018.

About 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. 285l-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 16 U.S. federal regulatory and research agencies that generate or use toxicological and safety testing information (see below). Warren Casey, Ph.D., serves as administrative director of ICCVAM.

- Agency for Toxic Substances and Disease Registry
- U.S. Consumer Product Safety Commission
- U.S. Department of Agriculture
- U.S. Department of Defense
- U.S. Department of Energy
- U.S. Department of the Interior
- U.S. Department of Transportation
- U.S. Environmental Protection Agency
- U.S. Food and Drug Administration
- National Cancer Institute
- National Institute of Environmental Health Sciences
- National Institutes of Health
- National Institute for Occupational Safety and Health
- National Institutes of Standards and Technology
- National Library of Medicine
- Occupational Safety and Health Administration

Related Links

Information on ICCVAM Activities

Complete List of Articles on ICCVAM Activities Published in Scientific Journals

Related Annual Report Pages:

Strategic Roadmap for New Approaches to Evaluate the Safety of Chemicals and Medical Products

ICCVAM Meetings

ICCVAM Test Method Evaluation Activities

ICCVAM International Validation Activities

A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States

ICCVAM coordinated the development of a strategic roadmap for incorporating new approaches into safety testing of chemicals and medical products in the United States. Sixteen federal agencies and multiple interagency workgroups developed the roadmap with input from a broad range of stakeholder groups. The final roadmap document was published in January 2018 and is available on the NTP website.

The roadmap creates a framework that guides the development of enabling technologies and promotes strategies to establish confidence in and ensure utilization of new approaches to toxicity testing that improve human health relevance and reduce or eliminate the need for testing in animals. The successful development and implementation of these new approaches will require coordinated efforts that address three strategic goals:

(1) Connect users with developers of new approach methodologies.

(1) Foster the use of efficient, flexible, and robust practices to establish confidence in new methods.

(2) Encourage the adoption and use of new methods and approaches by federal agencies and regulated industries.

Pages on the NTP website describe activities underway to address the roadmap goals in the following areas:

- Acute systemic toxicity
- Skin and eye irritation
- Skin sensitization

Related Links

Information on ICCVAM Activities

Complete List of Articles on ICCVAM Activities Published in Scientific Journals

Related Annual Report Pages:

About ICCVAM

ICCVAM Meetings

ICCVAM Test Method Evaluation Activities

ICCVAM International Validation Activities

ICCVAM Meetings

NICEATM supported eight teleconferences and two in-person meetings held by ICCVAM in FY 2018. NICEATM also supported eight ad hoc ICCVAM workgroups focused on acute systemic toxicity, ocular and dermal irritation, developmental and reproductive toxicity, skin sensitization, use of read-across in toxicity testing applications, in vitro-to-in vivo extrapolation, nanomaterials, and ecotoxicology.

The fourth ICCVAM Communities of Practice webinar was held on January 23, 2018. The webinar explored the fundamentals of machine learning approaches, including how they work, how they are interpreted, and precautions that should be taken when evaluating their output. Sean Ekins, Ph.D., Chief Executive Officer of Collaborations Pharmaceuticals, Inc., and NICEATM Deputy Director Nicole Kleinstreuer, Ph.D., addressed issues specific to machine learning approaches used in a regulatory context. Case studies were presented to highlight where such techniques have been successfully applied both nationally and internationally. Presentations from the webinar are available on the NTP website.

ICCVAM, with NICEATM support, held its fifth public forum on May 24, 2018, at the National Institutes of Health in Bethesda, Maryland. Representatives from eight ICCVAM member agencies were joined by attendees representing stakeholder groups and over 100 webcast viewers. ICCVAM members provided information about their agency activities on the development and validation of test methods and approaches that could replace, reduce, or refine animal use.

A main focus of this meeting was implementation of the strategic roadmap for establishing new approaches to evaluate the safety of chemicals and medical products in the United States. Commenters offered suggestions on specific actions that should be taken to advance the goals of the strategic roadmap and encouraged less active ICCVAM partners to take a greater role. The meeting agenda and presentations are available on the NTP website.

Related Links

Information on ICCVAM Activities

Complete List of Articles on ICCVAM Activities Published in Scientific Journals

Related Annual Report Pages:

About ICCVAM

Strategic Roadmap for New Approaches to Evaluate the Safety of Chemicals and Medical Products

ICCVAM Test Method Evaluation Activities

ICCVAM International Validation Activities

ICCVAM Test Method Evaluation Activities

ICCVAM welcomes submissions of innovative test methods that might be acceptable for specific regulatory use and for which adequate validation studies have been completed. To maximize effective implementation of new test methods or approaches, however, ICCVAM evaluates and recommends only those test methods proposed for regulatory uses that align with ICCVAM member agencies' needs and priorities. More information on ICCVAM test method submissions is available.

In FY 2018, the Genomic Allergen Rapid Detection (GARD™) assay was submitted by SenzaGen AB to ICCVAM to evaluate its ability to identify potential skin sensitizers. The ICCVAM Skin Sensitization Workgroup reviewed and discussed a validation study report provided by SenzaGen and in response to SenzaGen note deficiencies in the validation that precluded a recommendation being made on the assay. Ongoing ICCVAM test method evaluation activities in FY 2018 are summarized below.

Test Method Evaluation Activities in FY 2018

Test Method	ICCVAM Recommendations/Agency Status
Electrophilic allergen screening assay	This test method, nominated by the National Institute for Occupational Safety and Health (NIOSH), is an in chemico assay intended to identify potential skin sensitizers. A validation study of the method began in FY 2017 with four ICCVAM agencies participating in the study. NICEATM is coordinating the study, and members of the ICCVAM Skin Sensitization Workgroup are serving on the study management team. Phase 1 testing of 10 chemicals during FY 2018 showed that the method had sufficiently good reproducibility and accuracy rates to support further evaluation. Phase 2 testing will begin after a 96-well format is developed to increase throughput and accessibility of the assay.
OptiSafe	NICEATM coordinated a multi-laboratory validation study to determine the reliability and relevance of the OptiSafe test method. In this method, a test substance is applied to a semi-permeable membrane to assess the substance's potential to cause eye irritation. Testing was completed on 95 coded chemicals in three phases during FY 2018; a report on the study will be submitted for publication in FY 2019.
EpiAirway™	A cooperative agreement under the NIEHS Phase IIb Small Business Innovation Research provides funding to MatTek Corporation to validate its EpiAirway™ in vitro human bronchial tissue model to predict the toxicity of inhaled chemicals. Several ICCVAM agency representatives are members of the cooperative agreement steering committee. Testing is ongoing with chemicals selected by steering committee members. NICEATM provides scientific oversight of this NIEHS small business program supporting validation of alternative test methods.

The ICCVAM agencies are engaged in additional activities that support replacing, reducing, and refining animal use. Summaries of these additional activities are on the NTP website.

Related Annual Report Pages:

About ICCVAM

Strategic Roadmap for New Approaches to Evaluate the Safety of Chemicals and Medical Products

ICCVAM Meetings

ICCVAM International Validation Activities

ICCVAM International Validation Activities

NICEATM and ICCVAM participate in international test method validation activities through OECD. They also collaborate with countries and regions participating in the International Cooperation on Alternative Test Methods (ICATM), including the European Union, Japan, Korea, Canada, Brazil, and China.

Representatives from OECD and ICATM participating organizations in Canada, Brazil, and Korea attended the September 2018 meeting of the Scientific Advisory Committee on Alternative Toxicological Methods. In a separate meeting, attendees gave updates on their organizations' activities.

In FY 2018, ICCVAM agencies commented on draft OECD documents through the U.S. National Coordinator for the OECD Test Guidelines Programme, an ex officio ICCVAM member. Beginning in 2018, the U.S. National Coordinator will be joined at the annual meeting of the National Coordinators by one or more ICCVAM members who are subject matter experts in topics planned for discussion at the meeting. ICCVAM members and/or NICEATM staff supported the Test Guidelines Programme during FY 2018 by:

- Serving on an expert group developing a performance-based test guideline (PBTG) for defined approaches for skin sensitization. PBTGs describe acceptable performance standards for a general class of test methods that are intended to measure the same biological effect.
- Attending meetings of the OECD expert groups on eye irritation and skin sensitization, which produced six updated test guidelines published in 2018.

ICATM collaborations address three critical areas of cooperation: test method validation studies, independent peer review of validation studies, and development of formal recommendations on alternative testing methods. In October 2016, representatives of NICEATM and ICCVAM attended an ICATM coordination meeting and ICATM-sponsored workshop to develop criteria for evaluating non-animal approaches for skin sensitization potential. Products of this workshop included a white paper characterizing international regulatory requirements for skin sensitization testing (Daniel et al. 2018), a position paper covering workshop outcomes and ICATM recommendations (Casati et al. 2018), and a proposal to develop a PBTG for defined approaches to testing and assessment of skin sensitization, which was accepted by OECD in April 2017. NICEATM and ICCVAM representatives will attend an ICATM workshop in October 2018 on "Validation and Establishing Scientific Confidence."

In fiscal year 2018, NICEATM staff served on the validation management team for an allergic contact dermatitis test for an international amino acid derivation reactivity assay led by the Japanese Center for the Validation of Alternative Methods. In addition, an ICCVAM member served on the peer-review panel. The study is complete.

Related Annual Report Pages:

About ICCVAM

Strategic Roadmap for New Approaches to Evaluate the Safety of Chemicals and Medical Products

ICCVAM Meetings

ICCVAM Test Method Evaluation Activities

Literature Analysis

Noncancer Research

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

Report on Carcinogens

The Report on Carcinogens is a congressionally mandated listing of substances that either are known to be human carcinogens or might reasonably be anticipated to be human carcinogens and to which a significant number of people residing in the United States are exposed.

Noncancer Research

In addition to conducting analysis activities to identify cancer hazards, NTP also evaluates the scientific evidence to determine whether environmental chemicals, physical substances, or mixtures—collectively referred to as substances—cause adverse, noncancer, health effects. NTP also provides opinions on whether these substances might be of concern given what is known about current human exposure levels. The NIEHS/NTP Office of Health Assessment and Translation (OHAT) conducts health hazard assessments and other evidence evaluations, including scoping reviews, evidence maps, and state-of-the-science evaluations, which are published as NTP monographs, NTP research reports, and journal publications, and hosts workshops to address important issues in environmental health sciences. Andrew Rooney, Ph.D., served as acting director of OHAT in FY 2018.

In FY 2018, OHAT added evidence mapping as a new interactive data presentation format as an output option of its evidence evaluations. Evidence maps categorize or "map" the key concepts for a particular question or topic. When performed with a systematic literature search and selection process, the resulting evidence map allows readers to explore evidence categorized by health effect, exposure, evidence stream (e.g., human, experimental animal, or mechanistic data) and study design. The State-of-the Science Evaluation of Transgenerational Inheritance of Health Effects demonstrates this new interactive data presentation.

Ongoing Noncancer Health Effects Projects

Project Study Scientist	Project Summary	Status
Evaluation of long-term neurological effects of acute exposure to the organophosphorus nerve agent sarin Andrew Rooney	Sarin is a highly toxic organophosphorus nerve agent developed for chemical warfare during World War II that continues to be used as a weapon today. In partnership with the NIH Countermeasures Against Chemical Threats (CounterACT) Program, NTP has conducted a systematic review to evaluate the evidence for long-term neurological effects in humans following acute exposure to sarin.	Draft monograph released December 2018
Evaluation of inflammation-based atherosclerosis associated with environmental exposures Brandy Beverly and Andrew Rooney	This evaluation examines whether 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 that leads to it.	Evaluation ongoing
NIEHS-EPA pilot study of exposure to chemicals in consumer products Kyla Taylor	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 several consumer product categories, including personal and child care, household cleaning, lawn and garden, home improvement, and food packaging products. The pilot study addresses several research needs related to the measurement and modeling of human exposures.	Pilot study sample collection completed September 2018. Biological samples are being analyzed by CDC

Project Study Scientist	Project Summary	Status
Respiratory effects associated with exposure to biocides Vickie Walker	Biocides are commercial products used to kill or control the spread of harmful microorganisms like bacteria and viruses. The EPA Office of Pesticide Programs nominated biocides to NTP for evaluation of the evidence for respiratory outcomes from occupational exposure to biocides. The ongoing study includes developing a scoping review and evidence map on potential respiratory health effects of 10 major antimicrobial biocides commonly used for disinfection in hospitals.	Evaluation ongoing
State of the science for transgenerational inheritance of health effects Vickie Walker	Transgenerational inheritance is the phenomenon in which an individual's exposures have far-reaching consequences, affecting multiple generations removed from the original insult. NTP conducted a state-of-the-science or scoping review to examine the evidence for transgenerational inheritance of health effects associated with exposure to a wide range of stressors (e.g., environmental chemicals, drugs of abuse, nutrition and diet, pharmaceuticals, infectious agents, stress) in humans and animals. The evaluation, published in *Environment International* in February 2018, systematically compiled and categorized the literature to develop an evidence map for transgenerational inheritance by broad health-effect categories, exposures, and types of evidence, and identified areas of consistency, uncertainty, data gaps, and research needs. Evidence mapping illustrated that risk of bias (having generally few studies) and heterogeneity in exposures and endpoints examined present serious limitations to available bodies of evidence for assessing transgenerational effects.	Evaluation published February 2018
Evaluation of children's health and traffic-related air pollution Kembra Howdeshell and Brandy Beverly	Research on traffic-related air pollution and children's health has increased in the past decade, reflecting improvement in air monitoring technology and exposure methodology. Traffic-related air pollution has been measured in multiple ways, including direct traffic measures (such as traffic proximity or density) and surrogate measures of traffic-related air pollution (such as particulate matter, oxides of nitrogen, and other products of fossil-fuel combustion generated by motor vehicles including benzene, diesel exhaust, and PAHs). This topic is the subject of this series of evaluations on the evidence for an association between traffic-related air pollution and health outcomes impacting the fetus and children, beginning with hypertensive disorders of pregnancy and neurological development and function in children.	Evaluation ongoing

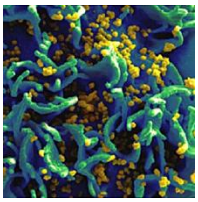
Project Study Scientist	Project Summary	Status
Evaluation of adverse health effects and occupational exposure to cancer chemotherapy agents Kembra Howdeshell	This evaluation examined the evidence that occupational exposure to cancer chemotherapy agents is associated with adverse health effects, including genetic toxicity, cancer, reproductive and developmental effects, and acute effects. The draft NTP monograph has been completed and is undergoing formatting for final publication.	Final monograph completed September 2018
Environmental influences on the epigenome: a scoping report Katie Pelch and Vickie Walker	This evaluation leveraged newly developed text mining and machine learning tools to carry out scoping activities that will explore the evidence linking environmental exposures to health outcomes via genome-wide alterations in DNA methylation.	Deferred
Chemical factors affecting breast cancer risk: a state-of-the-science review Vickie Walker and Jason Stanko	This evaluation is examining the evidence that environmental substances or factors influence breast cancer risk. In collaboration with the DNTP NTP Laboratory, OHAT is conducting an evidence evaluation of chemicals, pharmaceuticals, and dietary components as well as other factors that are associated with adverse effects on the breast or mammary gland and could potentially influence breast cancer risk.	Evaluation ongoing
Neonicotinoid pesticides and adverse health outcomes Windy Boyd	Neonicotinoid pesticides are a class of chemicals that act as insecticides by exerting neurotoxic effects through irreversible binding to insect nicotinic acetylcholine receptors. This scoping review is identifying the extent of evidence available to understand human health effects of seven neonicotinoid pesticides (acetamiprid, clothianidin, dinotefuran, imidacloprid, nitenpyram, thiacloprid, and thiamethoxam).	Evaluation ongoing
Parkinson's disease: associations with environmental exposures Windy Boyd	Although some Parkinson's disease cases can be attributed to genetic factors, the causes of many cases remain unknown. Many studies report associations between environmental exposures and Parkinson's disease or related symptoms. OHAT conducted two scoping reviews on this topic. The first systematically mapped the evidence of the associations between exposures to environmental chemicals considered broadly and Parkinson's disease. During scoping activities, hundreds of studies on the associations between exposure to the herbicide paraquat and Parkinson's disease were identified, making paraquat a candidate chemical for further systematic review. Therefore, a more detailed scoping review was developed to characterize reported associations between paraquat exposure and Parkinson's disease.	Evaluation ongoing
Systematic reviews on potential health effects of fluoride	This systematic review is evaluating potential neurobehavioral effects from exposure to fluoride during	Evaluation ongoing

Project Study Scientist	Project Summary	Status
Kyla Taylor	development that includes consideration of human epidemiological studies, experimental animal studies, and mechanistic data. The project includes an update to NTP's 2016 systematic review of published animal literature examining neurobehavioral effects of exposure to fluoride during development and adulthood in rodents. The 2016 report concluded that the level of evidence supporting adverse effects on learning and memory in animals exposed to fluoride in the diet or drinking water is low to moderate.	
Prenatal exposure to progestogens and adverse health outcomes Kembra Howdeshell	Progesterone and synthetic progesterone derivatives are administered to reproductive age women for a variety of health outcomes, including contraception, infertility, and treatment or prevention of miscarriage or preterm birth. Concern for possible adverse effects on the developing fetus stems from alterations in normal steroid hormone exposure during development that have been shown to cause adverse effects on offspring health and development. A scoping review is underway to identify and characterize the literature on the possible association between exposure to progestogens during pregnancy and adverse health outcomes in the offspring.	Evaluation ongoing
Evaluation of the findings from the consortium linking academic and regulatory insights on the toxicity of bisphenol A (CLARITY-BPA) program Kembra Howdeshell, Brandy Beverly, Retha Newbold, Andrew Rooney, and John Bucher	Bisphenol A is used in the manufacture of plastics, among other products, and has been identified as an endocrine disruptor. Its ubiquity in the environment has raised concerns about its potential health effects. Academic studies have identified several health effects of bisphenol A, while guideline compliant studies have failed to detect effects, except at high doses. As a result, NTP and NIEHS designed the Consortium Linking Academic and Regulatory Insights on the Toxicity of Bisphenol A (CLARITY-BPA) program to enhance the links between academic and guideline-compliant research. The findings of the CLARITY-BPA program will be summarized in two reports. The first report, authored by the CLARITY-BPA participants with background and publication summaries written by NTP, is an integrated assessment of the published findings from the guideline compliant and investigational research activities undertaken within the CLARITY-BPA program. The second report, authored by NIEHS/NTP, will attempt to synthesize and compare the CLARITY-BPA findings with prior studies on BPA from CLARITY-BPA participants to identify potential reasons for differences and assess whether there are additional scientific approaches to consider when performing guideline compliant studies of endocrine active agents.	Evaluation ongoing

Report on Carcinogens

About the Report on Carcinogens

A congressionally mandated listing of substances that either are known to be human carcinogens or might reasonably be anticipated to be human carcinogens and to which a significant number of people residing in the United States are exposed.



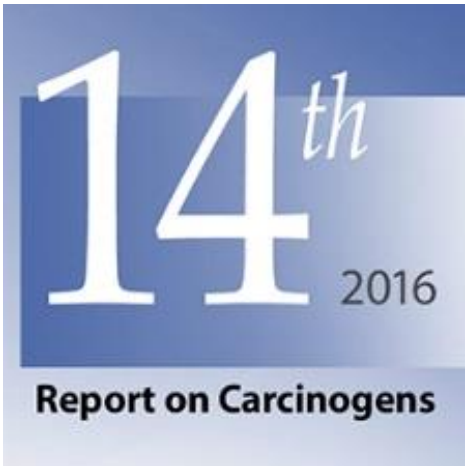
Report Activities

A summary of activities the Office of the Report on Carcinogens conducted during FY 2018.

Report Substances Selected for Evaluation

A list of substances the Office of the Report on Carcinogens selected for evaluation during FY 2018.

About the Report on Carcinogens



The Report on Carcinogens (RoC) is a congressionally mandated listing of substances that either are known to be human carcinogens or might reasonably be anticipated to be human carcinogens, and to which a significant number of people residing in the United States are exposed [Public Health Service Act, 42 U.S.C. 241(b)(4)]. Preparation of the RoC at NTP is under the direction of Ruth Lunn, Dr.P.H., director of the NIEHS/NTP Office of Report on Carcinogens (ORoC).

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

(1) NTP selects nominations for evaluation.

(2) ORoC conducts cancer hazard evaluations on the selected substances and prepares draft RoC monographs.

(3) Draft RoC monographs are released for public comment and external peer review is conducted before finalization.

(4) NTP submits the proposed listing of newly reviewed substances to the Secretary of Health and Human Services for review and approval, followed by transmittal to Congress and publication on the NTP website.

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

Additional Links for the Report on Carcinogens:

Report on Carcinogens

Report Activities

Report Substances Selected for Evaluation

Report Activities

Activities in FY 2018 primarily focused on carrying out cancer hazard evaluations and preparing monographs for several substances under consideration for possible listing in the RoC.

- Antimony trioxide. On January 24, 2017, the draft monograph was peer reviewed by a panel of experts. The panel agreed with NTP's preliminary recommendations to list antimony trioxide in the RoC as reasonably anticipated to be a human carcinogen based on sufficient evidence from studies in experimental animals and supporting mechanistic data.
- *Helicobacter pylori*: Chronic infection. Following its release for public comment, the draft monograph on *H. pylori* was reviewed by letter by three substance-specific experts. The reviewers agreed with NTP's preliminary recommendations to list *H. pylori* in the RoC as known to be a human carcinogen based upon sufficient evidence from studies in humans.
- Shift work at night, light at night, and circadian disruption. On October 5, 2018, NTP convened an external panel to peer review the draft monograph on shift work and light at night. The panel agreed with NTP's preliminary recommendation to list persistent night shift work that causes circadian disruption as known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans. The panel also accepted NTP's preliminary recommendation that certain lighting conditions that cause circadian disruption should be listed as reasonably anticipated to be a human carcinogen. The panel recommended that the supporting evidence should refer to "certain lighting conditions" and not "light at night."

For a list of ongoing evaluations, see Report Substances Selected for Evaluation. Preparations are ongoing for the 15th RoC. In addition, ORoC is conducting scoping activities to identify substances for review for future editions of the report.

Additional Links for the Report on Carcinogens:

Report on Carcinogens

About the Report on Carcinogens

Report Substances Selected for Evaluation

Report Substances Selected for Evaluation

Substances NTP Project Leader	Primary Uses/Exposures	Status
Antimony trioxide Amy Wang	This compound is used mainly as a synergist for halogenated flame retardants in plastics, rubber, and textiles, which are used in a diversity of plastics and other products. It also can be used as a catalyst in polyethylene terephthalate production, as an additive in glass manufacturing and in pigments, or as an additive in paints and ceramics.	Peer-review meeting January 2018 Revised monograph released September 2018
Goldenseal root powder (Hydrastis canadensis) ORoC staff	This herbal remedy (botanical product) is used to treat gastrointestinal disturbances; urinary disorders; hemorrhage; skin, mouth, and eye infections; and inflammation.	Deferred
Haloacetic acids found as water disinfection byproducts Gloria Jahnke	This includes 13 individual haloacetic acids or a potential class or subclass of these haloacetic acids. People are exposed to these haloacetic acids by ingestion of chlorinated drinking water and by inhalation and dermal contact during bathing or showering or when using swimming pools and spas that use chlorine for disinfection.	Final monograph published March 2018
Helicobacter pylori (*H. pylori*): Chronic infection Ruth Lunn	A gram-negative, multiflagellated bacterium, it colonizes the stomach and causes peptic ulcer. Bacterium is spread by person-to-person contact, especially among family members. Routes of exposure include oral-oral, fecal-oral, and iatrogenic; exposure from contaminated water is also possible. Risk factors for infection include age, race, socioeconomic status such as crowded living conditions, and poor sanitation/hygiene.	Draft monograph released May 2018 Revised monograph released September 2018
Shift work at night, light at night, and circadian disruption Ruth Lunn	Unnatural (e.g., ill-timed) electrical light, especially light at night, might disrupt sleep and biological processes controlled by endogenous circadian clocks. People, who by virtue of the nature of their work, lifestyle choices, or residence, are subjected to exposure to unnatural light. Shift workers who work at night can experience an extreme type of exposure to light at night and changes in other activities, such as changes in daily activities, eating, sleeping, lifestyle factors, and social behavior.	Draft monograph released August 2018

Additional Links for the Report on Carcinogens:

Report on Carcinogens

About the Report on Carcinogens

Report Activities

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 NCTR

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

NTP at NIOSH

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

NTP at NIEHS

Most NTP research testing and analysis activities are carried out at NIEHS. The following Division of NTP branches and offices at NIEHS are actively involved in NTP research activities.

- Biomolecular Screening Branch, Richard S. Paules, Ph.D., Acting Chief
- Cellular and Molecular Pathology Branch, Robert Sills, D.V.M., Ph.D., Chief
- NTP Laboratory, Michael DeVito, Ph.D., Acting Chief
- Program Operations Branch, Michelle Hooth, Ph.D., Chief
- Toxicology Branch, Nigel Walker, Ph.D., Acting Chief
- NTP Interagency Center for the Evaluation of Alternative Methods, Warren Casey, Ph.D., Chief

NIEHS/NTP Staff

Biomolecular Screening

The Biomolecular Screening Branch develops and implements programs in medium- and high-throughput screening of environmental substances for rapid detection of biological activities of significance to toxicology. Biomolecular Screening projects for FY 2018 are listed below.

Biomolecular Screening Projects in FY 2018

Project Study Scientists	Project Summary
Development of the S1500+ gene set Richard Paules, Scott Auerbach, Steve Ferguson and Sreenivasa Ramaiahgari	The development of the S1500+ gene set and its use in targeted sequencing approaches provides a new, cost-effective methodology for capturing broad biological responses to chemical exposures in a variety of in vitro and in vivo model systems, allowing for quantitative dose-response measurements and kinetic studies. S1500+ gene sets have been developed for use with human, mouse and rat samples, with a zebrafish set currently under development. Linking this high-throughput transcriptomic approach with novel organotypic cell culture model systems (i.e., models that behave like living tissue) allows for a more rapid and deeper investigation of biological responses for chemicals of concern and a better understanding of potential implications for human health. A proof-of-concept study utilizing the human liver cell line HepaRG in various states of differentiation—which were exposed to 24 reference chemicals and investigated utilizing the human S1500+ gene set platform for transcriptomics characterization of responses to those chemical exposures—has been submitted for publication in FY 2019.
Development of more sophisticated genetic analyses to make better use of current animal models Alison Harrill	Genetic and epigenetic differences between individuals in the human population have been proposed as major factors for determining individual susceptibility to environmental stressors. Safety assessments of environmental substances and drugs are currently conducted with a few commonly used animal models that have limited genetic diversity. Further, many layers of biological regulation can influence individual genetic susceptibility to chemical and drug toxicity. Animal models have inherent limitations for extrapolating results to human toxicity and disease. NTP is developing more sophisticated genetic analyses to make better use of current animal models while adopting biological systems that are more appropriate for modeling human toxicity and disease.

Project Study Scientists	Project Summary
Epigenetic study to examine DNA methylation and its possible role in development of liver tumors Alex Merrick and Paul Wade	Work continued in FY 2018 on an epigenetic study of mouse strains to examine DNA methylation and its possible role in the susceptibility of mice to develop liver tumors. Progress included computational analysis of genomic methylation sites in relation to known genes and transcriptionally active regions in both parental strains and first-generation offspring. The relationships between DNA methylation, gene expression, and possible heredity in offspring are being determined, and the genomic variations in mouse strains, genders, and first-generation offspring are being cataloged. The results describing the mouse methylome will be publicly released in a manuscript accepted for publication in late 2018 or early 2019. Additional studies in FY 2018 addressed the effect of sex hormone signaling on DNA methylation at a genome-wide level and the impact of DNA methylation at distal regulatory regions.

NTP Laboratory

NTP Laboratory conducts in-house, agent-specific, targeted research on the development and application of modern toxicology and molecular biology tools. These tools are used to:

- Evaluate specific substances of concern to NTP.
- Identify issues of central importance to programs within NTP.
- Develop methods to advance the NTP mission.

NTP Laboratory also studies the developmental origins of adult diseases. NTP Laboratory projects for FY 2018 are listed below.

NTP Laboratory Projects in FY 2018

Project Study Scientist	Project Objectives
Development of in vitro models of metal carcinogenesis Erik Tokar	Use in vitro cell transformation models (stem/progenitor and “mature” cells) of target-relevant cells to elucidate carcinogenic mechanisms and modes of action of metals (i.e., arsenic and cadmium).
In vitro evaluation of crumb rubber toxic effects Erik Tokar	Study the modes of action and metabolomics involved in the toxic effects of crumb rubber on various prospective human target tissues.
Role of microRNAs in malignant transformation Erik Tokar	Study genes 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: carcinogenesis, developmental toxicology, and developmental basis of adult disease Erik Tokar	Develop stem cell model systems (pluripotent, multipotent, progenitor) and methods for use in examining the role of these cells in carcinogenesis, evaluating developmental bases of adult disease, and assessing developmental toxicology. These studies will be used to help predict or categorize teratogens and developmental toxicants.
Evaluation of polycyclic aromatic hydrocarbon compounds using in vitro screens Erik Tokar	Apply in vitro assays to assess and categorize the biological effects of polycyclic aromatic hydrocarbon compounds.
Evaluation of the role of oxidative stress in the biological effects of glyphosate and its formulations Michael DeVito	Compare the effects of glyphosate to the effects of glyphosate formulations using measures of genotoxicity, oxidative stress, and cell viability. Compare the dose-response relationships among oxidative stress, genotoxicity, and cell viability.
Application of in vitro assays to evaluate botanicals Michael DeVito	Determine whether in vitro assays and chemical analysis of botanicals can aid in selecting botanicals for in vivo testing.

Project Study Scientist	Project Objectives
Chemical-induced transcriptomic and metabolomic changes in vitro Michael DeVito	Evaluate the transcriptomic and metabolomic changes in metabolically active cell lines with 24 chemicals that have been tested in vitro.
Incorporation of metabolism into high-throughput screening assays Michael DeVito	Develop in vitro methods that incorporate xenobiotic metabolism.
REACT PFAS Michael DeVito	Conduct screening efforts to evaluate the NTP library of per and polyfluorinated alkyl substances.
Utility of a five-day transcriptomic study in adult rats William Gwinn	Examine the differences in the transcriptomic bone mineral density and adverse effect bone mineral density for 20 chemicals that have been tested in vitro at NTP.
PCB 11: Screening for biological and toxicological activity Michael DeVito	Compare the biological and toxicological activity of polychlorinated biphenyl (PCB) 11 to prototype PCBs in response to a nomination from EPA.
Metalloestrogens and uterine/breast response Darlene Dixon, Suzanne Fenton	Test the ability of reported metalloestrogens such as cadmium and arsenic to cause estrogen receptor stimulation in the uterus as a mode of action for cancer development.
The role of ER-alpha36 in endocrine disruption and its localization in fibroid cells Darlene Dixon	Evaluate the role of endocrine disrupter alpha36 (ER-alpha36) in fibroid cells and the role of ER-alpha36 in the endocrine-disrupting effects of environmental and industrial chemicals.
Techniques for histologic visualization/ evaluation of 3D cultures/in vitro assessments Darlene Dixon	Develop techniques for taking 3D spheroid or embryoid cultures from 96-well plate into paraffin blocks for histochemical and immunohistochemical staining.
Literature-based evidence for environmental factors affecting the breast Suzanne Fenton, Jason Stanko, Vickie Walker	Review and categorize the evidence in the literature on environmental influences on breast development, disease, and function. This work should lead to development of systematic reviews on related topics.
Effects of TBBPA on developmental and reproductive endpoints in Harlan SD rats Suzanne Fenton, Linda Birnbaum	Evaluate the effects of TBBPA (tetrabromobisphenol A) following prenatal and early life exposure and determine the transcriptomic/metabolomic pathways involved in low-dose, hormone-driven responses.
Effects of PFOA and GenX on developmental and reproductive endpoints in CD-1 mice Suzanne Fenton	Evaluate the role of placental toxicity in the developmental effects of PFOA and GenX.

Project Study Scientist	Project Objectives
Screening of perfluorinated compounds for effects in human and mouse cell-based assays Suzanne Fenton, Michael DeVito	Compare the potencies and effect profiles of 40–75 perfluorinated compounds for their effects in cells known to be targets of PFOA and PFOS (perfluorooctanoic acid and perfluorooctane sulfonate, two perfluorinated compounds removed from the market due to reported health effects).
Toxicants and mammary gland development Suzanne Fenton	Determine the effects of different toxicants, including atrazine and bisphenols, on mammary gland development in rats or mice.
Use of in vitro screens to evaluate potential obesogens Suzanne Fenton	Develop orthogonal assays to evaluate findings from Tox21 that identified potential obesogens. Mechanisms of action for select chemicals are being investigated.
Refinement of developmental neurotoxicology methods G. Jean Harry	Improve methods for assessing differential changes as a function of developmental exposures, including in vivo molecular phenotypes, cellular phenotypes, maternal/developmental inflammation, and behavioral assessments.
Method development to assess neuroinflammation G. Jean Harry	Examine methods (from screening to mechanisms) for assessing in vitro and in vivo induction of inflammation in the nervous system following chemical exposures.
Evaluation of the developmental neurotoxicity of fluoride G. Jean Harry	Evaluate fluoride developmental neurotoxicity in rats. The study has been completed, and a manuscript has been submitted.

NTP at NCTR

About NTP at NCTR

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

NTP at NCTR: Interagency Agreement Projects

A list of projects funded by the NIEHS/NTP interagency agreement with FDA and conducted in FY 2018.

About NTP at NCTR

Research in Partnership with NCTR

The National Center for Toxicological Research (NCTR) partners with researchers from elsewhere in the U.S. Food and Drug Administration (FDA), other government agencies, academia, and industry to provide 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 research for NTP is funded by both voluntary allocations and an interagency agreement.

NCTR/NTP Staff

NCTR studies funded by voluntary allocations are listed below.

Biochemical and Molecular Basis of Toxicology

Project Study Scientist	Project Objectives
Role of peroxisome proliferator-activated receptor alpha (PPARa) and PPARa-mediated species differences in triclosan-induced liver toxicity Jia-Long Fang	Examine the role of human and mouse PPARa in triclosan-induced liver toxicity in vivo.
Development of a next-generation sequencing method for the quantification of low frequency somatic mutations in oncogenes Page Mckinzie	Develop a next-generation sequencing method for quantifying somatic mutations in oncogenes at fractions in the range of 10^{-5} to 10^{-2}.
Detection of rare genomic mutations induced by genotoxic carcinogens using next-generation sequencing Tao Chen	Establish tagging and duplex sequencing methods to detect rare mutations using synthesized DNA fragments containing known mutation fractions and types. Use the method to sequence genomic DNA from Salmonella strains treated with mutagens and compare the results with those from the Ames test conducted with the same treated Salmonella. Use the method to sequence exons of all expressed genes from the liver of rats or mice treated with different types of carcinogens and compare the results with those from previously published transgenic mutation assays and Sanger sequencing analysis conducted on the same animals.
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 Li Pang	Establish the in vitro model and positive control. Evaluate model sensitivity and specificity and tests of the possibility of high-throughput screening and ranking of QT-prolonging drugs for the risk of torsade de pointes.
Tumor mutational signatures of acrylamide and glycidamide Fred Beland	Determine the mutational signatures of tumors induced in experimental animals by acrylamide and glycidamide. Compare the mutational signatures obtained from acrylamide and glycidamide in experimental animals with mutational signatures obtained from acrylamide and glycidamide in experimental animals with mutational signatures of human tumors in published databases.
Evaluation of the effects of black cohosh on risedronate efficacy in perimenopausal rat model Amy Inselman	Determine the effects of risedronate and black cohosh (alone or combined) on bone density, bone turnover, and bone histology in a postmenopausal rat model.

Project Study Scientist	Project Objectives
Development and evaluation of a novel in vitro epigenomic screening model system for the hazard identification of FDA-regulated products Igor Pogribny	Determine the dose-dependent, in vitro genetic and epigenetic effects of compounds FDA regulates. Characterize the specific epigenetic changes induced in vitro by genotoxic and nongenotoxic compounds. Characterize the specific genetic and epigenetic effects of compounds FDA regulates using an in vitro three-dimensional organotypic liver culture model system.
Identification of mechanistic biomarkers of pyrrolizidine alkaloid (PA)-induced hepatocarcinogenesis William Tolleson	Use high-throughput profiling approaches to identify microRNAs that regulate genes involved in PA carcinogenicity in hepatic cell systems and investigation of the functions of microRNAs by bioinformatics tools and in vitro functional assays. These results will identify microRNA species for use as biomarkers for PA-induced carcinogenicity, with added benefits derived from mechanistic knowledge of how these microRNAs might function in the biological effects of PAs. Benefit food safety and human health by providing simple tools for assessing exposure to foodborne toxins.

Neurotoxicology

Project Study Scientist	Project Objectives
Effects of developmental sevoflurane exposure and pretreatment with acetyl-l-carnitine on complex brain function in rats John Talpos	Examine the effects of early developmental sevoflurane exposure on neurodegeneration and complex operant learning. Determine whether impairments in these measures can be attenuated by pretreatment with acetyl-L-carnitine. Examine the time course of acetyl-L-carnitine pretreatment on sevoflurane-induced neuroapoptosis.
Developmental neurotoxicity assessment of N-methyl-D-aspartate (NMDA) receptor antagonists in zebrafish Jyotshnabala Kanungo	Study wild-type zebrafish embryos exposed to NMDA receptor antagonists (MK-801, dextromethorphan, ketamine, and sevoflurane) to assess their effects on Rohon-Beard sensory neurons. The effects on the primary and secondary motor neurons and their axons are being assessed using hb9:GFP transgenic embryos. Postexposure washout experiments are being pursued to determine the effects of these drugs on the nervous system. Determine estradiol-17β levels in control and treated embryos and quantification of changes in gene expression for the two CYP aromatases/estrogen synthases (brain aromatase cyp19a1b and gonadal aromatase cyp19a1a) using quantitative polymerase chain reaction (qPCR). Assess phenotype-based cell signaling mechanisms, such as MAPK (mitogen-activated protein kinases) and neuron development-specific gene expression. Examine reversal of noted adverse effects of these compounds on neurons, particularly by treatment with acetyl L-carnitine.
Toxicity assessment of graphene sheets using primary striatal neurons	Evaluate the toxicity of graphene sheets using in vitro primary cultures of embryonic day 14 primary rat striatal neurons.

Project Study Scientist	Project Objectives
Syed Ali	Determine pathways involved in graphene toxicity using embryonic day 14 primary rat striatal neurons.
Rat blood-brain-barrier-on-a-chip model to study traumatic brain injury Syed Ali	Use soft lithograph and microfabrication techniques to engineer a multilayered blood-brain-barrier-on-a-chip model that can be subjected to different magnitudes and durations of mechanical stress that mimic mild and repetitive traumatic brain injury. Characterize the effects of traumatic brain injury on blood-brain-barrier integrity using the chip model.
High-throughput neurotoxicity screening of metallic nanoparticles: In vitro and in vivo imaging Syed Imam	Assess the utility of high-throughput neurotoxicity screening of metallic nanoparticles for detecting neurochemical and neurophysiological alterations in vitro for use in developing reference standards for metallic nanoparticles. Once developed and validated, these techniques can be optimized for analyzing other FDA-regulated nanomaterials.

Nanotoxicology

Project Study Scientist	Project Objectives
Proteomic assessment of the cytotoxic effects of nanoparticles on the blood-brain barrier Qiang Gu	Use proteomic 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. Establish proteomic parameters for toxicity of nanoparticles.
Complement assays for the detection of immune-sensitizing activity of nanomaterials Julian Leakey	Establish two complement assays for routine evaluation of immune-sensitizing activity of nanomaterials. Validate the assays using nanoparticles with known immunoreactivity. Determine the immune-sensitizing activity of novel nanomaterials.
Nonclinical modeling and risk assessment of FDA-regulated drug nanocrystals Kuppan Gokulan	Investigate various media milling/high pressure homogenization and spray/freeze drying process parameters and formulation parameters to determine the critical parameters that affect particle size and drug polymorphic form. The project includes the development of a predictive model of appropriate criteria to prepare stable crystalline solid nanoparticles using multiple linear regression analysis; an accelerated study to determine crystalline solid nanoparticle stability; and preliminary in vivo studies to show proof of principle of enhanced bioavailability of the crystalline nanoparticle formulation compared to crystalline macro-particles. Evaluate drug-nanocrystal effects on epithelial cell permeability and mucoadherence using in vitro and ex vivo culture models and drug permeability and stability using in vitro intestinal epithelial cells. Determine macrophage cell viability and proliferation during the treatment with different sizes of drug nanocrystals; evaluate the immunotoxic effects of drug nanocrystals on intestinal tissue by measuring pro-inflammatory cytokines; and determine the effect of drug nanocrystals on the intestinal commensal microbiota using in vivo model.

Project Study Scientist	Project Objectives
Evaluation of cadmium oxide nanoparticle as a nanoparticle-type positive control for toxicity assays Tao Chen	Characterize cadmium oxide nanoparticles and determination of their toxicity using in vitro toxicity and genotoxicity assays. Explore the possible mechanisms of cadmium oxide nanoparticle toxicity. Evaluate where cadmium oxide nanoparticles are suitable for use as a positive control according to their toxicity and genotoxicity responses.
In vitro genotoxicity of graphene-family nanomaterials using FDA-recommended short-term genetic toxicity test battery Nan Mei	Determine the genotoxicity of graphene and derivatives in standard regulatory test battery assays. Determine whether any mutagenicity in mouse lymphoma cells is due to loss of heterozygosity in chromosome 11. Investigate whether genotoxic and mutagenic responses are mediated through oxidative pathways. Establish the genotoxic and mutagenic mode of action using gene expression arrays.
Graphene-induced toxicity on the population of intestinal microbiota and gut-associated immune response Sangeeta Khare	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 Nanotechnology Core Facility Anil Patri	Provide the expertise and equipment for characterizing nanomaterials used in toxicology studies and for detecting nanomaterials in in vitro and in vivo derived samples. Serve as a resource for U.S. agencies for the design of toxicology studies and generation of standards for analytical methods.
Determination of cytotoxicity and genotoxicity of nanomaterials of interest to the FDA and their mechanism of action Peter Fu	Develop a set of cell-free and cell-based in vitro tests that can be used to rapidly identify nanomaterials of interest to the FDA that elicit oxidative damage. Determine whether, in the presence of nano-metal materials, endogenous and dietary antioxidants can display pro-oxidative activity.
Assessing epigenetic effects of nanoparticles in human cells George Hammons	Determine the effect of two types of nanoparticles, silver and titanium dioxide, at various particle sizes, surface coatings, dosages, and durations of exposure on global methylation and genome-wide DNA methylation using array profiling in four types of human cells (liver, lung, skin, and colorectal). Determine the effect of these nanoparticles on the pattern of global histone modifications and on genome-wide profiles of histone modifications in the four types of human cells. The analysis includes comparisons with disease-associated histone modifications. Correlate the nanoparticle effect on DNA methylation with its effect on DNA methyltransferase expression. Correlate the nanoparticle effect on global histone modifications with its effect on expression of histone-modifying enzymes as potential underlying mechanisms of the alteration in DNA methylation or histone modification patterns.

Project Study Scientist	Project Objectives
Immunotoxicity assessment of nanomaterials using human immune cell-based biomarkers of innate immunity Wei Ding	Assess the immunotoxicity of different categories of nanoparticles using biomarkers of innate immunity measured in vitro in human immune cells (monocytes, human peripheral blood mononuclear cells).
An assessment of the interactions of nanoscale (TiO_2 and zinc oxide) materials used in sunscreens on the skin microbiome Huizhong Chen	Examine human skin microbiota cell viability in the presence of nanoscale materials in cosmetics. Determine the effect of nanomaterials in cosmetics on human skin microbial ecology. Demonstrate the mechanisms of toxicity of nanoscale materials in cosmetics to skin microbiota using the human skin tissue model EpiDerm and reverse transcription polymerase chain reaction (RT-PCR) and whole genome microarray technologies. Elucidate the dose-response relationship of nanoscale materials in cosmetics on skin bacterial cell toxicity. Assess the potential health risk of human skin exposure to nanomaterials in cosmetics.
Evaluation of the migration and toxic potential of Ag nanoparticles in feminine hygiene products to vaginal tissue: In vivo rodent and in vitro 3D mucosal models Anil Patri	Use established qualitative methods to characterize different species of nanoscale Ag contained in five types of dry and five types of liquid feminine hygiene products. Evaluate the migration/uptake and toxicity of Ag nanoparticles and ions used in feminine hygiene products using a human cell-based in vitro three-dimensional culture model that has many of the structural and functional features of the human vaginal mucosal layer. Evaluate the effects of Ag nanoparticles and ions contained in feminine hygiene products on human vaginal microbiota using culture techniques and semiquantitative molecular methods.
Interaction of nanoparticles with gastrointestinal tract Sangeeta Khare	Determine the effect of nanomaterials on the permeability of epithelial cells and establishment of immune correlates. Delineate the interaction of nanomaterials with gastrointestinal tract and gut-associated microbiota using an ex vivo model (intestinal explants). Establish the effect of nanoparticles on the developmental stage of the intestine and assessment of the biodistribution of nanoparticles using the zebrafish model.
The effect of nanomaterials used in dentistry on biofilm formation and the oral microbiota John Sutherland	Compare the relative efficacy of FDA-regulated nanomaterials used in dentistry for inhibition of bacterial adhesion to surfaces and biofilm formation. Evaluate the effect of nanomaterials on growth and antimicrobial susceptibility profiles of typical species from the oral microbiota.

Bioassay and Biomarker Development and Evaluation

Project Study Scientist	Project Objectives
Development of cancer-relevant biomarkers for identification of potential carcinogens: Research to understand the normal background frequencies in rats Page McKinzie	Understand the distribution and range of spontaneous oncogene mutant frequencies in the major organs of rats and mice. Provide important basic information for the validation of these oncogene mutant frequencies as biomarkers of chemically induced carcinogenesis.
Cancer mutations as biomarkers of cancer risk: human studies with implications for personalized medicine Barbara Parsons	Develop the information necessary for the rational use of oncogene mutations as quantitative biomarkers of cancer risk; specifically, allele-specific competitive blocker PCR (ACP-PCR) are being used to determine normal and pathological levels of relevant oncogene mutations in multiple human tissues and tumors. Compare the information derived from human tissues with data generated in a parallel rodent protocol as an approach for incorporating carcinogenesis-relevant data into the rodent-to-human extrapolation necessary in cancer risk assessment. Validate a streamlined ACP-PCR methodology and development of the methodology necessary to measure oncogene mutant fractions in cell-free DNA isolated from plasma. Through a series of publications, convey to the regulatory risk assessment community the regulatory significance of the data regarding tumor-associated mutations which have and will be generated.
Study of translational biomarkers for drug-induced liver injury with next-generation sequencing Baitang Ning	Conduct a comprehensive survey of microRNAs using the next-generation sequencing technology. Findings will elucidate the molecular pathways and processes modulated by RNAs (including messenger RNAs, microRNAs, and other noncoding RNAs) and their importance in drug-induced liver injury risk and phenotypes.
A comprehensive characterization of induced pluripotent stem cell-derived cardiomyocyte (iPSC-CM) models for drug-induced arrhythmia using high-throughput screening assays Li Pang	Develop standard baseline criteria for high-throughput readouts of drug-induced arrhythmia in human iPSC-CMs from different suppliers. Assess individual variance and possible sex differences in drug-induced cardiotoxic responses across a panel of nongenetically modified iPSC lines.
Validating the rat Pig-a assay for regulatory use: Determining the molecular basis of mutants detected in the rat Pig-a gene mutation assay Vasily Dobrovolsky	Develop a method that could routinely identify Pig-a mutations in individual Pig-a mutant phenotype cells.
Developing in vitro approaches to assess drug-induced liver toxicity Lei Guo	Develop and use in vitro assays for assessing drug-induced liver toxicity by evaluating cytotoxicity and quantifying representative endpoints for assessing clinical-related outcomes such as apoptosis/necrosis, steatosis, and cholestasis.

Project Study Scientist	Project Objectives
Evaluation of microRNAs in blood and urine for detection of chemical-induced carcinogenicity Tao Chen	Determine microRNAs in blood and carcinogenic target tissues that respond to carcinogen exposures and the best time for sampling of their expression after treatments in rats. Determine microRNA profiles from the blood and target tissue samples of rats treated with different mode-of-action carcinogens, such as alkylating agents, aneugens, clastogens, and nongenotoxic carcinogens at the appropriate sampling time. Determine the functions and pathways of the dysregulated microRNAs by the carcinogen treatments and examine whether the microRNA changes can be anchored to the carcinogens with the known mode-of-actions and whether the changes in blood are related to those in the target tissues. Establish specific microRNA biomarkers in blood for assessing different types of carcinogens.
Development and characterization of a diet-induced obesity model using B6C3F1 mouse for evaluation of drug toxicity in obesity Vijayalakshmi Varma	Develop a B6C3F1 mouse model of obesity to investigate the effect of obesity on anthracycline-induced cardiotoxicity and the model's suitability to investigate other potential drug-induced toxicities under conditions of obesity.
Development of advanced safety assessments of FDA-regulated products using high-throughput and high-content quantitative approaches in cultured human cells to evaluate genotoxicity Carol Guo	Establish and demonstrate the feasibility of novel high-throughput and high-content in vitro genotoxicity assays conducted using human liver cells in conjunction with quantitative dose-response approaches for assessing and distinguishing the genotoxicity of FDA-regulated products.
Enhance the prediction of potential endocrine activity of chemicals by integrating multiple endpoints data Huixiao Hong	Augment different endocrine-related endpoint data and development of prediction models for screening chemicals with endocrine activity potential by integrating the augmented multiple types of endocrine-related endpoint data. Build an androgenic activity database and construction of integration-based prediction models.
Evaluation of an in vitro testis organ system as an alternative model for male reproductive toxicology Noriko Nakamura	Evaluate the in vitro testis organ system as an alternative model to assess male reproductive toxicology and establishment of a standardized protocol for the assay.

Project Study Scientist	Project Objectives
Using metabolically competent human cell lines to perform high-throughput genotoxicity testing Nan Mei	Develop HepG2-derived cell lines that simultaneously express 3-5 Phase I cytochrome P450s (CYPs). Develop HepG2-derived cell lines co-expressing multiple CYPs and Phase II UDP-glucuronosyltransferase (UGT) enzymes. Develop TK6-derived cell lines that express 14 CYP genes individually and TK6-derived cell lines simultaneously expressing 3-5 CYPs. Develop TK6 cells that co-express CYPs and Phase II UGT or sulfotransferase (SULT) enzymes. Assess the utility and feasibility of newly developed cell lines for toxicity studies using a small set of chemicals with known or postulated metabolism-related toxicity. Perform a pilot high-throughput genotoxicity study (HT-micronucleus assay, HT-Comet assay, and HT-γH2AX detection) using the established cell lines.
Modification of the Comet assay for in vitro and in vivo assessment of global and gene-specific methylation status Mugimane Manjanatha	Develop methods for in vitro assessment of global and gene-specific methylation using a modified Comet assay (methods development). Upon successful development of the in vitro modified Comet assay, extend these methods to modify the high-throughput micropatterned Comet assay developed by Ge et al (2015) to conduct pathway-focused, high-throughput, methylation assays using human cells.
Predictive clinical biomarkers for chemotherapy-induced cardiotoxicity Li-Rong Yu	Discover novel omics predictive biomarkers of cardiotoxicity and diagnostic biomarkers of cardiac injury from Dox-treated breast cancer patients. Verify and translate predictive and diagnostic preclinical miRNA and metabolomics biomarkers of cardiotoxicity in clinical plasma samples. Develop mass spectrometry-based multiplex assays and verification of proteomic biomarker candidates in plasma.
MicroRNAs as novel biomarkers for radiation-induced heart disease Li Pang	Identify miRNAs with time-dependent expression changes in heart tissue and plasma of radiation-treated rats. Evaluate the dose-dependencies of miRNA dysregulation in response to radiation. Identify potential targets of dysregulated miRNAs in the radiation-injured heart by combination of in silico miRNA target prediction and gene expression analysis. Investigate radiation-induced miRNA dysregulation in plasma and heart tissue of mast cell-deficient (Ws/Ws) and mast cell competent wild-type rats.
Prediction of tyrosine kinase inhibitor (TKI) induced cardiotoxicity using induced pluripotent stem cell-derived cardiomyocytes Li Pang	Present in vitro mechanistic analysis beyond proarrhythmic toxicity. Identify noninvasive biomarkers that detect and predict the severity of structural cardiotoxicity. Develop a systems-based database to capture the characteristics of TKI-induced cardiotoxicity.

Project Study Scientist	Project Objectives
Somatic oncomutations as biomarkers for translating preclinical safety data to human cancer risk Barbara Parsons	Identify the most promising human oncomutation biomarkers by next-generation sequencing (NGS). Analyze batteries of rat and mouse amplicons for hotspot oncomutations by NGS. Validate rodent oncomutations as biomarkers of carcinogenic effect.
Genetic and epigenetic mechanisms of sex differences in the kidney of a rat model system: developing safety biomarkers for FDA-regulated products James Fuscoe	Conduct whole genome expression profiling on 10 rat tissues of both sexes at nine ages. Conduct miRNA profiling of selected tissues, including liver. Conduct DNA methylation profiling of selected tissues, including liver. Use bioinformatics and statistical approaches to understand the genetic machinery operational at each developmental stage in each sex and relate the findings to potential susceptibility to adverse drug reactions and disease. Use bioinformatics approaches to extrapolate these findings of potential age- and sex-associated susceptibility in an animal model system to humans.
Development of a simple in vitro approach for the rapid detection of neurotoxicity Qiang Gu	Characterize FluoroJade-C (FJ-C) labeling in vitro. Validate FJ-C labeling in vitro. Develop an FJ-C based in vitro approach for high-throughput assessment of neurotoxicity. Explore the mechanism underlying FJ-C labeling.
Validating the rodent Pig-a gene mutation assay: development of a human reticulocyte Pig-a assay to evaluate the ability of the rodent Pig-a assay to predict the genotoxicity of FDA-regulated products in humans Vasily Dobrovolsky	Develop a sensitive high-throughput protocol for performing the flow cytometry and magnetic enrichment-based human RBC PIG-A assay that is capable of detecting GPI-anchored marker-deficient mutants among at least several million polychromatic RBCs and at least one hundred million normochromatic RBCs from human peripheral blood samples. Determine some basic properties of the high-throughput PIG-A assay that is developed and measurement of background PIG-A mutant frequency in the general population using blood samples from self-identified healthy human volunteers. Test the ability of the high-throughput RBC PIG-A assay that is developed to detect PIG-A mutation in human cancer patients receiving Pt-based drugs as part of their antineoplastic chemotherapy. Perform a comparative study in rats employing a chemotherapeutic treatment regimen similar to human cancer patient Pt-based therapy protocol using the most sensitive version of the rat PIG-A assay for detection of somatic mutation.

Project Study Scientist	Project Objectives
Quantification of in vivo genomic damage by whole genome clone analysis and high-fidelity next-generation sequencing Javier Revollo	Develop whole genome clone analysis, a method that detects somatic mutations in clones derived from individual cells, to quantify basal and xenotoxin-induced whole genome somatic mutations. Develop an efficient ultra-high-fidelity NGS method capable of detecting somatic mutations in genome pools. Direct identify and quantify by ultra-high-fidelity the frequency of somatic mutations in tissues derived from laboratory animals treated with known mutagens.

Computational Toxicology

Project Study Scientist	Project Objectives
Improving methods and algorithms for enhancing 3D-QSDAR Svetoslav Slavov	Test the feasibility and implementation of software code for enhancements to the three-dimensional quantitative spectral data-activity relationship (3D-QSDAR) technique and demonstration of the potential beneficial effect on the performance of 3D-QSDAR models for various data sets and endpoints.
Evaluation of transcriptomics-based predictions of sex and age-related susceptibilities to treatment-induced adverse effects in F344 rats James Fuscoe	Integrate hepatic life cycle basal gene expression data in male and female rats into a toxicogenomics model and enable the prediction of age- and sex-related differences in drug or chemical disposition and downstream adverse events in primary rat hepatocytes.
Defining applicability domains in 3D-QSDAR Iva Stoyanova-Slavova	Select three to four data sets having differing degrees of heterogeneity. Analysis of data to determine how heterogeneity of the data affects the internal predictivity of the models. Compare the external predictive power for models based on data sets of different heterogeneity and external test sets of equal size. Derive and test different hypotheses and determination pf which applicability domain definition results in models with maximum predictivity for an external test set of compounds. Draw conclusions about the applicability domains of 3D-QSDAR models.
Of text and gene: using text mining methods to uncover hidden knowledge in toxicogenomics Weida Tong	Investigate the utility of topic modeling in toxicogenomics as an enhanced knowledge discovery means to uncover hidden knowledge for which otherwise are difficult to discover using the conventional approaches.
Computational toxicology for safety and risk assessment Jeffery Fisher	Assist other FDA Centers and research organizations outside of FDA with their requests for support from staff scientists within NCTR and other scientists on safety and risk assessment issues of interest to FDA.
Pilot study to examine a population-based computational framework for assessing xenobiotic disposition and interaction effects in pregnant women	Demonstrate proof of concept for using emerging computational techniques in understanding pregnancy-related alterations in drug pharmacokinetics.

Project Study Scientist	Project Objectives
Annie Lumen	Assist in developing recommendations for dose adjustments and drug labeling in the pregnant population, thus promoting women's health during this crucial period.
Statistical methods for whole transcriptome sequencing data analysis Vivian Zhuang	Develop and evaluate one-sided and two-sided gene set analysis methods for RNA-seq data with discrete counts. Develop and evaluate methods for combining correlation estimates and sequencing depth to determine sample size calculations in RNA-seq experimental design. Develop and evaluate methods for identifying outlier samples in RNA-seq data.
The design and development of machine learning algorithms to assist with automated pattern recognition of persistent organic pollutants in foods and feeds Huixiao Hong	Identify trends and potential risks using historical results. Reduce analyst hours spent reviewing data to determine quality and data usability. Expand automated algorithms outside of the POPs field.
Hepatoxicity of herbal/dietary supplements Weida Tong	Assemble a comprehensive list of herbal and dietary supplements that have potential to cause drug-induced liver injury in humans into a web-based database that can be used for reference in regulatory processes when hepatotoxicity issues arise.

NTP at NCTR: Interagency Agreement Projects

NCTR research for NTP is funded by voluntary allocations and an interagency agreement. Below are FY 2018 projects funded through an NIEHS/NTP interagency agreement with FDA.

Food Additives and Contaminants

Project Study Scientist	Project Summary
Two-year chronic toxicology study of BPA in rats Barry Delclos	This study is characterizing the long-term toxicity of orally administered BPA (bisphenol A), including developmental exposure, in NCTR Sprague Dawley rats over a broad dose range. Animals generated in this study are being assigned to separate protocols for assessment of a range of molecular, morphological, and functional endpoints to determine if these endpoints are predictive of long-term toxic effects or reveal potential effects undetected by standard toxicological evaluations.
Evaluation of molecular, morphological, and functional endpoints in rats treated with BPA Barry Delclos	This study includes an evaluation of a range of molecular, morphological, and functional endpoints in rats dosed orally with a wide range of 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 are being conducted at various ages (postnatal days 1, 21, and 90 and 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) Gonçalo Gamboa da Costa	This study of rats orally co-exposed with melamine and cyanuric acid for 90 days is assessing the degree of functional and histological recovery after 30- and 90-day recovery periods.
Comparison of the dose-response and temporal dynamics of traditional and novel biomarkers of nephrotoxicity upon a combined exposure to melamine and cyanuric acid in rats Luisa Camacho	The objectives of this study are to: Compare the dose-response and temporal dynamics of circulating microRNAs, blood urea nitrogen, and serum creatinine in rats co-exposed to melamine and cyanuric acid over a 90-day treatment period and a subsequent 90-day recovery period. Compare the dose-response relationships of the kidney gene expression level of biomarkers of nephrotoxicity and kidney histopathology in rats co-exposed to melamine and cyanuric acid for 90 days and upon a 90-day recovery period.
Role of perinatal development on toxicokinetics of inorganic arsenic Daniel Doerge	The objective of this study is to determine serum pharmacokinetics and metabolism of low-dose inorganic arsenic in adult female CD-1 mice, Sprague Dawley rats, and rhesus monkeys.
Evaluation of brominated vegetable oil in rats Gonçalo Gamboa da Costa	The objectives of this study are to: Assess the dose-response relationships of a 90-day dietary exposure to brominated vegetable oil in Sprague Dawley rats. Evaluate the bioaccumulation and clearance of inorganic and organic bromine in organs and tissues of Sprague Dawley rats upon dietary exposure to brominated vegetable oil.

Project Study Scientist	Project Summary
Long-term evaluation of cognitive, neurochemical, and histopathological effects of developmental inorganic arsenic (iAs) exposure in Sprague Dawley rats Sherry Ferguson	The objective of this study is to determine the effects of developmental iAs exposure on cognitive behaviors, neurochemistry, and histopathology in Sprague Dawley rats.

Dermal Toxicology Program

Project Study Scientist	Project Summary
Two-year dermal carcinogenicity of triclosan in B6C3F1 mice Jia-Long Fang	The objective of this study is 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 Mary Boudreau	This evaluation seeks to determine whether 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.
Effects of fibrinolytic enzymes nattokinase and lumbrokinase alone or in combination with aspirin in blood parameters Luisa Camacho	This study includes an evaluation in an animal model of the effects of nattokinase and lumbrokinase on blood parameters and an assessment of their effects in combination with pharmacological doses of aspirin.

Drugs Program

Project Study Scientist	Project Summary
Toxicokinetic profile and toxicity of high-molecular-weight polyethylene glycols in rats Jia-Long Fang	The objectives of this study are to: Evaluate the toxicokinetic profile of high-molecular-weight polyethylene glycols in Sprague Dawley rats given a single dose of the substances via subcutaneous injection. Evaluate the bioaccumulation of high-molecular-weight polyethylene glycols in organs/tissues of rats upon repeated subcutaneous injection for 24 weeks. Assess the toxicities resulting from the bioaccumulation of the substances.

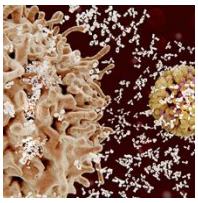
Enhancing Toxicology Program

Project Study Scientist	Project Summary
NTP capability building for microbiome assessment on toxicology studies: Assessing the role that the microbiome might play in the toxicity of xenobiotics Carl Cerniglia	This study is addressing critical knowledge gaps in the microbiome field using the latest advances in microbiome analysis through in vitro, in vivo, and ex vivo models in toxicity testing risk assessments.
Developing an in vitro system to evaluate the disease-related toxic effects of inhaled test agents in human airway tissue models Xuefei Cao	The objectives of this study are to: Develop exposure and dosimetry methods for exposing human air-lung interface airway cultures to aerosolized test agents. Use previously developed disease-related endpoints and air-lung interface culture exposure methods to evaluate the respiratory toxicity of two known airway toxicants, two presumed nontoxicants, and one compound of current interest.

NTP at NIOSH

About NTP at NIOSH

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



NTP at NIOSH: Immunotoxicology Research

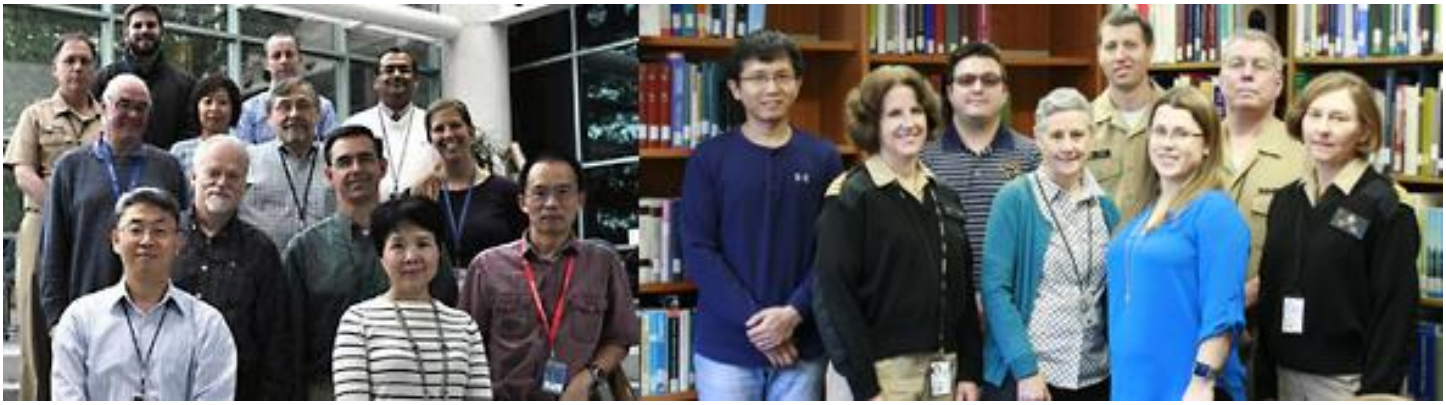
A list of studies to evaluate unique cohorts of individuals from professions associated with immune-mediated occupational diseases.

NTP at NIOSH: Occupationally Relevant Exposures

A summary and list of projects to identify and assess worker exposures in FY 2018.

About NTP at NIOSH

In accordance with its mandate to protect worker health and safety, the National Institute for Occupational Safety and Health (NIOSH) carries out research projects with NTP funded through an interagency agreement and voluntary allocations. These projects focus on comprehensive assessment of occupationally relevant exposures and immunotoxicology research. Setting priorities in occupational toxicological research is based on several sources of information NIOSH develops and maintains. Sources 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 (left) and Division of Surveillance, Hazard Evaluations, and Field Studies (right)

NIOSH/NTP projects in FY 2018 funded through voluntary allocations are listed below.

Biomonitoring, Biomarker Development, and Health Assessment

Project Study Scientist	Project Summary
Exposure assessment research and support John Snawder	The support of multiple branch and interdivisional projects includes (1) managing and planning field sample collection, (2) developing new classical and immunochemical biomonitoring methods, and (3) validating and adapting existing methods. This project also includes the design of low-cost, rapid immunochemical and analytical chemistry biomonitoring methods to identify exposures and evaluate potential interventions as well as the identification of and development of new multiplex immunochemical methods to evaluate biomarkers of occupational illness or subclinical signs of occupational illness.

Project Study Scientist	Project Summary
Ultraviolet native fluorescence-based monitor for workplace exposures John Snawder	This project includes the development and evaluation of a readily adaptable, next-generation, direct-reading personal monitor to measure worker exposure to a wide variety of chemicals, including naphthalene and components of asphalt fume. Personal monitors for volatile and semivolatile workplace chemicals will help to rapidly assess chemical exposure and result in more realistic occupational exposure assessments. These assessments will allow for rapid interventions and lead to reduced worker exposures and prevention of occupational illness and disease.
Evaluation of welding fumes as a lung carcinogen in mice exposed by inhalation Patti Erdely	This investigation of both carcinogenic metal-containing and non-carcinogenic metal-containing welding fumes as lung carcinogens is 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 also is generating valuable data regarding the carcinogenic potential of fumes from different types of welding processes that do and do not contain carcinogenic metals. In addition, the project is providing information on which metal oxide components of the welding fume have the greatest carcinogenic potency.
Systematic assessment of cobalt oxide (CoO) and lanthanum oxide (La_2O_3) in pulmonary disease Yong Qian	Metal oxide nanoparticles are an important class of engineered nanomaterials with broad application in many industrial products. Concerns over potential metal oxide nanoparticle-induced toxicity have emerged, particularly due to the propensity of these nanoparticles to induce oxygen radicals and oxidative stress. This assessment of cobalt oxide (CoO) and lanthanum oxide (La_2O_3) nanoparticle-induced pulmonary injury in vivo and cellular toxicity in vitro will reveal the toxicological modes of action for CoO and La_2O_3 nanoparticles. Results obtained from this study indicate that a tiered approach is required to predict subchronic responses following inhalation of these nanoparticles, which will lead to development of methods for early detection and interventions of CoO- and La_2O_3 -induced pulmonary diseases, particularly fibrosis, in humans.
Industry-wide studies of workers exposed to carbon nanotubes and nanofibers Matt Dahm	This project includes the collection of exposure data and exposure factors from participating pilot-scale or full-scale manufacturers or users of single-walled carbon nanotubes (SWCNTs) or multiwalled carbon nanotubes and carbon nanofibers. A study of biomarkers for early pulmonary, cardiovascular, and carcinogenic effects was conducted among workers at these facilities. The project will result in the creation of a predictive model using the collected exposure factors that will allow for the estimation of exposure for future registry and cohort studies.
Mortality, cancer incidence, and biomarker studies James Yiin	This study is clarifying exposure-outcome associations, especially dose-response relationships, for risk assessment; examining relationships between biomarkers of exposure, susceptibility, and oncogene expression; and determining health effects.

Environmental Monitoring

Project Study Scientist	Project Summary
Analytical research and development infrastructure Robert Streicher	This work supports administrative needs and analytical instrumentation repair and maintenance for Chemical Exposure and Monitoring Branch chemists conducting research on sampling and developing analytical methods for workplace chemicals. Development, evaluation, validation, and/or use of methods for hazardous drugs, peracetic acid, isocyanates, glyphosate, and flame retardants were among the FY 2018 activities. Also investigated in FY 2018 were thermal desorption technology coupled with portable gas chromatography-mass spectrometry and integration of volatile organic compound monitoring with time and location determination.
Direct-reading methods for metal-containing aerosol Pramod Kulkarni	Globally, exposure to hazardous metal-containing aerosols remains a serious health concern, with growing attention on fine, ultrafine, and nanosized aerosol particles. Emerging technologies, such as nanotechnology and additive manufacturing, are rapidly advancing our ability to create nanomaterials—3D printed products with potential for aerosol exposure. A near-real-time, field-portable instrument for measuring hazardous metal-containing aerosol has been developed as part of this project. The methods used in this study have general application to exposure monitoring, rapid hazard identification, and evaluation of engineering controls.
Direct-reading methods for silica measurement Pramod Kulkarni	The monitoring of respirable crystalline silica (RCS) concentrations in the workplace is essential for a comprehensive assessment of worker exposures. This project is developing direct-reading methods that allow onsite estimation of RCS. These methods allow either short-time (15–30 min) or end-of-shift quantification of RCS content onsite. A new field-portable instrument that can continuously measure RCS in near real time at concentrations well below the new OSHA PEL of 50 µg/m^3 is being developed. These methods are expected to improve worker exposure monitoring and guide the implementation of effective engineering controls.

Exposure Assessment

Project Study Scientist	Project Summary
Exposure assessment for toxicologically important chemicals Brian Curwin	This assessment is characterizing workplace exposures to chemicals of toxicological concern as identified by NTP and NIOSH. Current studies evaluate occupational exposure to carbon nanotubes and nanofibers, flame retardants, and PAHs in coal tar sealants. Goals of these studies include: (1) identifying industries, workplaces, uses, and users; (2) determining occupational health relevance; (3) estimating the number of workers exposed; and (4) conducting exposure sampling.
Industry-wide studies, branch research, development, and planning	This project supports strategic planning and feasibility studies of high-priority issues and emerging problems in occupational health.

Project Study Scientist	Project Summary
Elizabeth Whelan	
Nanotechnology field evaluations Charles Geraci	This project entails the collection of information from as many different facilities in the field as possible regarding the (1) nature of engineered nanomaterials, (2) processes involved in the manufacture and use of nanomaterials, (3) potential worker exposures to nanomaterials, and (4) practices and control procedures in the workplace where nanomaterials are produced or used. As toxicology studies identify the biological hazards of nanomaterials, gaining a better understanding of actual workplace exposures is essential.

Immunotoxicity and Immunology

Project Study Scientist	Project Summary
Immunotoxicological evaluation of occupational chemicals Stacey Anderson	This study includes the identification of occupational and environmental chemical hazards and evaluation of immune function and mechanisms associated with exposure. This research is contributing to better risk assessment and increased identification of immunological hazards encountered in the workplace, which ultimately will establish occupational exposure limits.
Identification of occupational allergens John Noti	The objectives of this project are 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. Develop improved techniques for detecting such immune reactions before adverse clinical outcomes occur. Develop improved techniques for detecting and identifying inciting occupational agents. This project is analyzing 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 Justin Hettick	This study is determining the molecular targets of inhaled diisocyanate particulates and increase comprehension of the pathogenic mechanism of isocyanate-induced allergic disease. The project will clarify the fate of diisocyanate in vivo following occupational exposure by increasing understanding of disease and identifying potential biomarkers of exposure.
Exosomes as biomarkers and immune modulators of diisocyanate asthma Justin Hettick	This study is defining mechanisms of occupational asthma associated with exposure to methylene diphenyldiisocyanate (MDI) by identifying biomarkers of MDI exposure and immune regulatory factors that influence the progression and severity of MDI-associated occupational asthma.

Project Study Scientist	Project Summary
	This project is identifying response and legacy biomarkers found in exosomes secreted into the bloodstream that would indicate isocyanate exposure and sensitization. These biomarkers can be incorporated into a human exosome database and be used in future studies to distinguish MDI-associated occupational asthma from general environmental asthmas. The study is also attempting to determine how exosome genetic content can influence asthma progression.

Genetics

Project Study Scientist	Project Summary
Immunotoxicity of subchronic fungal exposures Brett Green	This study is determining the pulmonary immunopathological outcomes of subchronic exposures to certain fungi nominated to NTP. Subchronic exposure studies with mycotoxin-producing strains of *Stachybotrys chartarum* and *Aspergillus versicolor* have been completed. Future subchronic exposure studies will focus on an atranone-producing strain of *S. chartarum*, *A. versicolor, A. alternata*, and fungi identified in NIOSH Health Hazard Evaluations and collaborative exposure assessment studies. Proposed studies will provide further insight into the mechanisms of pulmonary toxicity to fungi encountered in the workplace.
Immunomodulatory effects of triclosan on effector CD4 T-cell development Hillary Shane	This study is identifying the cellular and molecular mechanisms behind the immune-modulating effects of the antibacterial chemical, triclosan. This information is providing the basis for evaluating other nonsensitizing antimicrobial chemicals and helping to identify potentially conserved mechanisms that contribute to allergic disease. Results of this project will help assess the need to evaluate these types of workplace chemicals, leading to better risk assessment and establishment of occupational exposure limits.
Highly sensitive and practical biomarkers for nanotoxicity Pius Joseph	This project includes the development, validation, and testing (using a rat model) of highly sensitive and minimally invasive biomarkers for early detection of pulmonary toxicity that is potentially associated with exposure to toxic nanomaterials. The study is also conducting bioinformatic analysis of the global transcriptomics data 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. Results obtained from preliminary studies have demonstrated that rats exposed to multiwalled carbon nanotubes can be distinguished from those exposed to crystalline nanocellulose using blood gene expression profiles.

Project Study Scientist	Project Summary
Toxicological investigations of nitrogen-doped multiwalled carbon nanotubes Dale Porter	These studies are examining the potential effect of altering the chemical composition of multiwalled carbon nanotubes (MWCNTs) on their bioactivity in vivo by comparing two with different chemical compositions: MWCNTs and nitrogen-doped MWCNTs. Knowledge of doping modification could allow for the development and use of MWCNTs with reduced bioactivity, which might help reduce the hazard from workplace exposures. Such information might enable material scientists to incorporate a prevention-through-design philosophy into new nanoparticle-based technologies using nanomaterials that pose lower risks to human health. These studies should increase our understanding of the toxicological mechanisms responsible for MWCNT-induced pathologies and could help identify extrapulmonary sites of toxicity resulting from systemic transport of MWCNTs after pulmonary exposure.
Neurological risks associated with workplace chemicals and nanomaterials Krishnan Sriram	This is an evaluation of potential neurotoxicological effects associated with exposure to chemical agents, incidental nanoparticles, and engineered nanomaterials in experimental models. This study includes identifying hazards, evaluating molecular mechanisms of neurotoxicity, and identifying potential biomarkers of neurotoxicity. Findings from this study will contribute to the development of novel biomarkers for monitoring exposures and health effects, pre-job planning protocols, hazard and risk assessment paradigms, and occupational safety standards for neurotoxic exposures.
Occupational heat stress, toxicant exposure, and neurological health risks Krishnan Sriram	High environmental temperature is a natural stressor that can influence physiological and behavioral functions. Emerging evidence suggests that the central nervous system is particularly vulnerable to protracted or excessive hyperthermia. Although the physiological effects of hyperthermia are well known, limited information exists on how high-temperature environments influence the neurotoxicological outcome of workplace toxicants. In this project, laboratory-based studies will model relevant worker exposures to mild or moderate heat as well as co-exposure to select chemical and particulate agents. Neurochemical, molecular, and neuropathological assessments will be conducted. High-throughput analysis of the brain genome and proteome will help determine the underlying mechanisms and identify biomarkers that might serve as reliable predictors of neural injury.
Mechanism of carbon nanotube-induced carcinogenesis and aneuploidy Linda Sargent	In vitro exposure of human cells to 1- to 4-nm-diameter single-walled carbon nanotubes disrupts the mitotic apparatus, resulting in errors of chromosome number. Data comparisons with 10- to 20-nm-diameter multiwall carbon nanotubes (MWCNTs) suggest the diameter of the nanotube is important in the genotoxic response and that carbon nanotubes are potentially carcinogenic. This study is exploring the relationship between carbon nanotube diameter and mechanism of carcinogenesis and aneuploidy. Ongoing research is investigating the dose-response relationship of lung tumor promotion in a mouse model.

Project Study Scientist	Project Summary
Nano-metal oxide property affecting fibrogenesis or carcinogenesis Liying Rojanasakul	Metal oxide nanoparticles are increasingly used in a variety of applications having the potential to release particles into the workplace air. Limited published studies using animal models have shown lung inflammation and fibrosis with pulmonary exposure to metal oxide nanoparticles at human exposure-relevant doses. This project is determining the effects of physicochemical properties (size and coating) on metal oxide nanoparticles toxicity and the underlying mechanisms. Results thus far have shown that cerium oxide nanoparticles in mice cause lung inflammation that is particle-size dependent. In addition, consistent fibrogenic effects from cerium oxide nanoparticles are observed in vitro and in an animal model. These results support the development of an economical in vitro tool for predicting the potential toxicity of metal oxide nanoparticles in vivo.
Hydraulic fracturing: toxicological effects of silica and diesel exhaust exposure Jeffrey Fedan	This study of the toxicities of inhaled hydraulic fracturing sand dust (silica)—alone and in combination with inhaled diesel exhaust to mimic worker exposures during hydraulic fracturing operations—is using a battery of in vivo and in vitro experiments to examine the effects of exposure on the lungs, cardiovascular system, immune system, brain, skin, and blood. The initial exposures to silica, using two exposure doses, are complete. Exposures to a low dose of diesel exhaust from a type II diesel engine are underway and exposures to a high dose are complete. The assessment of inhalation exposures to silica in combination with diesel exhaust will be the next phase of this study.
Pulmonary function and nanoparticle inhalation: in vivo and in vitro effects Jeffrey Fedan	In vivo experiments have demonstrated changes in pulmonary function and airway reactivity in animals exposed to multiwall carbon nanotubes (MWCNTs). A comparison of the relative pulmonary toxicities of pristine and nitrogen-doped MWCNTs indicates that doping of MWCNTs with nitrogen might decrease its relative toxicity in comparison to MWCNTs with regard to its effects on pulmonary function. This study is characterizing MWCNT effects on critical aspects of lung function in vivo and airway function in vitro and provide metrics to enable risk assessment strategies.
Health effects of inhaled crude oil Jeffrey Fedan	This project includes the design and building of an inhalation exposure system that delivers crude oil vapor to rats to study the effects of its inhalation on the lungs, cardiovascular system, immune system, brain, skin, and blood. Acute and subchronic inhalation exposures have been completed.
Toxicity assessment of carbon nanotubes and carbon nanofibers from U.S. facilities Aaron Erdely	This study is assessing general pulmonary and systemic toxicity, pathology, biodistribution, and genotoxicity of carbon nanotubes and carbon nanofibers obtained from U.S. facilities. To date, few studies have examined the toxicity of such a broad range of materials collected from manufacturing facilities with direct relevance to U.S. worker health.
Toxicity associated with the life cycle of carbon nanotubes	In vivo and in vitro data suggest that exposure to carbon nanotubes has significant adverse health effects. Few data are available to define the toxicity of carbon nanotubes at each stage of the production life cycle (as

Project Study Scientist	Project Summary
Aaron Erdely	produced, modified post-production, and incorporated into composites), although the numbers of potentially exposed workers increase with each stage. This project is evaluating the pulmonary response and genotoxicity of carbon nanotubes at different stages of production.
A translational in vitro approach to assess cardiovascular risk Aaron Erdely	Respiratory exposure to particulates has been associated with increased mortality from cardiovascular diseases. This project is developing and testing methods to assess cardiovascular risk following pulmonary exposure to engineered nanomaterials and other occupational exposures. It will establish a translational model using ex vivo and in vitro techniques to assess cardiovascular risk from particulate exposures.

NTP at NIOSH: Immunotoxicology Research

Interagency Agreement on Immunotoxicology Research

The NIEHS and NIOSH interagency agreement provides for 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 FY 2018 studies listed below evaluate unique cohorts of individuals from professions associated with immune-mediated occupational diseases.

Immunotoxicology Studies

Project Study Scientist	Project Summary
Identification and characterization of cross-reactive fungal biomarkers Brett Green	Monoclonal and polyclonal antibodies to recombinant fungal biomarker antigens are being developed in this project. The utility of these antibodies is important for quantifying occupationally relevant fungal biomarkers, particularly to those fungi nominated to NTP.
Toxicity of subchronic fungal exposures Brett Green	A model that replicates human exposure is being used to characterize the toxicological and pulmonary immune responses associated with subchronic fungal exposures. This model uses an acoustical generator system and nose-only exposure chamber to characterize toxicological endpoints following subchronic exposures to spores derived from fungi nominated to NTP. Subchronic exposure studies with *Aspergillus fumigatus*, two mycotoxin-producing strains of *Stachybotrys chartarum*, and *A. versicolor* have been completed. Future subchronic exposure studies will focus on an atranone-producing strain of *S. chartarum*, *A. versicolor, Alternaria alternata*, mixed fungal exposures, and other occupationally relevant fungi identified in concurrent NTP-funded fungal diversity studies. These toxicological studies will provide novel data sets that will be used to characterize the hazards that fungal exposure might present to human and occupational health.
Identification and characterization of fungal exposures Brett Green	These studies are investigating and characterizing the diversity of fungi in indoor and occupational environments using internal transcribed spacer region sequencing. In collaboration with intramural and external stakeholders, results from these studies have provided new insight into the complex diversity of mold present in these environments. This methodological approach has been used to support NIOSH Health Hazard Evaluations to characterize microbial hazards in the workplace.
Analysis of mycotoxins in dust samples from a water-damaged building Ju-Hyeong Park	This examination of effects of exposure to fungal secondary metabolites, including mycotoxins, is focused on occupant health in water-damaged buildings. Cost-effective and robust methods have been developed using ultraperformance liquid chromatography-tandem mass spectrometry for simultaneous analysis of 31 fungal secondary metabolites in environmental samples.

Project Study Scientist	Project Summary
	The accuracy of the method has been improved by using eight isotopically labeled (^{13}carbon) mycotoxin internal standards to compensate for extraction loss and matrix effects. The developed method has been applied to (1) examine stability of secondary metabolites in spiked dust samples stored in different temperature conditions at seven different points of time for 2 years, and (2) analyze 500 dust samples collected from our Philadelphia School Study. The project team is currently examining stability of standard materials of fungal metabolites stored at -20^{0}C and 4^{0}C for a year. We will examine the effect of exposure to fungal secondary metabolites on occupants' health using statistical models adjusted for exposures to other microbial agents that were quantified in the epidemiological studies.

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. The FY 2018 efforts listed below address worker exposures to welding fumes, nanosized materials, food flavorings, and other industrial chemicals.

NIOSH mobile lab for field studies

Occupationally Relevant Exposures

Project Study Scientist	Project Summary
Administrative support Elizabeth Whelan	Under this project, support is being provided to NIOSH scientists for (1) participating in review and oversight of NTP activities and (2) attending NTP-related meetings at NIEHS in Research Triangle Park, NC, and Washington, DC.
Occupational exposure assessment of welding fumes with emphasis on manganese compounds Kevin Hanley	In this characterization of welding fume exposures, with a focus on manganese, welders' exposures to total and respirable manganese were evaluated using a novel sequential chemical extraction method to (1) identify industries, such as construction, shipbuilding, manufacturing companies, and unions, involved in welding operations for which the potential for substantial manganese exposure exists; (2) develop methods to identify manganese compounds and different oxidation states based on selective solubility with various welding fume matrices; and (3) characterize welding fume exposures based on welding-associated jobs, tasks, and processes. To date, three manuscripts have been published (and a fourth has been submitted to a journal) that demonstrated excessive manganese exposures associated with welding fumes, often exceeding Threshold Limit Values of the American Conference of Governmental Industrial Hygienists (ACGIH TLVs) by an order of magnitude.
Exposure assessment of engineered nanoparticles Charles Geraci	This identification of workplaces engaged in the synthesis, manufacture, and use of engineered nanomaterials is characterizing workplace exposures to selected engineered nanoparticles.
Durability of nanoscale cellulose fibers in artificial human lung fluids Aleksandr Stefaniak	This project is investigating the in vitro durability of nanocellulose materials in artificial lung fluids. Data generated from this study will be used to inform larger in vivo inhalation studies.
Assessment of occupational exposures to flame retardants Cheryl Estill	This study is comparing exposures among industries, processes, and tasks; determining the routes of exposure; and making 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 data. The results will aid in the design, understanding, and use of toxicological studies and risk assessment. Exposure has been assessed at 19 facilities involved in the manufacture, installation, or use of goods containing these flame retardants. Worksite categories included are manufacture of products that use flexible polyurethane foams; fabrication and manufacture of rigid polystyrene foam; cutting, installing, or spraying polyurethane foam insulation at construction sites; gymnasiums; nail salons; and the fire service industry.
Assessment of occupational exposure to polycyclic aromatic hydrocarbons (PAHs) in coal tar sealant applications Kevin Hanley	This study focuses on the assessment of occupational exposure to PAHs among coal tar sealant workers. Currently, no data are available in the scientific literature on exposure to PAHs and their metabolites for workers applying coal tar sealant-based coatings on pavements. The study is providing data regarding levels of exposure to airborne chemicals for comparison to current NIOSH recommended exposure limits, if available.

Project Study Scientist	Project Summary
	Results for specific PAH chemicals using NIOSH analytical methods will be reported. PAHs were measured in skin wipe samples, and PAH metabolites were measured in biological samples collected from workers to characterize levels present in this workforce. In FY 2018, construction surveys increased the database by 264 PAH measurements for air exposure time-weighted-average calculations; 396 skin wipe PAH measurements; and 252 PAH metabolite analyses in urine specimens.

Appendix: Publications during FY 2018

NTP Reports and Documents

Research Reports

National Toxicology Program. 2017. *NTP Research Report on Biological Activity of Bisphenol A (BPA) Structural Analogues and Functional Alternatives*. NTP Research Report 4. Research Triangle Park, NC: National Toxicology Program (RR-04):1-80.
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Toxicity Reports

National Toxicology Program. 2018. *NTP Technical Report on the Toxicity Studies of Triethylamine (CASRN 121-44-8) Administered by Inhalation to F344/N Rats and B6C3F1/N Mice*. NTP Toxicity Report 78. Research Triangle Park, NC: National Toxicology Program (TOX-78): 1-118.
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Technical Reports

National Toxicology Program. 2017. *NTP Technical Report on the Toxicology and Carcinogenesis Studies of Antimony Trioxide (CASRN 1309-64-4) in Wistar Han [Crl:WI (Han)] Rats and B6C3F1/N Mice (Inhalation Studies)*. NTP Technical Report 590. Research Triangle Park, NC: National Toxicology Program (TR-590): 1-250.
https://ntp.niehs.nih.gov/results/pubs/longterm/reports/longterm/tr500580/listedreports/tr590/index.html

National Toxicology Program. 2018. *NTP Technical Report on the Toxicology and Carcinogenesis Studies of 2,3-Butanedione (CASRN 431-03-8) in Wistar Han [Crl:WI (Han)] Rats and B6C3F1/N*

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Journal Articles and Book Chapters

Research funding sources for each publication are indicated as follows:

[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

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