National Toxicology Program
U.S. Department of Health and Human Services

ANNUAL REPORT for Fiscal Year 2016

Welcome to the 2016 Annual Report

https://ntp.niehs.nih.gov/go/2016annualreport

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

Read the 2016 Letter from the NTP Director.

FY 2016 at a Glance

- Cell Phone Radiofrequency Radiation Program
- NIEHS Celebrated 50 Years of Public Health
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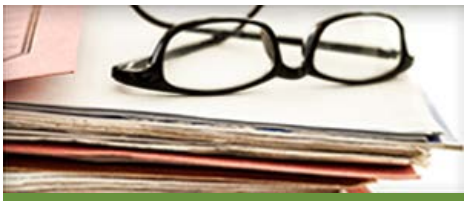

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- Noncancer Research
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Director of Office of Liaison, Policy, and Review and Editor-in-Chief: Mary Wolfe | Managing Editor: Rachel McIntosh-Kastrinsky

Letter From the NIEHS and NTP Director

In fiscal year (FY) 2016, NTP continued to advance toxicology and inform public health policy by providing information about substances in our environment to decision makers and the public. Numerous studies were published on substances of public health concern, such as viruses, metals, and widely used industrial chemicals. NTP also developed more efficient approaches to predict how chemicals may affect human health through the Tox21 initiative.

NTP submitted the 14th Report on Carcinogens to the Health and Human Services Secretary for review and approval in FY 2016. On November 30, 2016, HHS Secretary Sylvia Burwell released the 14th Report on Carcinogens. The newly reviewed listings, include trichloroethylene, five viruses, all listed as known to be a human carcinogen; and the class cobalt and cobalt compounds that release cobalt in vivo, listed as reasonably anticipated to be a human carcinogen. There are a total of 248 substances listed in the report.

In May 2016, NTP released preliminary study findings on cancer and cell phone radiofrequency radiation in rats. Previous human observational studies have found limited evidence for an increased risk of cancer from cell phone use. In these new studies, NTP scientists found low incidences of tumors in the brains and hearts of male rats, but not in female rats. These findings have been shared with federal regulatory partners to ensure they have the latest information available for public health guidance on cellular telephones and other radiofrequency radiation emitting devices.

I invite you to read this report to learn about what we accomplished in FY 2016 to safeguard public health by informing policy with the best science.

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

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)

FY 2016 at a Glance

Cell Phone Radiofrequency Radiation Program

NTP released preliminary findings on cancer and cell phone radiofrequency radiation in rats.

NIEHS Celebrated 50 Years of Public Health

NIEHS celebrated 50 years of public health with commemorative activities throughout the year.

Completed NTP Reports

NTP studies are published in NTP report series after undergoing peer review. NTP reports that have been published in FY 2016, or are expected for peer review in FY 2017 are listed.

Timeline of Events

Highlighted NTP activities in FY 2016.

NTP Workshop Explores Challenges of Botanical Dietary Supplement Safety

NTP hosted workshop to discuss challenges of testing botanical dietary supplements.

Workshop Held on Health Effects of Light at Night

International panels of experts discuss how disruptions to circadian rhythms may affect health.

NTP and Partners Launch Tox Testing Challenge

NTP in partnership with the NIH National Center for Advancing Translational Sciences and the Environmental Protection Agency to launch the “Transform Tox Testing Challenge: Innovating for Metabolism.”

NTP Partners with EPA to Reduce Animal Use for Pesticide Testing

Scientists at the U.S. Environmental Protection Agency (EPA) and NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) conducted an analysis to determine if acute oral toxicity data can be used to reliably assign EPA acute dermal hazard classifications.

14th Report on Carcinogens

NTP submitted the 14th Report on Carcinogens to the Health and Human Services Secretary for review in FY 2016.

NTP Impact on Regulatory Agencies

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

Additional Activities

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

Publications

Full citations for NTP reports, journal publications, and book chapters published during FY 2016.

Cell Phone Radiofrequency Radiation Program

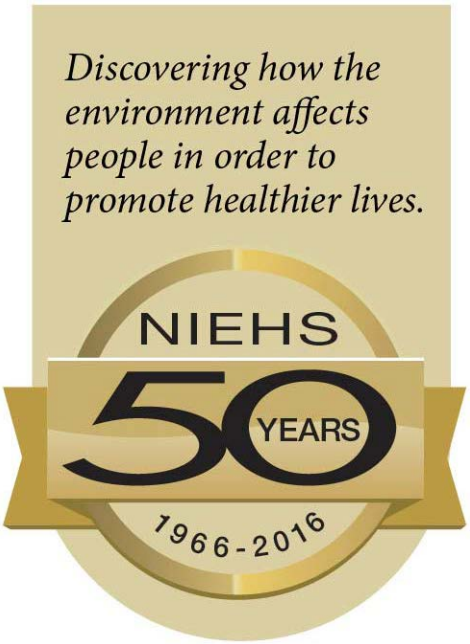
In May 2016, NTP released preliminary study findings on cancer and cell phone radiofrequency radiation in rats. Previous human observational studies have found limited evidence for an increased risk of concern from cell phone use. In these new studies, NTP scientists found low incidences of tumors in the brains and hearts of male rats, but not in female rats. Mice studies are ongoing.

The Food and Drug Administration nominated cell phone radiofrequency radiation to the NTP for review in 2000. NTP conducted these studies in multiple phases to determine the correct field strengths that would not raise animal body temperature and to study the toxicity and cancerous effects at different time periods. Animals were exposed to the two radiofrequency radiation technologies and frequencies widely used in the United States – Code Division Multiple Access (CDMA) and Global System for Mobile (GSM) communications.

These findings have been shared with federal regulatory partners to ensure they have the latest information available for public health guidance on cellular telephones and other radiofrequency radiation emitting devices. The complete results from all the rat and mice studies are tentatively scheduled for peer review and public comment by the end of 2017.

NIEHS Celebrated 50 Years of Public Health

NIEHS celebrated 50 years of environmental public health in FY 2016. Throughout FY 2016, NIEHS hosted events to celebrate and commemorate the institute's history and achievements. Linda Birnbaum, Ph.D., director of NIEHS and NTP, with input and help from NIEHS staff, created and buried a time capsule with items representing NIEHS' work. Several organizations and companies partnered with NIEHS to host seminars, workshops, and public forums to honor NIEHS and to share information about environmental health and the value of NIEHS' research.



In July 2016, the Society of Toxicology and NIEHS hosted a day-long symposium, reflecting on the decades of collaboration and new opportunities to come in the future. During the symposium, Birnbaum lauded the important toxicology work conducted by the NTP over the years. Birnbaum highlighted the establishment of NTP in 1978, NTP's 2004 roadmap for toxicology in the 21st century, and the 2016 publication of the 14th Report on Carcinogens. Speakers commended and thanked Birnbaum and John Bucher, Ph.D., associate director of NTP, for their guidance and perseverance in helping to improve toxicology research applications. The symposium ended with Nigel Walker, Ph.D., NTP deputy division director for research, leading a panel discussion on advice for early-career scientists.

Completed NTP Reports

The results of NTP studies undergo peer review and are published in NTP report series. Long-term toxicology and carcinogenicity studies, generally two-years in length, are reported in the NTP Technical Report series. Toxicity reports are for shorter-term studies, generally up to 13 weeks. NTP Research Reports provide results of peer-reviewed NTP research and literature-analysis activities that do not fall under the scope of existing NTP report series, such as research studies, rapid communications, and literature surveys. All peer reviewers are screened for conflict of interest prior to confirming their service. These reports are available on the NTP website and catalogued in PubMed.

Technical Reports Published During FY 2016 Reporting Levels of Evidence of Carcinogenic Activity

NTP technical reports published in FY 2016 are listed in the table below. NTP used established criteria to evaluate the findings and determine the strength of the evidence for conclusions regarding the carcinogenic activity of each substance. The conclusions for level of evidence of carcinogenic activity are included in the table. NTP anticipates three draft technical reports will undergo peer review in FY 2017, as listed in the second table below.

Chemical	Technical Report Number/CASRN*	Use	Male Rats	Female Rats	Male Mice	Female Mice
Bromodichloroacetic Acid	TR-583 71133-14-7	Forms when drinking water supplies containing natural organic matter are disinfected with chlorine-containing oxidizing compounds and when bromide is present in the source water.	Clear evidence	Clear evidence	Clear evidence	Clear evidence
Green Tea Extract	TR-585 N/A	Nutraceutical supplements and medicinal uses containing green tea extract are commonly consumed for weight loss. Green tea extracts are popular ingredients in sunblocks, cream rinses, and other cosmetics.	No evidence	No evidence	No evidence	No evidence
Pentabromodiphenyl Ether Mixture [DE-71 (Technical Grade)]	TR-589 32534-81-9	Flame retardant in furniture materials.	Clear evidence	Clear evidence	Clear evidence	Clear evidence

Technical Reports Expected to Undergo Peer Review in FY 2017

Chemical	Technical Report Number/CASRN*	Use
2,3 Butanedione	TR-593 431-03-8	Artificial flavor formulations, such as cake mixes, flour, beer, wine, margarine, cheese, candy, crackers, cookies, ice cream, and many others food and beverage products.
p-Chloro-a,a,a-trifluorotoluene	TR-594 98-56-6	Solvent used in paints and coatings, and as an industrial intermediate in the productions of other chemicals (e.g., herbicides, dyes, pharmaceuticals).
Zinc, dietary	TR-592 5263-02-5	Used in wide range of industries including rubber production, animal feed supplement, fertilizer additive, cosmetics, drugs, paint pigment, dental cements, wood preservatives, batteries, galvanizing and metal work, textile production, television screens, watches, and smoke bombs.

Toxicity Reports Published During FY 2016

NTP Toxicity Reports evaluate and characterize the toxicologic potential of a substance under study conditions. NTP toxicity reports published in FY 2016 are listed in the table below.

Chemical	Toxicity Report Number/ CASRN*	Use
Octahydro-tetramethyl-naphthalenyl-ethanone	TOX-92 54464-57-2 (β-isomer) 68155-67-9 (α-isomer) 68155-66-8 (γ-isomer)	Perfume ingredient in soap, shampoo, cologne, liquid detergent compounds, and malodor-reducing compounds
p-Toluenesulfonamide	TOX-88 70-55-3	Formed from chloramine-T, an antimicrobial agent used by the aquaculture industry to treat fish intended for human consumption. Chloramine-T is also widely used as a disinfectant in the medical, dental, veterinary, food processing, and agricultural industries.
alpha-Pinene	TOX-81 80-56-8	Main component in turpentine and is used as a fragrance and flavoring ingredient.
Sodium thioglycolate	TOX-80 367-51-1	Antioxidant, depilating agent, hair waving/straightening agent, and reducing agent ingredient in cosmetic industry.

Research Reports Published During FY 2016

The NTP research report series was launched in FY 2016 to promote transparency and reproducibility. The series also strengthens the science base and provide information useful for public health decision-makers. NTP research reports published in FY 2016 are listed in the table below.

Report Title	Research Report Number
Systematic Literature Review on the Effects of Fluoride on Learning and Memory in Animal Studies	RR-01
Organotin and Total Tin Levels in Danish Women of Reproductive Age	RR-02

*CASRN = Chemical Abstracts Service Registry Number

FY 2016 Timeline

October 2015

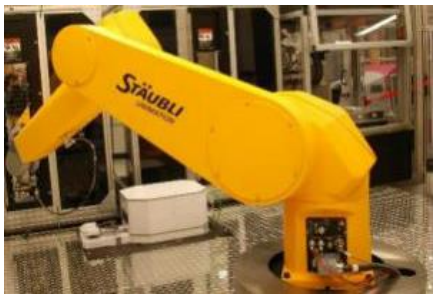
NTP Technical Report on Bromodichloroacetic Acid

Bromodichloroacetic acid occurs as a by-product of water disinfection. In October 2015, NTP released a technical report on bromodichloroacetic acid (TR-583).

December 2015

NTP Board of Scientific Counselors Meeting

At the December Board of Scientific Counselors meeting, members reviewed the NTP Cellular and Molecular Pathology Branch, voted on a contract concept, and were updated on NTP meetings and draft reports, such as the Report on Carcinogens peer-review meeting on cobalt.



January 2016

Toxicity Testing Challenge Launched

To spur innovation and advance predictive toxicology, NTP partnered with the NIH National Center for Advancing Translational Sciences and the U.S. Environmental Protection Agency to launch the Transform Tox Testing Challenge: Innovating for Metabolism. The goal of the challenge is to improve Tox21 bioassays by incorporating metabolism capabilities.

January 2016

ICCVAM Communities of Practice Webinar: Predictive Toxicology

The second ICCVAM Communities of Practice webinar, Fundamentals of Using Quantitative Structure-Activity Relationship Models and Read-across Techniques in Predictive Toxicology, was held on January 26, 2016.

February 2016

NICEATM Workshop: In Vitro to In Vivo Extrapolation

NICEATM and the U.S. Environmental Protection Agency presented a webinar series from October 2015 through January 2016 that was background for a workshop held on February 17-18, 2016."

February 2016

NTP Technical Report on Pentabromodiphenyl Ether

Pentabromodiphenyl ether mixture [DE-71 (technical grade)] was used in the past as an additive flame retardant, often in furniture. In February 2016, NTP released a technical report on pentabromodiphenyl ether mixture [DE-71 (technical grade)].

March 2016

Workshop on Health Effects of Light at Night

In March 2016, NTP hosted a workshop to obtain external scientific input on strategies for integrating data, identifying data gaps and research needs on the potential health effects of light at night.

March 2016

NTP Partners with EPA to Reduce Animal Use for Pesticide Testing

Scientists at the U.S. Environmental Protection Agency and NICEATM conducted an analysis to determine if acute oral toxicity data can be used to reliably assign EPA acute dermal hazard classifications.

March 2016

NICEATM Workshop: Acute Inhalation Toxicity

NICEATM and the People for the Ethical Treatment of Animals International Science Consortium co-hosted a webinar series on Alternative Approaches for Acute Inhalation Toxicity to Address Global Regulatory and Non-regulatory Data Requirements.

April 2016

NTP Workshop Explores Challenges of Studying Hazards of Botanicals

In April 2016, NTP hosted a workshop to discuss current knowledge about the safety of botanicals and what research gaps may exist.

April 2016

NTP Board of Scientific Counselors Meeting

At the April 2016 Board of Scientific Counselors meeting, members reviewed two draft Report on Carcinogens concepts on (1) di- and tri-haloacetic acids found as water disinfection by-products and
(2) *Helicobacter pylori* (chronic infection).

April 2016

NTP Technical Report on Green Tea Extract

Green Tea Extract is used in nutraceutical supplements for weight loss and as an ingredient in skincare products. In April 2016, NTP released a technical report on green tea extract.

May 2016

Cell Phone Radiofrequency Radiation Program

In May 2016, NTP released preliminary study findings on cancer and cell phone radiofrequency radiation in rats. In these new studies, NTP scientists found low incidences of tumors in the brains and hearts of male rats, but not in female rats.

May 2016

ICCVAM Public Forum

ICCVAM held its third public forum on May 25, 2016, at NIH in Bethesda, Maryland. The forum highlighted a proposal for a roadmap to replace animal use in U.S. safety testing.

June 2016

NTP Board of Scientific Counselors Meeting

At the June 2016 Board of Scientific Counselors meeting, members were updated on NTP research activities such as glyphosate research scoping, studies of synthetic turf, and other topics.

July 2016

NIEHS Celebrates 50th Anniversary

NIEHS celebrated 50 years of environmental public health in FY 2016. Throughout the year, NIEHS hosted events to celebrate and commemorate the institute's history and achievements.

September 2016

14th Report on Carcinogens

NTP submitted the 14th RoC to the Secretary, Department of Health and Human Services, for review and approval in FY 2016 with recommendations for listing seven newly reviewed substances.

September 2016

SACATM Meeting

Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) met on September 27, 2016, at NIEHS. The meeting focused on a strategy for implementing the vision for regulatory toxicity testing in the 21st century.

September 2016

NTP Monograph on Perfluorooctanoic Acid and Perfluorooctane Sulfonate

In FY 2016, NTP published the NTP Monograph on Immunotoxicity Associated with Exposure to Perfluorooctanoic Acid or Perfluorooctane Sulfonate, the first evaluation using a systematic review approach.

NTP Workshop Explores Challenges of Botanical Dietary Supplement Safety

Botanical dietary supplements, such as green tea extract and black cohosh, are regularly used by Americans, but recent public concern has raised questions about their safety. NTP is working to identify any adverse health effects that may occur from taking botanicals.

In April 2016, NTP hosted a workshop to discuss current knowledge about the safety of botanicals and what research gaps may exist. The workshop brought together representatives of federal agencies, industry, and research institutions to examine this issue. One of the issues the workshop reviewed was how a well-characterized reference botanical may relate to its peers in the marketplace. NTP toxicologist Cynthia Rider, Ph.D., presented case studies on *Ginkgo biloba*, black cohosh extract, and *Echinacea purpurea* extract. The case studies highlighted complex study issues, such as the number of botanical supplement constituents, the large fraction of constituents that may be unidentified, and the multiple interactions that could occur between constituents.

The workshop helped highlight issues and considered paths forward in research. For more information on this workshop, go to the NTP workshop website. NTP will continue its work on botanical dietary supplements in FY 2017.

Workshop Held on Health Effects of Light at Night

Artificial light at night disrupts many people's circadian rhythm (or light-dark cycles due to things like electronic device usage, urban light pollution, and working at night (or night shift work. This disruption can alter biological processes that may result in adverse health outcomes. NTP's Office of the Report on Carcinogens and Office of Health Assessment and Translation plan to conduct health hazard assessments to review cancer and noncancer outcomes.

In March 2016, NTP hosted a workshop to obtain external scientific input on strategies for integrating data across evidence streams and exposure scenarios, data gaps, and research needs. The workshop considered circadian disruptions from:

- Exposure to light at night, including use of electronic devices at night and urban light pollution.
- The complex scenario of shift work, which can involve interruptions in light-dark cycles and changes in sleep patterns.
- Changes in the timing of exposures to natural light, including jet lag.

Participants helped define the scope of the literature-based evaluations, including defining the topic, identifying the most relevant types of studies, and selecting approaches to synthesize across studies. Participants noted it is important to define circadian rhythm before scientists can address circadian disruptions, especially when considering seasonality. Participants also remarked on the need to address the different study designs in published papers, such as the type of light used and a species' sensitivity to light.

NTP is using the input from the workshop to guide the cancer and noncancer health assessments. More information on the health assessment can be found on the Report on Carcinogens Substances Selected for Evaluation page.

NTP and Partners Launch Tox Testing Challenge

To spur innovation and advance predictive toxicology, NTP partnered with the NIH National Center for Advancing Translational Sciences and the U.S. Environmental Protection Agency to launch the “Transform Tox Testing Challenge: Innovating for Metabolism.” In many chemicals shown to have toxicity, the toxicity mechanism results from the chemical breaking down during metabolism into more reactive metabolites (similar chemical structures. The goal of the challenge is to improve Tox21 bioassays by incorporating metabolism capabilities.

The three-stage challenge issued in January 2016 offered to provide up to $1 million in total prizes for modifications to existing high throughput screening (HTS assays that allow both chemicals and their metabolites to be evaluated. Stage 1 of the challenge asked participants to submit concepts on how to integrate metabolism into Tox21 assays. The Stage 1 winners were asked to present their concepts at a workshop hosted by the challenge partners in July 2016. During the workshop, challenge partners and participants discussed the concepts and how to turn the concepts into prototypes for Stage 2 of the Challenge.

In September 2016, challenge partners launched Stage 2, where participants were asked to create a prototype and produce proof-of-concept data. During Spring 2017, partners will review the Stage 2 data and announce the winners that will move on to Stage 3 of the challenge. In Stage 3, participants will demonstrate a standardize method for incorporating metabolism into Tox21 bioassays.

NTP Partners with EPA to Reduce Animal Use for Pesticide Testing

Scientists at the U.S. Environmental Protection Agency (EPA) and NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) conducted an analysis to determine if acute oral toxicity data can be used to reliably assign EPA acute dermal hazard classifications. The analysis was the basis for a draft guidance document issued by EPA in March 2016. The draft guidance provides a rationale for waiving all acute dermal toxicity studies for pesticide formulations. This waiver is expected to reduce animal use for acute toxicity testing by at least 2,500 animals per year.

Acute dermal toxicity tests, which assess the likelihood that a chemical will cause illness when absorbed through the skin, are used by the EPA to determine labeling and personal protective equipment requirements for users of pesticides. The guidance on acute toxicity testing will be finalized in FY 2017, and is part of a broader effort by EPA to significantly reduce animal use for acute effects testing.

14th Report on Carcinogens

NTP submitted the 14th Report on Carcinogens (RoC) to the Health and Human Services (HHS) Secretary for review and approval in FY 2016 and HHS released the 14th RoC on November 3, 2016. This cumulative report contains 248 listings, of which seven were newly reviewed.

The chemical trichloroethylene (TCE), and the metallic element cobalt and cobalt compounds that release cobalt ions in vivo, were recommended to be added to the list, as well as five viruses that have been linked to cancer in humans. The five viruses include human immunodeficiency virus type 1, human T-cell lymphotropic virus type 1, Epstein-Barr virus, Kaposi sarcoma-associated herpesvirus, and Merkel cell polyomavirus.

Newly Listed Substances

Substance	Listing Status	Description
Human immunodeficiency virus type 1 (HIV-1)	Known to be a human carcinogen	Virus
Human T-cell lymphotropic virus type 1 (HTLV-1)	Known to be a human carcinogen	Virus
Epstein-Barr virus (EBV)	Known to be a human carcinogen	Virus
Kaposi sarcoma-associated herpesvirus (KSHV)	Known to be a human carcinogen	Virus
Merkel cell polyomavrius (MCV)	Known to be a human carcinogen	Virus
Trichloroethylene (TCE)	Known to be a human carcinogen	Industrial solvent
Cobalt and cobalt compounds that release cobalt ion in vivo	Reasonably anticipated to be a human carcinogen	A metal and its compounds

The Report on Carcinogens is a congressionally mandated report prepared for the HHS Secretary by NTP. The report identifies many different types of environmental factors, collectively called substances,

including chemicals; infectious agents, such as viruses; physical agents, such as X-rays and ultraviolet radiation; mixtures of chemicals; and exposure scenarios in two categories — known to be a human carcinogen and reasonably anticipated to be a human carcinogen. The new report is available at https://ntp.niehs.nih.gov/go/roc14.

It's important to note that a listing in the report indicates a cancer hazard, but does not by itself mean that a substance or a virus will cause cancer. Many factors, including an individual's susceptibility to a substance, and the amount and duration of exposure, can affect whether a person will develop cancer. In the case of viruses, a weakened immune system may also be a contributing factor. People should talk to their health care providers about decreasing their cancer risk from viruses.

The Report on Carcinogens, 14th Edition, is prepared by the National Toxicology Program (NTP). NTP is a federal, interagency program, headquartered at the NIEHS, whose goal is to safeguard the public by identifying substances in the environment that may affect human health. For more information about NTP and its programs, visit https://ntp.niehs.nih.gov.

NTP Impact on Regulatory Agencies

Federal and state regulatory agencies use NTP study data and recommendations in considering the need to regulate and test specific chemicals to protect human health. Below is a table highlighting the NTP data and recommendations used by other agencies in FY 2016. A full listing is also available on the NTP website.

Use of NTP Study Data or Recommendations by Federal and State Regulatory Agencies in FY 2016

Notice	Summary of Notice	NTP Information Cited
Chemical listed effective August 5, 2016, as known to the state of California to cause cancer: 1-bromopropane	Effective August 5, 2016, the Office of Environmental Health Hazard Assessment is adding 1-bromopropane (CASRN* 106-94-5) to the list of chemicals known to the state to cause cancer for purposes of Proposition 65. August 05, 2016 -- Proposition 65	National Toxicology Program (NTP, 2011). National Toxicology Program. Toxicology and Carcinogenesis Studies of 1 Bromopropane (CASRN 106-94-5) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). Technical Report Series No. 564. NIH Publication No. 11-5906. U.S. Department of Health and Human Services, NTP, Research Triangle Park, NC.
Chemical listed effective July 29, 2016 as known to the state of California to cause cancer: bromodichloroacetic acid	Effective July 29, 2016, Office of Environmental Health Hazard Assessment is adding bromodichloroacetic acid (CASRN* 71133-14-7) to the list of chemicals known to the state to cause cancer for purposes of Proposition 65. July 29, 2016 -- Proposition 65	National Toxicology Program (NTP, 2015). Toxicology Studies of Bromodichloroacetic Acid (CASRN 71133-14-7) in F344/N Rats and B6C3F1 Mice and Toxicology and Carcinogenesis Studies of Bromodichloroacetic Acid in F344/NTac Rats and B6C3F1/N Mice (Drinking Water Studies). NTP Technical Report Series No. 583. US Department of Health and Human Services, NTP, Research Triangle Park, NC.
Chemical listed effective April 22, 2016 as known to the state of California to cause cancer: styrene	Effective April 22, 2016, Office of Environmental Health Hazard Assessment is adding styrene (CASRN* 100-42-5) to the list of chemicals known to the state to cause cancer for purposes of the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65). The listing of styrene is based on formal identification by the National Toxicology Program, an authoritative body, that the chemical causes	National Toxicology Program (NTP, 2011). Report on Carcinogens, Twelfth Edition, US Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina, page 383-391.

	cancer. The criteria used by Office of Environmental Health Hazard Assessment for the listing of chemicals under the “authoritative bodies” mechanism can be found in Title 27, Cal. Code of Regs., section 25306. April 22, 2016 -- Proposition 65	
Final Rule: diflubenzuron; pesticide tolerances	Through this regulation the U.S. Environmental Protection Agency establishes tolerances for residues of diflubenzuron in or on multiple commodities. Interregional Research Project Number 4 (IR–4) requested these tolerances under the Federal Food, Drug, and Cosmetic Act. February 12, 2016 -- 81 FR 7466	PCA, a plant metabolite of diflubenzuron, tested positive for splenic tumors in the male rats and hepatocellular adenomas/carcinomas in male mice in a NTP study.
Final Rule: benzyl acetate; exemption from the requirement of a tolerance	Through this regulation the U.S. Environmental Protection Agency establishes an exemption from the requirement of a tolerance for residues of benzyl acetate (CASRN* 140–11–4), when used as an inert ingredient (solvent) in pesticide formulations applied to growing crops only under 40 CFR 180.920. Technology Sciences Group, on behalf of the Huntsman Corporation, submitted a petition to EPA under the Federal Food, Drug, and Cosmetic Act, requesting establishment of an exemption from the requirement of a tolerance. This regulation eliminates the need to establish a maximum permissible level for residues of benzyl acetate. February 12, 2016 -- 81 FR 7473	Because of the confounding effects of corn oil on the incidences of pancreatic neoplasm and because of the controversy over the use of the gavage route of administration, the NTP decided to re-study benzyl acetate using the dosed feed route of administration. In 1993, the NTP conducted a second set of carcinogenicity studies in rats and mice using the dose feed route of administration. The point of departure for benzyl acetate is 110 mg/kg/day from the NTP 2-year carcinogenicity study in mice (dietary study) based on decreased in body weights in both sexes at the LOAEL of 345/375 mg/kg/day. There was no evidence of carcinogenicity in mice and rats.
Final Rule: addition of 1-bromopropane; community right-to-know toxic chemical release reporting	The U.S. Environmental Protection Agency is adding 1-bromopropane to the list of toxic chemicals subject to reporting under section 313 of the Emergency Planning and Community Right-to-Know Act of 1986 and section 6607 of the Pollution Prevention Act of 1990. 1-Bromopropane has been classified	NTP, 2014. National Toxicology Program. Report on Carcinogens, Thirteenth Edition. Released October 2, 2015. U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, Research Triangle Park, NC 27709.

	by the NTP in their 13th Report on Carcinogens as ‘‘reasonably anticipated to be a human carcinogen.’’ EPA has determined that 1-bromopropane meets the EPCRA section 313(d)(2)(B) criteria because it can reasonably be anticipated to cause cancer in humans. November 23, 2015 -- 80 FR 72906	NTP, 2013. Report on Carcinogens Monograph on 1-Bromopropane Office of the Report on Carcinogens, Division of the National Toxicology Program, National Institute of Environmental Health Sciences, U.S. Department of Health and Human Services. NIH Publication No. 13-5982, September 25, 2013

*CASRN = Chemical Abstracts Service Registry Number

Additional Activities

NTP participated in a number of meetings with stakeholders and the scientific community. At the 2016 annual meeting of the Society of Toxicology in New Orleans, staff from NTP and NIEHS participated in more than 35 workshops, symposia, platform sessions, education and information sessions, and poster sessions. The full program, including all NTP and NIEHS activities, can be found at on the Society of Toxicology website.

NIEHS postdoctoral fellow Erin Quist, D.V.M., center, showed Sagi Gillera, left, and Deirdre Tucker, both from the NTP Reproductive Endocrinology Group, updates to the NTP Nonneoplastic Lesion Atlas. (Photo courtesy of Robin Mackar)

NTP also hosts symposiums and workshops to discuss the state of the science, and advances to the field. For example, the 2016 annual NTP Satellite Symposium, Pathology Potpourri, was held in San Diego and the 2017 symposium will be held in Montreal, Canada on June 24. These symposiums are held the day before the Society of Toxicologic Pathology annual meeting. The goal of this annual symposium is to present current diagnostic pathology or nomenclature issues to the toxicologic pathology community, including diagnostically difficult, interesting, or rare lesions, or challenging nomenclature issues. Proceedings of the symposiums will be published in the journal Toxicologic Pathology, along with summaries of presentations on diagnostic or nomenclature issues, and specific pathologic images that were used for audience voting and discussion.

NTP also hosted three webinar series in FY 2016 related to alternative methods development:

- In Vitro to In Vivo Extrapolation for High Throughput Prioritization and Decision Making
- Fundamentals of Using Quantitative Structure-Activity Relationship Models and Read-across Techniques in Predictive Toxicology
- Alternative Approaches for Acute Inhalation Toxicity to Address Global Regulatory and Non-regulatory Data Requirements

Publications

NTP Reports and Documents

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[1] Funded by the NIEHS/NIOSH Interagency Agreement

[2] Funded by NIOSH voluntary allocations to the NTP

[3] Funded by the NIEHS/NCTR Interagency Agreement

[4] Funded by NCTR voluntary allocations to the NTP

[5] Funded by NIEHS voluntary allocations to the NTP

Learn About Us

Mission and Goals

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

Organizational Structure and Oversight

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

Funding

The total NTP budget for FY 2016 and contracts that support NTP research.

Program Contact Information

General inquiries, websites, and staff directory information.

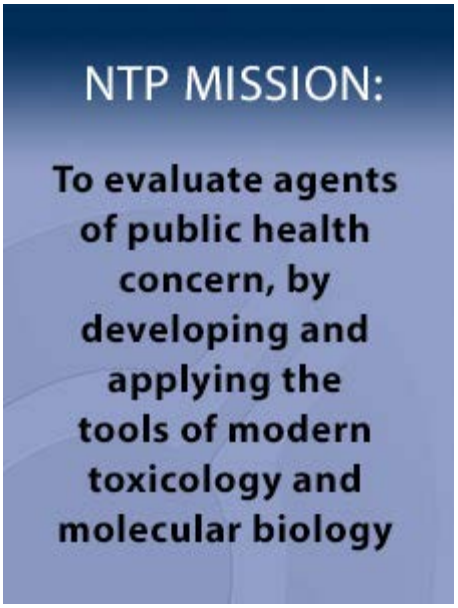
Training Opportunities

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

Interagency Agreements

In FY 2016, NIEHS provided support for NTP activities through interagency agreements with other federal agencies.

Mission and Goals



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

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

NTP provides scientific data, interpretation, and guidance in the appropriate uses of these data to regulatory agencies and other health-related research groups. The American people and government agencies, at state and federal levels, rely on NTP to provide a strong scientific basis for making credible decisions that will protect public health. In the past 38 years, NTP has studied and shared information on the health effects of more than 2,500 substances, including dietary supplements, industrial chemicals, consumer products, and complex mixtures.

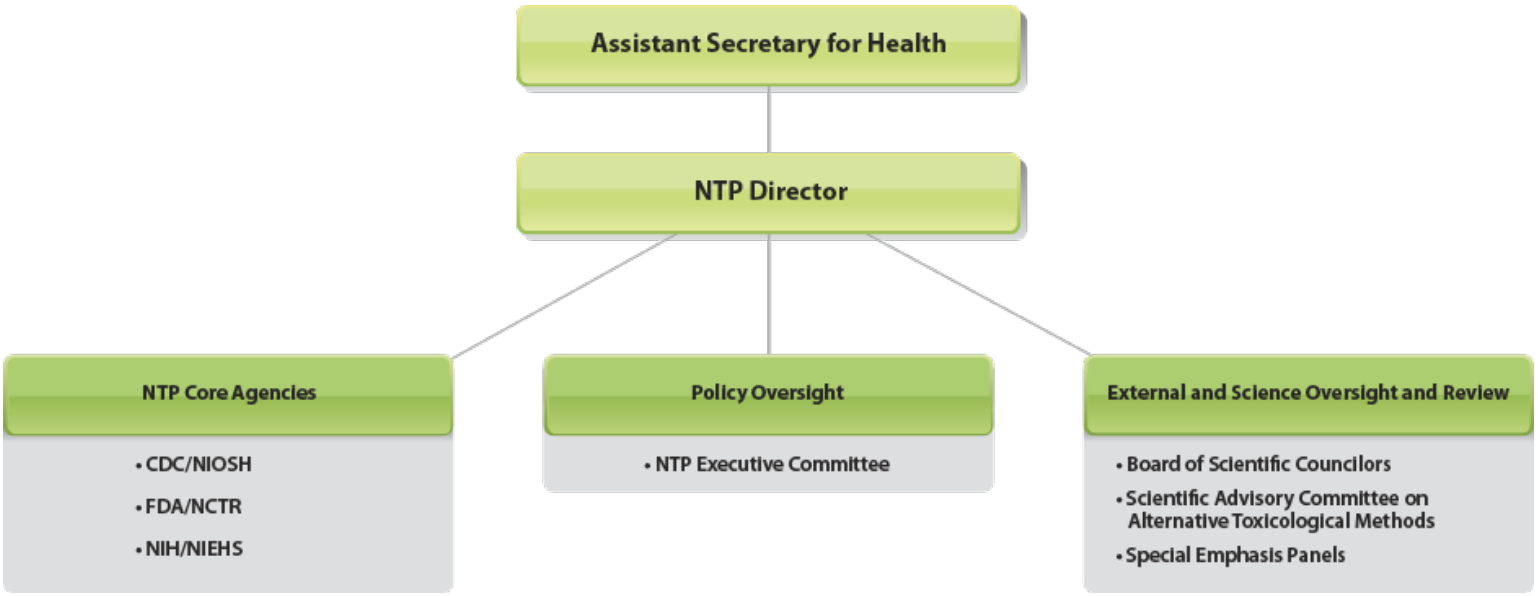
In following government-wide efforts to increase access to the results of federally funded scientific research, NTP maintains open communications and dialogue with federal and state agencies, industry, nongovernmental organizations, academia, and the public. The NTP website provides the public with a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

The public and other interested parties can stay abreast of NTP activities and events by subscribing to the NTP listserv, an email notification system. In addition, requests for information can be made through the Central Data Management office via email or calling 919- 541-3419, or Freedom of Information Act coordinator.

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

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

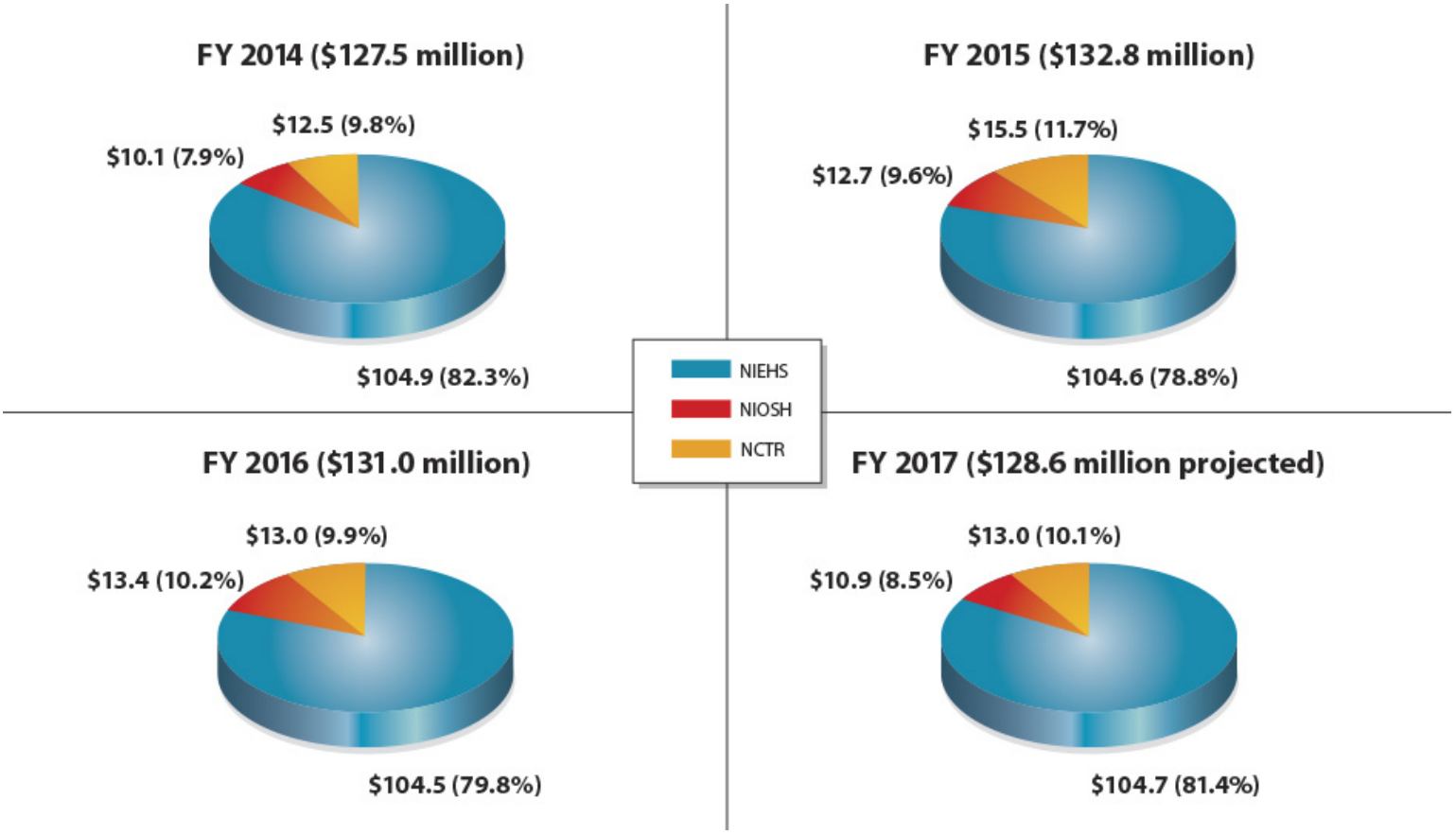
John Howard, M.D., is director of NIOSH, and Elizabeth Whelan, Ph.D., chief of the Industrywide Studies Branch of the Division of Surveillance, Hazard Evaluations, and Field Studies, manages NTP activities within NIOSH, herein referred to as NIOSH/NTP. Staff from three NIOSH divisions participate in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

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

William Slikker Jr., Ph.D., is director of NCTR, and Paul Howard, Ph.D., associate director of the Office of Scientific Coordination, manages NTP activities within NCTR, herein referred to as NCTR/NTP. NCTR staff scientists, in partnership with researchers from elsewhere in FDA, other government agencies, academia, and industry, provide innovative technology, methods development, vital scientific training, and technical expertise. NCTR conducts an array of studies that reflect the NTP mission and are critical in supporting FDA product centers and their regulatory roles.

Funding

NTP relies on voluntary allocations from the three core agencies, NIEHS, FDA/NCTR, and NIOSH, to support its activities. These allocations are specified after annual appropriations have been determined. As shown in the figure, the total NTP budget for FY 2016 was $131.0 million.



NTP conducts its research studies through contract laboratories, in-house at the three core agencies, or through interagency agreements with other agencies. In FY 2016, NIEHS funded 30 contracts, listed in the table below, held three workshops, three special emphasis panel peer-review meetings, and one scientific advisory meetings for NTP. There may be additional contracts at the other agencies that support some of their voluntary NTP efforts.

NIEHS Contracts That Supported NTP Activities in FY 2016

Description	Contractor
Absorption, Distribution, Metabolism & Excretion	Research Triangle Institute
Accelerating Dev/Use of Computational Methods and models	U.S. Environmental Protection Agency
Analytical Chemistry Services	Battelle Battelle Memorial Midwest Research Institute Research Triangle Institute

Archives and Specimen Repository	Experimental Pathology Laboratories
Assessment of Bioavailability following Exposure to 30 Compounds with potential for Developmental Toxicity in Zebrafish Embryos	BBD Biophenix USA, LLC
Bioinformatics and Computational Support	Kelly Scientific
Bioinformatics Methylation Project	Laboratory Corp of America
Evaluate Toxicity Following Early Life Exposure	Southern Research Institute
Evaluation of Alternative Toxicological Methods	Integrated Laboratory Systems
Genetic Toxicity Testing Support Services	Integrated Laboratory Systems
Immunotoxicity Potential of Environmental and Therapeutic Agents	Burleson Research Technologies
In Life Data Collection and Management System	INSTEM, LSS
NTP Computer and User Support	Vistronix Inc.
NTP Information Systems Support	Signature Consulting Group, LLC
NTP Statistical and Computer Support	SRA International
NTP Technical Reports Preparation Support Services	Biotechnical Sciences, Inc.
Pathology Support	Experimental Pathology Laboratories Integrated Laboratory Systems PAI/Charles River Laboratories
Production of B6C3F1 Mice	Taconic Biosciences, Inc.
Production of Harlan Sprague Rats	Envigo
Reproductive Assessments by Continuous Breeding	Research Triangle Institute
Provision for Animals and Specialized Services	Charles River, Jax, Taconic
Quality Assessment Support/Audits & Inspections	CSS-Dynamac Corporation
Receptor Activation Assays	University of California - Irvine
Scientific Information Management and Literature Based Evaluations for the NTP	ICF
Screening for Cardiotoxicity and Neurotoxicity Combined with Heptatotoxicity in Zebrafish	BBD Biophenix USA, LLC
Statistical Support	Social and Scientific Systems
Support for preparation of the Report on Carcinogens	Integrated Laboratory Systems
Support for Toxicological Data	Vistronix, LLC.
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
919-541-3419
cdm@niehs.nih.gov (or use our contact form).

A **Staff Directory** is available.

Training Opportunities

NIEHS/NTP offers a limited number of postdoctoral training fellowships to prepare trainees for careers in pharmaceutical and chemical industries, regulatory agencies, and academia. Full details on opportunities, benefits, and the application process can be found on the NIEHS training website. The training program has six focal areas: applied toxicology and carcinogenesis, biomolecular screening and computational toxicology, health assessment and translation, laboratory animal medicine, systems and mechanistic toxicology, and toxicological pathology. In FY 2016, NIEHS/NTP staff mentored 18 postdoctoral fellows at NIEHS.

NIEHS/NTP Training Program Postdoctoral Fellows in FY 2016

Training Program	Fellow
Applied toxicology and carcinogenesis	Natasha Catlin Anika Dzierlenga Georgia Hinkley Kristen Ryan Kelly Shipkowski
Biomolecular screening and computational toxicology	Jui-Hua Hsieh Sreenivasa Ramaiahgari
Health assessment and translation	Katie Pelch
Laboratory animal medicine	Vivian Chen Sheba Churchill
Systems and mechanistic toxicology	Adam Filgo Xiaohua Gao Ngome Makia Ntube (Olive) Ngalame Miaofel Xu
Toxicological pathology	Gregory Krane Erin Quist Eui Jae Sung

Interagency Agreements

In FY 2016, NIEHS provided support for NTP activities through interagency agreements with other federal agencies.

FDA/NCTR

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

This interagency agreement has supported studies on endocrine active agents, dietary supplements, food contaminants, AIDS therapeutics, pediatric medicines, electromagnetic radiation, cosmetics, and nanoscale materials. Studies in these areas have produced 18 published NTP Technical Reports and over 250 peer-reviewed journal publications. Some of the data from the interagency agreement-supported studies have led to an increased understanding of the pharmacokinetics, mechanism of action, or dose-response of substances. Other data have led to refinement of risk assessment models.

CDC/NIOSH

NIEHS/NTP has two interagency agreements with NIOSH. One interagency agreement was established in the early 1990s in response to increased efforts by NTP to study noncancer endpoints. NIOSH and NIEHS/NTP have conducted studies to assess the potential toxicity of exposures to substances such as fungi, mycotoxins, volatile organics, lead, latex, nickel, isocyanates, nanomaterials, and beryllium in occupationally exposed populations. Studies have included workers such as miners, farmers, health care workers, autoworkers, and firefighters exposed to mixtures of chemicals. Several studies examine how genetic variability in immune-inflammatory-antioxidant responses contributes to the development and severity of inflammatory and allergic disease in people of different occupations. NIEHS/NTP and NIOSH are also leveraging the capability of a unique acoustical generating system located at NIOSH to evaluate the potential health effects of exposure to airborne molds in short-term toxicology studies.

The second interagency agreement involves multiple projects. NIEHS/NTP and NIOSH have worked to establish methodologies to assess complex mixtures, such as asphalt fume, welding fume, and tungsten fibers, and to conduct exposure assessments in occupational settings to identify toxicologically relevant exposures. During FY 2016, NIEHS/NTP and NIOSH completed a study evaluating occupational exposure to bisphenol A. Two additional projects are ongoing. The first focuses on an assessment of occupational exposure to alternative flame retardants used in manufacturing, construction, and service industries. The second project assesses exposure to polycyclic aromatic hydrocarbons by applicators of coal tar sealants.

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

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 an ongoing collaboration among federal agencies to characterize the potential toxicity of chemicals by using cells and isolated molecular targets instead of

laboratory animals. This collaboration between NIEHS/NTP and NCATS/DPI should produce data for substances lacking needed toxicological information that can be used to prioritize substances for further studies, including toxicological evaluation, mechanisms of action investigation, and development of predictive modeling for biological response. The use of the assays should greatly increase the number of substances tested and decrease the cost of testing.

Additional Agreements

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

Additional Interagency Agreements in FY 2016

Study-Agency	Description
Development of Tools for Evaluating NTP's Effectiveness - U.S. Department of Energy	Research and development of tools, such as web-mining, that NIEHS can use in its research evaluations of the NTP's effectiveness.
Accelerating Development and Use of Computational Methods and Models - U.S. Environmental Protection Agency	Accelerate development and use of computational methods and models for quantitative and qualitative assessments of the risks of environmental chemicals.

Scientific and Public Input Opportunities

Nominations

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

NTP Board of Scientific Counselors

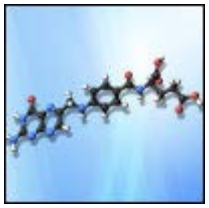
The NTP Board of Scientific Counselors (BSC) provides scientific oversight to NTP on the scientific merit of its programs and activities.

SACATM

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

NTP Executive Committee

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



Special Emphasis Panels

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

Nominations

NTP continually accepts and reviews nominations for studies in its research and testing program. The NTP nomination process is open to the public, and nominations can be submitted via the NTP website. Agencies represented on the NTP Executive Committee also identify and forward nominations to NTP.

For new studies or research projects of substantial scope and complexity, NTP research concepts or project plans are prepared to facilitate external review as part of a multi-step process with input from NTP participating federal agencies, Board of Scientific Counselors, and the public. In addition to new research programs, NTP also conducts targeted studies to extend or explain findings observed in previously conducted studies and address nominations that are closely aligned with current research efforts.

In November 2015, the California Office of Environmental Health Hazard Assessment nominated synthetic turf/recycled tire crumb rubber as part of its Environmental Health Study of Synthetic Turf. In response, NTP formulated plans to conduct a number of studies to enhance the understanding of potential health impacts of chemicals released from synthetic turf with an emphasis on the crumb rubber. The NTP presented the proposed research program to the Board of Scientific Counselors in June 2016.

Also in FY 2016, in response to a nomination from the Environmental Protection Agency's Office of Land and Emergency Management, NTP formulated plans to evaluate the potential for water-soluble thallium compounds to induce neurological, reproductive, and developmental toxicity following subchronic exposure in rodents. The NTP Research Concept was released and presented to the Board of Scientific Counselors in June 2016

Questions about the nomination, review, and selection process can be sent to Scott Masten, Ph.D.

Research and Testing Projects Initiated in FY 2016

Project CASRN* Study Scientist	Nomination Rationale and Project Aims
Synthetic Turf/Recycled Tire Crumb Rubber N/A Roberts	In recent years, public health concern for playing on synthetic turf fields has increased. Crumb rubber, manufactured from recycled tires and used in synthetic turf and playground mats, contains numerous potential carcinogenic and toxic substances. The NTP research program is considering potential routes of human contact with crumb rubber and aims to understand what exposure conditions in an experimental laboratory setting have the potential to impact the risk of developing adverse health outcomes.

Thallium and Thallium Salts: • Metallic Thallium (Tl); 7440-28-0 • Thallium (I) Acetate; 563-68-8 • Thallium (I) Carbonate; 6533-73-9 • Thallium (I) Chlorate; 13453-30-0 • Thallium (I) Chloride; 7791-12-0 • Thallium (I) Nitrate; 10102-45-1 • Thallium (I) Oxide; 1314-12-1 • Thallium (III) Oxide; 1314-32-5 • Thallium Selenide; 15123-92-9 • Thallium Sulfate; 7446-18-6 Shipkowski	Potential for widespread human exposure to thallium exists primarily due to its presence as a contaminant in drinking water near hazardous waste and industrial sites, and from instances of accidental or deliberate poisoning. There is a lack of adequate data to support risk evaluations for human health following thallium exposure. The goal of this research program is to evaluate the potential for water-soluble thallium compounds to induce neurological, reproductive, and developmental toxicity following subchronic exposure in rodents.

*CASRN = Chemical Abstracts Service Registry Number

NTP Board of Scientific Counselors

The NTP Board of Scientific Counselors (BSC), a federally chartered advisory group, provides scientific oversight to NTP on the scientific merit of its programs and activities. The HHS secretary appoints members to the BSC. The BSC can consist of up to 20 scientists, primarily from the public and private sectors, with scientific expertise relevant to NTP activities. The BSC charter and current roster are available on the NTP webpage. Lori White, Ph.D., served as the designated federal officer and manager of the BSC. Below is the roster for FY 2016.

The BSC met three times in FY 2016. During the meeting on December 1-2, 2015 the BSC:

- Reviewed the NTP Cellular and Molecular Pathology Branch and Drs. Robert Sills and David Malarkey.
- Voted on a contract concept on Bioinformatics Support.
- Heard a report on the RoC peer review meeting on cobalt and certain cobalt compounds held in July 2015.
- Reviewed two draft OHAT concepts (1) Mountaintop Removal Mining; Impacts on Health in the Surrounding Community and (2) Proposed NTP Evaluation on Fluoride Exposure and Potential for Developmental Neurobehavioral Effects.
- Heard a report on a draft NTP Technical Report peer reviewed in June 2015 on pentabromodiphenyl ether mixture [DE-71 technical grade].

The second BSC meeting was held April 11, 2016. During this meeting, the BSC reviewed two draft RoC concepts (1) Di- and Tri-Haloacetic Acids Found as Water Disinfection By-Products and (2) *Helicobacter pylori* (Chronic Infection).

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

- Heard an update on new NTP research projects including (1) research problem formulation, (2) a draft research concept on thallium compounds, (3) the synthetic turf/crumb rubber research program, and (4) glyphosate research scoping.
- Heard a report on draft NTP Technical Reports peer reviewed in February 2016 on antimony trioxide and TRIM VX.
- Heard a report on NTP studies of cell phone radiofrequency radiation.
- Heard a report on the RoC peer review meeting on selected viruses held in December 2015.
- Received an update on activities at the FDA National Center for Toxicological Research.
- Heard a report on NTP projects utilizing the NIEHS Clinical Research Unit and then toured the unit.
- Heard reports on three workshops (1) In Vitro to In Vivo Extrapolation for High Throughput Prioritization and Decision Making, held in February 2016; (2) Shift Work at Night, Artificial Light at Night, and Circadian Disruption, held in March 2016; and (3) Addressing Challenges in the Assessment of Botanical Dietary Supplement Safety, held in April 2016.

BSC members and NTP staff at the June 2016 BSC meeting.

NTP Board of Scientific Counselors Membership Roster FY 2016

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. VP and Global Head	Johnson and Johnson Spring House, Pennsylvania	6/30/19
Robert E. Chapin, Ph.D. Laboratory Director	Pfizer Groton, Connecticut	12/27/15
George B. Corcoran, Ph.D., A.T.S. Chair and Professor Department of Pharmaceutical Sciences Eugene Applebaum College of Pharmacy and Health Sciences	Wayne State University Detroit, Michigan	12/27/16
David C. Dorman, D.V.M., Ph.D. Professor College of Veterinary Medicine	North Carolina State University Raleigh, North Carolina	12/27/15

Mary Beth Genter, Ph.D. Associate Professor Department of Environmental Health	University of Cincinnati Goshan, Ohio	6/30/17
Jack R. Harkema, D.V.M., Ph.D., D.A.C.V.P. Distinguished Professor Department of Pathobiology and Diagnostic Investigation	Michigan State University East Lansing, Michigan	12/27/15
Dale Hattis, Ph.D. Research Professor George Perkins Marsh Institute	Clark University Worcester, Massachusetts	12/27/15
Daniel Kass, M.S.P.H. Executive VP Environmental Health	Vital Strategies New York, New York	6/30/19
Steven Markowitz, M.D., Dr.P.H. Professor and Director Center for the Biology of Natural Systems	Queens College City University of New York Flushing, New York	6/30/17
Kenneth McMartin, Ph.D. Professor Pharmacology, Toxicology, and Neuroscience	Louisiana State University Health Science Center Shreveport, Louisiana	6/30/19
Lisa A. Peterson, Ph.D. (BSC Chair Professor Division of Environmental Health Sciences and Masonic Center School of Public Health	University of Minnesota Minneapolis, Minnesota	12/27/16
Kenneth Ramos, M.D., Ph.D. Associate Vice President Precision Health Sciences Center	Arizona Health Sciences Center Tucson, Arizona	6/30/19
Sonya Sobrian, Ph.D. Associate Professor Department of Pharmacology	Howard University Washington, D.C.	12/27/15
James Stevens, Ph.D. Distinguished Research Fellow	Lilly Research Laboratories Indianapolis, Indiana	6/30/19
Iris G. Udasin, M.D. Professor Department of Environmental and Occupational Medicine	Rutgers – Robert Wood Johnson Medical School Piscataway, New Jersey	6/30/16
Karina 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 January 9, 2002, in response to the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Authorization Act of 2000 (42 U.S.C. 285l-3(d)). SACATM advises ICCVAM, the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), and the director of NIEHS and NTP regarding statutorily mandated duties of ICCVAM and activities of NICEATM. SACATM provides advice on priorities and activities related to the development, validation, scientific review, regulatory acceptance, implementation, and national and international harmonization of new, revised, and alternative toxicological test methods. The SACATM charter and current roster are available on the NTP website. The table below provides the roster for FY 2016. SACATM typically meets once a year and members serve rotating terms of up to four years. Lori White, Ph.D., served as the designated federal officer and manager of SACATM.

SACATM met once during FY 2016 on September 27, 2016, at NIEHS. At the meeting, ICCVAM and NICEATM updated SACATM on the activities since the last meeting. The focus of the meeting was a strategy for implementing the vision for regulatory toxicity testing in the 21st century. SACATM was updated on ICCVAM's strategy for the six most commonly used acute animal tests and their roadmap for skin sensitization testing. Additional presentations included (1) moving away from animal models for toxicity testing, (2) impediments to adoption of alternative approaches, (3) coordinating activities between the federal government and stakeholders, (4) promoting adoption of alternative testing strategies, and (5) the next steps toward developing a strategy for implementing the vision for toxicity testing in the 21st century.

Members of SACATM, ICCVAM, and staff from NIEHS and NTP at the September 2016 SACATM meeting

SACATM Membership Roster FY 2016

Name and Title	Affiliation	Term End Date
Brian Berridge, D.V.M., Ph.D., D.A.C.V.P. Director, WW Animal Research Strategy	GlaxoSmithKline King of Prussia, Pennsylvania	11/30/19
Lauren E. Black, Ph.D. Senior Scientific Advisor Navigators Services	Charles River Laboratories Reno, Nevada	11/30/16
Tracie E. Bunton, D.V.M., Ph.D. Consultant	Eicarte LLC Gettysburg, Pennsylvania	11/30/15
Joan M. Chapdelaine, Ph.D. Senior Immunologist and Director, Business Development	Calvert Laboratories, Inc. Scott Township, Pennsylvania	11/30/15
Mark G. Evans, D.V.M., Ph.D., A.C.V.P. Research Fellow La Jolla Laboratories	Pfizer San Diego, California	11/30/15
Hisham 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 (Chair) Executive Director of Lead Discovery	Epizyme, Inc. Cambridge, Massachusetts	6/30/17
Safdar A. Khan, D.V.M., M.S., Ph.D., D.A.B.V.T. Associate Director Global Pharmacovigilance	Zoetis Kalamazoo, Michigan	11/30/16
Lawrence 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. Director of Regulatory and Product Stewardship	ANGUS Chemical Company Buffalo Grove, Illinois	11/30/19
Catherine E. Willett, Ph.D. Director Regulatory Toxicology, Risk Assessment and Alternatives	The Humane Society of the United States Gaithersburg, Maryland	11/30/17
Wei Xu, Ph.D. Associate Professor Department of Oncology McArdle Laboratory for Cancer Research	University of Wisconsin at Madison Madison, Wisconsin	11/30/17
Hao Zhu, Ph.D. Assistant Professor Department of Chemistry	Rutgers University at Camden Camden, New Jersey	11/30/19

NTP Executive Committee

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

- U.S. Consumer Product Safety Commission
- U.S. Department of Defense
- U.S. Environmental Protection Agency
- U.S. Food and Drug Administration
- National Cancer Institute
- National Center for Environmental Health/Agency for Toxic Substances and Disease Registry
- National Institute of Environmental Health Sciences
- National Institute for Occupational Safety and Health
- Occupational Safety and Health Administration

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

Special Emphasis Panels

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

NTP Technical Report Peer Review Panels

NTP Technical Reports are published results of long-term studies, generally two-year rodent toxicology and carcinogenesis studies. NTP convenes external scientific panels to peer review draft technical reports at public meetings held at NIEHS. All reviews provide the opportunity for public comment. For each technical report, the panel is charged with peer reviewing the scientific and technical elements and presentation of the study, and determining whether the study's experimental design and conduct support the NTP conclusions regarding the carcinogenic activity of the substance tested. There was one technical report meeting in FY 2016.

NTP convened a meeting on February 16, 2016, to peer review the draft technical report on antimony trioxide and the draft technical report on TRIM VX. The peer review panel included individuals with expertise in molecular carcinogenesis, physiology, pharmacology, inhalation pathology, statistics, inhalation toxicology, genetic toxicology, occupational health, and general toxicology and pathology. Yun Xie, Ph.D., served as designated federal officer for the meeting.

The meeting was open to the public with time scheduled for oral public comment. The charge to the panel was to (1) review and evaluate the scientific and technical elements of the study and its presentation; and (2) determine whether the study's experimental design, conduct, and findings support the NTP conclusions regarding the carcinogenic activity and toxicity of the substance tested. The panel agreed with the NTP conclusions in the draft technical reports. Additional information about NTP Technical Report peer review meetings can be found on the NTP Technical Reports Peer Review Panels Web page.

NTP Monograph Peer Review Panels

Monographs are publications on a single, detailed specific topic. NTP convened a meeting on July 19, 2016, to peer review the draft NTP Monograph on Immunotoxicity Associated with Exposure to Perfluorooctanoic Acid (PFOA) or Perfluorooctane Sulfonate (PFOS). The peer review panel included individuals with expertise in immunotoxicology, molecular biology, statistics, pharmacokinetics, neurodevelopment, endocrine disrupting chemicals, epidemiology, and toxicology. Yun Xie, Ph.D., served as designated federal officer for the meeting.

The meeting was open to the public with time scheduled for oral public comment. The charge to the panel was to (1) review and evaluate the scientific and technical elements of the study and its presentation; and (2) determine whether the study's experimental design, conduct, and findings support the NTP conclusions regarding whether immunotoxicity is associated with exposure to PFOA or PFOS. The panel agreed with the NTP conclusions in the draft monograph. Additional information about NTP monograph peer review meetings can be found on the Peer Reviews of Draft Monographs Web page.

Report on Carcinogens Peer Review Panels

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

On December 17, 2015, NTP convened a panel at NIEHS to peer review the draft RoC monograph on selected viruses. The panel voted on the draft level of evidence for carcinogenicity determination, based on the available scientific evidence in experimental animals and human cancer studies, and whether the information cited in the draft substance profile supported the NTP preliminary listing recommendation in the RoC. The review covered the viral properties and human exposure, cancer studies in experimental animals, metabolism and mechanistic data, human cancer studies, an overall cancer evaluation, and the draft substance profile. Lori White, Ph.D., served as designated federal officer for the peer review meeting. After the meeting, the input from the panel was considered in finalizing the monograph. Additional information about this meeting and other RoC monograph peer review meetings can be found on the Peer Reviews of Report on Carcinogens Monographs Web page.

NTP Expert Panels

NTP expert panels provide independent advice to NTP on agents of public health concern, new and revised toxicological test methods, or other topics. There were no NTP Expert Panel meetings in FY 2016. Additional information about NTP Expert Panel meetings can be found on the NTP Expert Panels Web page.

Research and Testing

Tox21

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

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), an office within NIEHS/NTP, supports the development and evaluation of new, revised, and alternative methods to identify potential hazards to human health and the environment, with a focus on replacing, reducing, or refining animal use.

ICCVAM

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

Tox21

About Tox21

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

Tox21 Projects

A list of NTP Tox21 projects conducted in FY 2016.

About Tox21

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

In June 2015, the Memorandum of Understanding for High Throughput Screening, Toxicity Pathway Profiling, and Biological Interpretation of Findings was renewed to support continuation of the Tox21 program.

Through this memorandum, NIEHS/NTP partnered with the NIH Chemical Genomics Center (NCGC) part of National Center for Advancing Translational Sciences (NCATS), the EPA National Center for Computational Toxicology, and FDA, to foster the advancement of toxicology to a more predictive science, based on development and implementation of the most relevant and meaningful tools of modern molecular biology and chemistry. This partnership makes it possible to pool resources and overcome the resource limitations of a single agency, build on existing expertise, and avoid the need to create a new administrative and support structure.

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

- Prioritize substances for further in-depth toxicological evaluation.
- Identify mechanisms of action for further investigation, such as disease-associated pathways.
- Develop models that better predict how chemicals will affect biological responses.

Related Links

- Tox21 Projects in 2016

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

Tox21 Phase III was initiated in FY 2013 to increase biological diversity and relevance of screening activity by (1) focusing on more physiologically relevant in vitro cell systems, such as human stem cell-derived differentiated cell populations; (2) incorporating cell types, such as HepaRG, in 2-D and 3-D in vitro models that incorporate xenobiotic metabolism and allow for longer-term exposures; (3) increasing the characterization and use of computational models to predict metabolism and toxicity; (4) increasing the testing of compounds in alternative animal models such as zebrafish; (5) increasing the use of models that provide information concerning the genetic diversity in population responses to exposures; and (6) developing and implementing a high throughput transcriptomics platform for human, rat, mouse, and zebrafish.

Tox21 Projects

Also see:
Tox21 Background

This table describes the NTP Tox21 projects in FY 2016 that are being carried out by NIEHS/NTP staff. Click the project title for a brief summary.

View Research Areas in

Assay Development
Data Analysis
Testing Projects
NTP WormTox Laboratory Projects

Show All

Search Projects

Assay Development

Project & Study Scientist	Project Summary
Developing a stable cell line to screen compounds that affect the estrogen-related receptor/peroxisome proliferator-activated receptor coactivator pathway Study Scientist: Merrick, Teng	To develop an assay that will detect compounds that interfere with the estrogen-related receptor/peroxisome proliferator-activated receptor gamma coactivator pathway, a critical pathway for metabolic homeostasis. Stable human cell lines expressing the appropriate reporter construct were successfully generated. Quantitative high throughput screening efforts with the LOPAC library were completed and a manuscript is in press. Quantitative high throughput screening of the 10K library was completed in FY 2016 and data analysis is ongoing for a manuscript in preparation.
High content screening with HepaRG cells Study Scientist: Ferguson, Ramaiahgari	To establish metabolically functional human HepaRG liver cells in 96-well or 384-well format for carrying out multiplex, high-content screening assays in collaboration with the NIH Chemical Genomics Center. In FY 2015, the focus was on establishing metabolically competent HepaRG cells grown in 2-D and 3-D formats. Studies to characterize the metabolism of xenobiotic compounds in these cells began in FY 2016.

Testing for gene signatures and profiles in NTP archival tissues project Study Scientist: Merrick	To determine if RNA can be extracted from fixed tissue blocks there were produced from NTP studies and are located in the NTP Archives and used to measure gene signatures and develop chemically induced transcriptomics profiles. The goal is to measure molecular changes caused by chemical exposures in different organs of the rat and mouse. An effort to establish a relational database to allow identification and linkage of all tissues in the NTP Archives is underway.
Stem cell projects Study Scientist: Ferguson, Parham, Hsieh, Behl	To screen for chemical toxicity in human or mouse stem cell lines (undifferentiated or differentiated) by quantitative high throughput screening at National Chemical Genomics Center, or by using lower throughput assays at NIEHS. Initially, the project focuses on fostering collaborations with stem cell technology providers and assessing control compounds and subsets of NTP chemicals using various assay approaches. Stem cell technology platforms and model systems shown to be useful for in vitro toxicology screening will be employed with larger sets of chemicals for hazard identification and chemical prioritization for toxicity testing. Data have been generated on a library of 80 predominantly developmental neurotoxicants evaluated for effects on neurite outgrowth in a human stem cell-derived neural cell population, cytotoxicity in different neural populations derived from human stem cells, and effects on the beating of human stem cell derived cardiomyocytes. Dose-response analysis has been carried out on the data from these assays. Two manuscripts were published in February and August 2016.
Use of high throughput assays and computational models to replace current EPA Endocrine Disruptor Screening Program Tier 1 tests Study Scientist: Casey (NICEATM)	To develop an approach 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. EPA solicited public comments on the plan in June 2015. A description of the method has been published.

Data Analysis

Project & Study Scientist	Project Summary
Modeling mixtures of androgen receptor-active and estrogen receptor-active compounds screened in Tox21 quantitative high throughput screening (qHTS) assays Study Scientist: Parham	To determine (1) which mathematical models can best describe the toxicity of mixtures of these compounds; and (2) whether the behavior of the mixtures can be predicted from the behavior of individual components.

Analysis of Tox21 quantitative high throughput screening assay data Study Scientist: Hsieh	To develop data analysis pipelines for Tox21 Phase II quantitative high throughput screening data to determine the activity of compounds in assays. The developed ranking or calling procedure takes into account compound potency, efficacy, and data reproducibility. A manuscript describing this pipeline was published.
Prioritization of Tox21 compounds for genotoxicity Study Scientist: Hsieh, Witt, Smith-Roe	To develop a prioritization approach that includes compounds showing clear evidence of activity in the quantitative high throughput screening genotoxic assays and compounds that are weakly active based on chemical structure-activity relationship analysis. A manuscript is in preparation using this data.
Design of Tox21 data exploration graphical user interface Study Scientist: Hsieh	To develop two graphical user interfaces for viewing Tox21 data. One graphical user interface is to explore the concentration-response data in a line chart, and the second graphical user interface is to explore compound similarity relationships in terms of their activities in Tox21 quantitative high throughput screening assays and their chemical structures. Prototype graphical user interfaces were developed during FY 2013 and made public in FY 2015.
Low-dose extrapolation for Tox21 Phase I quantitative high throughput screening data Study Scientist: Parham	To determine points of departure for low-dose extrapolation by using signal-to-noise ratios and a benchmark-dose method. Data generated by this approach will be used to help prioritize compounds for more extensive toxicological testing.
Unsupervised, data-driven analysis of Tox21 assay data project Study Scientist: Auerbach	To employ unsupervised data analysis methods (data organization based on patterns and performed by software) to identify chemicals that exhibit biological properties similar to those of well-characterized toxicants from the quantitative high throughput screening assays used to screen the 10K library. The results are being used to help prioritize compounds for more extensive toxicological testing.
Next generation sequencing in toxicology project Study Scientist: Merrick	To develop bioinformatics pipelines for genomic and transcriptomic gene expression and mutational analysis on a genome-wide level, using next generation sequencing technologies to build signatures of toxicity and chemical exposure.

Development of a reference database for estrogenic activity
Study Scientist: Casey-NICEATM

To support future validation of high throughput in vitro test methods and in silico models of estrogenic activity. NICEATM created a comprehensive database of high quality in vivo data from over 1,000 scientific articles describing uterotrophic assay experiments for over 2,660 different combinations of chemicals, studies, and protocols. These data have potential utility for leading to development of adverse outcome pathways or models of estrogenic activity, prioritizing chemicals for further testing, or evaluating species-specific responses to chemicals. The database is described in a manuscript was published in FY 2016.

In vitro to in vivo extrapolation using Tox21 data
Study Scientist: Casey-NICEATM

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

Evaluation of Tox21 data for predicting acute oral toxicity
Study Scientist: Casey-NICEATM

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

In silico prediction of metabolism project
Study Scientist: Ferguson

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

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

Study Scientist: Paules

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

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

Study Scientist: Casey-NICEATM

To explore whether domain-specific, quantitative, structure–activity relationship (QSAR) models might provide improved predictions of activity and potency of estrogenic activity. Using data from Tox21 and ToxCast assays, NICEATM is working with scientists at EPA and the University of North Carolina at Chapel Hill to develop QSAR models to predict specific activity and relative potency of phenolic compounds. The domain-specific models consistently yield higher balanced accuracies, sensitivity, and specificity than global models. A manuscript was submitted in FY 2016.

Development of a computational model for androgen receptor pathway activity

Study Scientist: Casey-NICEATM

To integrate data from nine Tox21 and ToxCast assays into a computational model that predicts agonist and antagonist activity against the androgen receptor pathway. A manuscript is in preparation.

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

Study Scientist: Casey-NICEATM

To develop quantitative structure-activity relationship (QSAR) models to predict androgen receptor (AR) binding and activity. Using the computational model of the AR pathway, NICEATM developed QSAR models to predict AR binding and activity. These QSAR models are currently being refined, with a goal of using them to predict AR pathway activity of chemicals in the EPA Endocrine Disruptor Screening Program. A manuscript was submitted in FY 2016.

Development of a reference database for androgen receptor activity

Study Scientist: Casey-NICEATM

To develop a reference chemical list for in vitro androgen receptor binding and transactivation assay activity. NICEATM is conducting literature reviews to identify information about in vitro androgen receptor binding and transactivation assays for 127 putative androgen-active or

	androgen-inactive chemicals. The final database will be made available to the public on the NTP website. A parallel EPA data curation effort is focusing on in vivo androgen activity data. These data will be used for evaluating high throughput screening approaches, testing strategies, and further development of alternative test methods.
Development of a bioactivity-based read-across approach Study Scientist: Casey-NICEATM	To use bioactivity data from ToxCast to characterize untested environmental chemicals based on their similarities to chemicals with known toxicological effects. NICEATM used computational methods to create clusters of tested chemicals based on their activity in ToxCast assays. Clusters containing known toxicants were examined to identify similar in vitro bioactivity patterns in environmental chemicals lacking in vivo data.

Testing Projects

Project & Study Scientist	Project Summary
Epigenetic changes in chemical toxicity project Study Scientist: Merrick	To determine methylation patterns on a genome-wide basis and validate selected CpG sites (regions of DNA where a cytosine nucleotide occurs next to a guanine nucleotide) altered by chemical exposure. Methylation of CpG sites can turn a gene off, while demethylation can cause transcriptional activation. A generalized approach for methylated DNA enrichment, by MBD2 capture following bisulfite reduction and sequencing, has been developed, and a manuscript describing the findings was submitted for publication.
Polycyclic aromatic hydrocarbon (PAH) Study Scientist: Ferguson	To evaluate approximately 20 PAHs considered relevant to human exposure in metabolism-competent HepaRG cells (derived from a human hepatic progenitor cell line), using multiplexed high content screening assays and gene expression platforms. Studies are in progress.
Analysis of 52 compounds in the EPA ToxCast Phase II program Study Scientist: Casey-NICEATM	To screen 52 compounds nominated by NTP, identified based largely on immunological relevance, in the EPA ToxCast program. NICEATM used in vitro chemical profiling data to examine activity profiles in primary human cell systems and identify predictive signatures anchored to in vivo endpoints and toxicity pathways. These analyses will be used (1) to develop adverse outcome pathways and (2) to enable chemical prioritization and hazard predictions.

NTP WormTox Laboratory Projects

Project & Study Scientist	Project Summary
Mitochondrial toxicants project Study Scientist: Boyd	To determine the effects of the mitochondrial toxicant subset from the Tox21 10K library on *Caenorhabditis elegans* growth and in vivo adenosine-5'-triphosphate levels and membrane potential. Compounds for testing were received in late FY 2014. Testing occurred in FY 2015, and a manuscript reporting the findings is in preparation for publication.

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

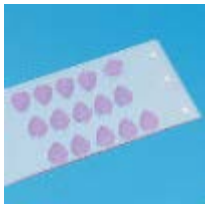
A list of substances evaluated through disposition, metabolism, and toxicokinetic studies.

Genetic Toxicity

A list of substances tested for genetic toxicity.

Organ System Toxicity

A list of substances tested for toxicity in organ systems.

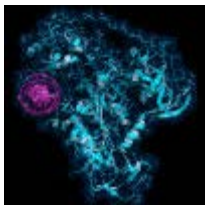


Modified One-Generation Reproduction Studies

A list of planned or ongoing modified one-generation studies in FY 2016.

Toxicology and Carcinogenicity Studies

A list of prechronic and chronic toxicity and carcinogenicity studies that were initiated, ongoing, or completed during FY 2016.



Toxicogenomic Studies

A list of planned or ongoing toxicogenomic studies in FY 2016.

Project Review Committee Approved

A list of studies approved by either the internal NIEHS/NTP protocol approval committee or the internal NIEHS/NTP project review committee, but were not started during FY 2016.

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 2016 are listed in this section. Of note are the multiple study types initiated, scheduled, or approved for bisphenol S, phenolic benzotriazoles, sodium metavanadate, triclocarban, and trimethylsilyldiazomethane.

Related Links

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

Disposition, Metabolism, and Toxicokinetic Studies

Complete dosimetry of a chemical or physical agent describes its absorption, distribution, metabolism, and excretion in the body in both humans and test animals at differing levels of exposure, over all ages, via several routes of exposure, and under varying genetic backgrounds. Substances evaluated during FY 2016 are listed in the table below.

Disposition, Metabolism, and Toxicokinetics Studies During FY 2016

Test Article	CASRN*	Species	Route	Status	Study Scientist
Bisphenol S	80-09-1	Mice, rats	Gavage, intravenous	Ongoing	Sutherland
N-Butylbenzenesulfonamide	3622-84-2	Mice, rats	Gavage, intravenous	Ongoing	Rider
Ethylene glycol 2-ethylhexyl ether	1559-35-9	Mice, rats	Gavage	Completed	Blystone
2-Ethylhexyl p-methoxycinnamate	5466-77-3	Mice, rats	Dermal, gavage, intravenous	Ongoing	McIntyre
Hydroquinone	123-31-9	Mice, rats	Gavage, intravenous, topical application	Ongoing	Sutherland
Nanoscale silver	7440-22-4	Rats	Gavage	Ongoing	Walker
Silver acetate	563-63-3	Rats	Gavage	Ongoing	Walker
Sulfolane	126-33-0	Mice, rats	Gavage, intravenous	Ongoing	Blystone
Triclocarban	101-20-2	Mice, rats	Dermal, gavage	Initiated	Sutherland
Triclosan	3380-34-5	Mice	Topical application	Ongoing	Sutherland
Tris(4-chlorophenyl)methane	27575-78-6	Mice, rats	Gavage, intravenous	Completed	Surh
Tris(4-chlorophenyl)methanol	3010-80-8	Mice, rats	Gavage, intravenous	Completed	Catlin

*CASRN = Chemical Abstracts Service Registry Number

Genetic Toxicity

Genetic toxicity test results are used to help interpret general toxicity, carcinogenicity, or other in vivo test results, and provide a database for use in structure-activity relationship analysis. Substances tested for genetic toxicity during FY 2016 are listed in the table below.

Genetic Toxicity Studies During FY 2016

Test Article	CASRN*	Species	Testing Battery	Status
Aspergillus fumigatus mold	N/A	Mice	Micronucleus	Completed
Black cohosh	84776-26- 1	Salmonella	Salmonella	Completed
N-Butyl glycidyl ether	2426-08-6	Mice	Micronucleus	Ongoing
N-Butyl glycidyl ether	2426-08-6	Rats	Micronucleus	Ongoing
N-Butylpyridinium chloride	1124-64-7	Rats	Micronucleus	Completed
Corn oil	8001-30-7	Rats	Micronucleus	Completed
2,2'-Dimorpholinodiethyl ether	6425-39-4	Salmonella	Salmonella	Ongoing
Echinacea purpurea extract	90028-20-9	Salmonella	Salmonella	Completed
Echinacea purpurea extract	90028-20-9	Salmonella	Salmonella	Completed
Echinacea purpurea extract	90028-20-9	Salmonella	Salmonella	Completed
Echinacea purpurea extract	90028-20-9	Salmonella	Salmonella	Completed
Echinacea purpurea extract	90028-20-9	Salmonella	Salmonella	Completed
Echinacea purpurea extract	90028-20-9	Salmonella	Salmonella	Completed
Echinacea purpurea extract	90028-20-9	Salmonella	Salmonella	Completed
Echinacea purpurea extract	90028-20-9	Salmonella	Salmonella	Completed

2-Nitro-2-ethyl-1,3-propanediol	597-09-1	Salmonella	Salmonella	Completed
Perfluorodecanoic acid	335-76-2	Rats	Micronucleus	Completed
Sulfolane	126-33-0	Rats	Micronucleus	Ongoing
Sulfolane	126-33-0	Mice	Micronucleus	Ongoing
Vinpocetine	42971-09-5	Mice	Micronucleus	Ongoing
Vinpocetine	42971-09-5	Mice	Micronucleus	Ongoing
Zinc carbonate, basic	5263-02-5	Rats	Micronucleus	Completed
Zinc carbonate, basic	5263-02-5	Rats	Micronucleus	Completed
Zinc carbonate, basic	5263-02-5	Rats	Micronucleus	Completed
Zinc carbonate, basic	5263-02-5	Rats	Micronucleus	Completed

*CASRN = Chemical Abstracts Service Registry Number

Organ System Toxicity

NTP studies toxicity of environmental substances on organ systems for development, reproduction, and the immune system. NTP immunotoxicity studies address adverse effects on the immune system that may result from exposure to environmental chemicals, biological materials, or therapeutic agents. Identifying substances with the potential to alter immune system function is critical to the public health field as these substances may lead to increased incidence of hypersensitivity disorders, autoimmune disease, infectious disease, or neoplasia. The table below lists organ systems toxicity studies during FY 2016.

Neurotoxicity, Developmental Toxicity, and Reproductive Toxicity Studies During FY 2016

Test Article	CASRN*	Species	Testing Battery	Length	Route	Status	Study Scientist
Acrylamide	79-06-1	Rats	Neurotoxicology assessment	Phase 1: 3 and 6 months; phase 2:12 and 24 months	Gavage	Ongoing	Beland
Autumn sunset true color concentrate	N/A	Mice	Immunotoxicity	6 days	Subcutaneous injection	Ongoing	Howard
Benzo(a)pyrene	50-32-8	Mice	Immunotoxicity	28 days	Gavage	Ongoing	Rider
Bisphenol AF	1478-61-1	Rats	Immunotoxicity	GD 6 - PND 96	Dosed-feed	Initiated	Sutherland
Dibenz(a,h)anthracene	53-70-3	Mice	Immunotoxicity	8 GD - PND 42	Subcutaneous injection	Ongoing	Germolec
Diethylene glycol dimethyl ether	111-96-6	Mice	Conventional teratology	11 GD (PLUG=GD0)	Gavage	Ongoing	Hardin
Dimethylethanolamine	108-01-0	Rats	Conventional teratology	GD 6 to GD 20	Gavage	Completed	McIntyre
Double dark fudge true color concentrate	N/A	Mice	Immunotoxicity	7 days	Subcutaneous injection	Ongoing	Howard
Double fudge concentrate	N/A	Mice	Immunotoxicity	8 days	Subcutaneous injection	Ongoing	Howard
Efavirenz	154598-52-4	Mice	Teratology pilot studies	GD 5 - PND 21	Gavage	Ongoing	McIntyre
Ethylene oxide	75-21-8	Rabbit	Conventional teratology	7 to 19 GD or 1 to 19 GD	Inhalation	Ongoing	Hardin
2-Hydroxy-4-methoxybenzophenone	131-57-7	Rats	Developmental toxicity	GD 6 to GD 15	Dosed-feed	Ongoing	Hansen
2-Hydroxy-4-methoxybenzophenone	131-57-7	Rats	Developmental toxicity	GD 6 to GD 15	Dosed-feed	Ongoing	Hansen
2-Hydroxy-4-methoxybenzophenone	131-57-7	Rats	Developmental toxicity	GD 6 to PND 21	Dosed-feed	Ongoing	Hansen
4-Methylcyclohexanemethanol	34885-03-5	Mice	Immunotoxicity	7 days	Topical application	Completed	Auerbach

4-Methylcyclohexanemethanol, crude	N/A	Mice	Immunotoxicity	7 days	Topical application	Completed	Auerbach
4-Methylcyclohexanemethanol, crude	N/A	Mice	Immunotoxicity	7 days	Topical application	Completed	Auerbach
Nonylphenol	84852-15-3	Rats	Multigenerational screen	20 weeks	Dosed-feed	Ongoing	Newbold, Delclos
Phenanthrene	85-01-8	Mice	Immunotoxicity	28 days	Gavage	Ongoing	Rider
Pyrene	129-00-0	Mice	Immunotoxicity	28 days	Gavage	Initiated	Germolec
Rosewood true color concentrate	N/A	Mice	Immunotoxicity	6 days	Subcutaneous injection	Ongoing	Howard
Sodium metavanadate	13718-26-8	Mice	Immunotoxicity	28 days	Dosed-water	Initiated	Roberts
Sulfolane	126-33-0	Mice	Immunotoxicity	13 weeks	Gavage	Ongoing	Blystone
Sulfolane	126-33-0	Rats	Immunotoxicity	13 weeks	Gavage	Ongoing	Blystone
Tenofovir disoproxil Fumarate	202138-50-9	Mice	Teratology pilot studies	GD 5 - PND 21	Gavage	Initiated	McIntyre
Tricombination FTC:TDF:EFV (1:1.5:3)	N/A	Mice	Maternal transfer	GD 5-15	Gavage	Initiated	McIntyre
Tricombination FTC:TDF:EFV (1:1.5:3)	N/A	Mice	Teratology pilot studies	GD 5 - GD18	Gavage	Initiated	McIntyre
Vinpocetine	42971-09-5	Rats	Conventional teratology	GD 6 to GD 20	Gavage	Completed	Catlin
Vinpocetine	42971-09-5	Rabbit	Conventional teratology	GD 7 to GD 28	Gavage	Completed	Catlin
Vinyl toluene	2501315-4	Rats	Dominant lethal	5 consecutive days	Intraperitoneal injection	Ongoing	Boorman

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

Modified One-Generation Reproduction Studies

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

Modified One-Generation Studies in FY 2016

Test Article	CASRN*	Species	Planned Cohorts	Route	Status	Study Scientist
2,2'-Dimorpholinodiethyl ether	6425-39-4	Rats	Repeated dose	Gavage	Initiated	Roberts
Ethylene glycol 2-ethylhexyl ether	1559-35-9	Rats	Dose range finding	Gavage	Initiated	Blystone
Isopropylated phenol phosphate	68937-41-7	Rats	Dose range finding	Dosed-feed	Ongoing	Behl
Resveratrol	501-36-0	Rats	F0 generation	Gavage	Ongoing	Germolec
Simvastatin	79902-63-9	Rats	Dose range finding	Gavage	Ongoing	McIntyre
Triphenyl phosphate	115-86-6	Rats	Dose range finding	Dosed-feed	Ongoing	Behl
Valerian (Valeriana officinalis L.) root extract	8057-49-6	Rats	Dose range finding	Gavage	Ongoing	Roberts

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

Toxicology and Carcinogenicity Studies

NTP performs toxicity studies to provide dose-setting information for chronic studies and address specific deficiencies in the toxicology database for the chemical. Toxicology and carcinogenicity studies fall into two categories: prechronic toxicity studies and 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 Toxic and Carcinogenic Potential of Chemical, Biological, and Physical Agents in Laboratory Animals for the National Toxicology Program (January 2011). The tables below list prechronic and chronic toxicity studies and carcinogenicity studies, that were initiated, ongoing, or completed during FY 2016.

Prechronic Toxicology and Carcinogenicity Studies FY 2016

Test Article	CASRN*	Species	Length	Route	Status	Study Scientist
1020 Long multiwalled carbon nanotube	N/A	Mice,rats	30 days	Inhalation	Initiated	Morgan
2-Ethylhexyl diphenyl phosphate	1241-94-7	Rats	5 days	Gavage	Ongoing	Auerbach
2-Ethyltoluene	611-14-3	Mice,rats	14 days	Inhalation	Initiated	Roberts
2,2'-Dimorpholinodiethyl ether	6425-39-4	Mice	28 days	Gavage	Initiated	Roberts
2,2',4,4'-Tetrabromodiphenyl ether	5436-43-1	Rats	GD 6 to PND 21	Gavage	Ongoing	Dunnick
3-Ethyltoluene	620-14-4	Mice,rats	14 days	Inhalation	Initiated	Roberts
3,3,4,4,5-Pentachlorobiphenyl	57465-28-8	Rats	GD 6 to PND 21	Gavage	Ongoing	Dunnick
4-Ethyltoluene	622-96-8	Mice,rats	14 days	Inhalation	Ongoing	Roberts
4-Methylcyclohexanemethanol	34885- 03-5	Rats	5 days	Gavage	Completed	Auerbach
5-Amino-o-cresol	2835-95-2	Mice,rats	13 weeks	Topical Application	Completed	Dunnick
Aloin	1415-73-2	Rats	13 weeks	Dosed-Water	Ongoing	Boudreau
alpha-Pinene	80-56-8	Mice,rats	14 days	Inhalation	Completed	Rider
alpha-Pinene	80-56-8	Mice,rats	13 weeks	Inhalation	Completed	Rider
Aspergillus versicolor mold	N/A	Mice	13 weeks	Inhalation	Completed	Germolec
Bis(2-Chloroethoxy)methane	111-91-1	Mice	10 days, 3 days	Gavage	Ongoing	Dunnick
Black cohosh	84776- 26- 1	Mice	90 days	Gavage	Ongoing	Cora
4-Methylcyclohexanemethanol, crude	N/A	Rats	5 days	Gavage	Completed	Auerbach
Cumene	98-82-8	Mice,rats	14 days	Inhalation	Ongoing	Roberts
Dimethylamine borane	74-94-2	Mice,rats	2 weeks	Dermal	Ongoing	Germolec
Ephedrine + caffeine combination	N/A	Mice	10 days, 3 days	Gavage	Ongoing	Dunnick
Formaldehyde	50-00-0	Mice	2 weeks	Inhalation	Ongoing	Morgan
Formaldehyde	50-00-0	Mice	8 weeks	Inhalation	Ongoing	Morgan
Fumonisin B1	116355-83-0	Mice,rats	13 weeks	Dosed-Feed	Ongoing	Walters

Garcinia cambogia extract	90045-23-1	Mice,rats	14 days	Dosed-Feed	Completed	Rider
Ginkgo biloba extract	90045-36-6	Rats	5 days	Gavage	Initiated	Rider
Goldenseal extract	84603-60-1	Rats	5 days	Gavage	Initiated	Rider
Green tea extract	N/A	Rats	5 days	Gavage	Initiated	Rider
Green tea extract	N/A	Mice,rats	13 weeks	Gavage	Completed	Blystone
Hydroxyurea	127-07-1	Mice,rats	14 days, 13 weeks	Intraperitoneal Injection	Ongoing	Ryan
Ionic Liquid: 1-butyl-1-methylpyrrolidinium chloride	479500-35-1	Mice,rats	90 days	Dosed-Water	Ongoing	Ryan
Ionic Liquid: 1-butyl-3-methylimidazolium chloride	79917-90-1	Mice,rats	90 days	Dosed-Water	Ongoing	Ryan
Ionic Liquid: 1-ethyl-3-methylimidazolium chloride	65039-09-0	Mice,rats	90 days	Dosed-Water	Ongoing	Ryan
Ionic Liquid: N-butylpyridinium chloride	1124-64-7	Mice,rats	90 days	Dosed-Water	Ongoing	Ryan
Isodecyl diphenyl phosphate	29761-21-5	Rats	5 days	Gavage	Ongoing	Auerbach
Isopropylated phenol phosphate	68937-41-7	Mice	2 weeks	Dosed-Feed	Ongoing	Behl
Isopropylated phenol phosphate	68937-41-7	Rats	5 days	Gavage	Ongoing	Auerbach
Melamine + cyanuric acid combination	N/A	Rats	90 days	Gavage	Ongoing	Gamboa
Melamine + cyanuric acid combination	N/A	Rats	90 days	Gavage	Ongoing	Gamboa
Melamine + cyanuric acid combination	N/A	Rats	90 days + recovery	Gavage	Initiated	Gamboa
TRIM VX	N/A	Mice,rats	13 weeks	Inhalation	Ongoing	Ryan
Microbiome	N/A	N/A	14 days	N/A	Ongoing	Cerniglia
N-Butylbenzenesulfonamide	3622- 84- 2	Mice	14 days	Dosed-Feed	Ongoing	Rider
N,N-Dimethyl-p-toluidine	99-97-8	Rats	5 days	Gavage	Ongoing	Dunnick
Nanoscale silver	7440- 22- 4	Rats	13 weeks	Gavage	Ongoing	Boudreau
p-Toluidine	106-49-0	Rats	5 days	Gavage	Ongoing	Dunnick
Pentabromodiphenyl ether mixture [DE-71 (Technical Grade)]	32534-81-9	Mice,rats	13 weeks	Gavage	Completed	Dunnick
Pentabromodiphenyl ether mixture [DE-71 (Technical Grade)]	32534-81-9	Rats	GD 6 to PND 21	Gavage	Ongoing	Dunnick
Pentachlorophenol, purified	87-86-5	Mice	4 weeks	Dosed-Feed	Ongoing	Goldstein
Perfluorohexane sulfonate potassium salt	3871-99-6	Rats	28 days	Gavage	Ongoing	Blystone
Perfluorohexanoic acid	307-24-4	Rats	28 days	Gavage	Ongoing	Blystone
Perfluorooctanoic acid	335-67-1	Rats	28 days	Gavage	Ongoing	Blystone
Phenolic benzotriazoles (2-(2H-benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl)phenol)	70321-86-7	Rats	14 days	Gavage	Initiated	Blystone
Phenolic benzotriazoles (2-(2H-benzotriazol-2-yl)-4-tert-butylphenol)	3147-76-0	Rats	14 days	Gavage	Initiated	Blystone

Phenolic benzotriazoles (2-(2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylpropyl)phenol)	25973-55-1	Rats	14 days	Gavage	Initiated	Blystone
Phenolic benzotriazoles (2-(2H-benzotriazol-2-yl)phenol)	10096-91-0	Rats	14 days	Gavage	Initiated	Blystone
Phenolic benzotriazoles (2-(5-chloro-2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)phenol)	3864-99-1	Rats	14 days	Gavage	Initiated	Blystone
Phenolic benzotriazoles (3-(2H-benzotriazol-2-yl)-5-(1,1-dimethylethyl)-4-hydroxybenzenepropanoic acid, octyl ester)	84268-23-5	Rats	14 days	Gavage	Initiated	Blystone
Phenolic benzotriazoles (bumetrizole)	3896-11-5	Rats	14 days	Gavage	Initiated	Blystone
Phenolic benzotriazoles (drometrizole)	2440-22-4	Rats	14 days	Gavage	Initiated	Blystone
Phenolic benzotriazoles (octrizole)	3147-75-9	Rats	14 days	Gavage	Initiated	Blystone
Propylene glycol phenyl ether	770-35-4	Rats	5 days	Gavage	Completed	Auerbach
Sodium metavanadate	13718-26-8	Mice,rats	90 days	Dosed-Water	Initiated	Roberts
Sodium thioglycolate	367-51-1	Mice,rats	2 weeks	Topical Application	Completed	Mercado-Feliciano
Sodium thioglycolate	367-51-1	Mice,rats	13 weeks	Topical Application	Completed	Mercado-Feliciano
tert-Butylphenyl diphenyl phosphate	56803-37-3	Rats	5 days	Gavage	Ongoing	Auerbach
Tetrabromobisphenol A	79-94-7	Rats	13 weeks	Gavage	Ongoing	Dunnick
Triclosan	3380-34-5	Mice	90 days	Dermal	Ongoing	Fang
Tricresyl phosphate	1330-78-5	Rats	5 days	Gavage	Ongoing	Auerbach
Trimethylsilyldiazomethane	18107-18-1	Mice,rats	10 days	Inhalation	Initiated	Gwinn
Triphenyl phosphate	115-86-6	Mice	2 weeks	Dosed-Feed	Ongoing	Behl
Usnea lichen	N/A	Mice,rats	2 weeks	Dosed-Feed	Ongoing	Leakey
(+)-Usnic acid	7562-61-0	Mice,rats	2 weeks	Dosed-Feed	Ongoing	Leakey
(+)-Usnic acid	7562-61-0	Mice,rats	90 days	Dosed-Feed	Ongoing	Leakey
Valerian (Valeriana officinalis L.) root extract	8057-49-6	Mice	90 days	Gavage	Ongoing	Roberts
Vanadyl sulfate	27774-13-6	Mice,rats	90 days	Dosed-Water	Initiated	Roberts

Chronic Toxicity and Carcinogenicity Studies Ongoing During FY 2016

Test Article	CASRN*	Species	Length	Routes	Status	Study Scientist
Aging cohort study, mouse strains: • 129S1/SvImJ • B6C3F1 (Jackson) • C3H/HeJ • C57BL/6J (Jackson) • CAST/EiJ (M. m. castaneus) • NZO/HiLtJ • PWK/PhJ • WSB/EiJ (M. m. domesticus) • A/J • NOD. B10Sn-H2(b)/J	N/A	Mice	2 years	N/A	Ongoing	Dunnick
alpha-Pinene	80-56-8	Mice, rats	2 years	Inhalation	Ongoing	Rider
Antimony trioxide	1309-64-4	Mice, rats	2 years	Inhalation	Ongoing	Stout
AZT drug combinations, transplacental/carcinogenesis study	N/A	Mice	2 years	In utero	Ongoing	Beland
AZT drug combinations, transplacental/neonatal study	N/A	Mice	2 years	Gavage	Ongoing	Beland
Bisphenol A	80-05-7	Rats	2-years	Gavage	Ongoing	Delclos
Black cohosh	84776-26-1	Mice, rats	2 years	Gavage	Ongoing	Blystone
1,3-Butadiene	106-99-0	Mice	2 years	Inhalation	Ongoing	Bucher
2,3-Butanedione	5263-02-5	Rats	2 years	Dosed-feed	Ongoing	Catlin
2,3-Butanedione	335-67-1	Rats	2 years	Dosed-feed	Ongoing	Blystone
2,3-Butanedione	431-03-8	Mice, rats	2 years	Inhalation	Ongoing	Morgan
Cell phone radiation: code division multiple access	N/A	Mice, rats	2 years	Whole body exposure	Ongoing	Wyde
Cell phone radiation: global system for mobile communication	N/A	Mice, rats	2 years	Whole body exposure	Ongoing	Wyde
Di(2-ethylhexyl) phthalate	117-81-7	Rats	Perinatal + 2 years	Dosed-feed	Ongoing	Foster
Di(2-ethylhexyl) phthalate	117-81-7	Rats	2 years	Dosed-feed	Ongoing	Foster
Dibutyl phthalate	84-74-2	Mice, rats	2 years	Dosed-feed	Ongoing	Blystone
Furan	110-00-9	Rats	2 years	Gavage	Ongoing	Beland
2-Hydroxy-4-methoxybenzophenone	131-57-7	Mice, rats	2 years	Dosed-feed	Ongoing	McIntyre
Insertional mutagenesis, definitive vector study	N/A	Mice	14 months	Intravenous	Ongoing	Germolec
1020 Long multiwalled carbon nanotube	N/A	Mice, rats	2 years	Inhalation	Initiated	Morgan
TRIM VX	N/A	Mice, rats	2 years	Inhalation	Ongoing	Ryan
Nitrofurazone	59-87-0	Mice	2 years	Dosed-feed	Ongoing	Davis
p-Chloro-a,a,a-trifluorotoluene	98-56-6	Mice, rats	2 years	Inhalation	Ongoing	Stout
Perfluorooctanoic acid	335-67-1	Rats	2 years	Dosed-feed	Ongoing	Blystone
Resveratrol	501-36-0	Mice, rats	2 years	Gavage	Ongoing	Germolec
Sodium fluoride	7681-49-4	Rats	2 years	Dosed-water	Ongoing	Irwin
Sodium tungstate dihydrate	10213-10-2	Mice, rats	2 years	Dosed-water	Ongoing	Behl
Sulfolane	126-33-0	Mice, rats	2 years	Dosed-water	Ongoing	Blystone
Triclosan	3380-34-5	Mice	2 years	Dermal	Ongoing	Fang
Tris(chloropropyl)phosphate	13674-84-5	Mice, rats	2 years	Dosed-feed	Ongoing	Ryan

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

Toxicogenomic Studies

NTP is incorporating the latest toxicogenomic technologies into its testing program to gain further insight regarding the toxicity of environmental substances. Toxicogenomics examines how the entire genetic structure, or genome, is involved in an organism's response to environmental toxicants. Microarray, next-generation (NextGen) sequencing, proteomics, and metabolomics are among the advanced technologies that NTP is using to study the way chemical exposures change the expression of genes, proteins, and metabolites in critical cells and tissues. Measuring genome-wide changes in affected tissues may be useful for identifying biomarkers of disease or exposure to toxic substances, and for understanding individual genetic susceptibilities. Once biomarkers are validated, they can be repeatedly sampled during long-term NTP studies to determine whether chemical exposures can be detected, or whether developing cancers provide a genetic signature.

NTP is researching whether gene expression pattern analysis can provide indicators of toxicity (1) at earlier time points and (2) at lower doses than is possible for traditional toxicology parameters. Evaluating patterns of gene expression may provide more than just a link between genetics and morphology. It is also expected to provide insights into the pathogenesis of the disease and how different rodent models respond to toxicants. In addition, metabolomics represents a promising area of study, as it can elucidate how chemicals affect metabolism within cells relative to changes in gene expression.

Several FY 2016 toxicogenomic studies used NextGen sequencing technologies, which provided improvements to gene expression analysis, including base-pair level resolution of accuracy and increased sensitivity compared to microarray platforms. While microarrays are a stable and well understood technology for assaying gene expression, NextGen sequencing methods like RNA-Seq will likely become more common as sequencing costs drop and bioinformatic pipelines become standardized and integrated with genomic sequencing. A promising area of research is the use of exome sequencing (Exome-Seq) that can be applied to either frozen or formalin fixed, paraffin embedded tissues. DNA can be extracted from either frozen or archival tissues. Coding portions of DNA, or exons, are captured by libraries of hybridization-based probes targeting over 200,000 exons and transcriptionally active regions. Exon-enriched DNA can be sequenced by DNA-Seq and then genomically aligned to find mutations; indels, which are insertions or deletions; and other genetic abnormalities associated with disease. Three NTP studies are using Exome-Seq as a means for mutation profiling at a genome-wide scale to understand differences between spontaneous and chemically induced tumors.

NTP is evaluating study conditions that may contribute to differential gene expression, such as animal and tissue variability, methods for tissue sampling, and standards for conducting toxicogenomic studies under laboratory conditions. Efforts have been made to optimize methods for DNA and RNA extraction from archival tissues for molecular analysis. FY 2016 planned or ongoing NTP toxicogenomic studies are listed in the table below.

Toxicogenomic Studies Planned or Ongoing in FY 2016

Chemical	CASRN*	Species/ Cell Line	Route	Length	Test Type (Platform)	Study Scientist
Aging cohort study, mouse strains: • 129S1/SvImJ B6C3F1 • (Jackson) C3H/HeJ • C57BL/6J (Jackson) • CAST/EiJ (*M. m. castaneus*) • NZO/HiLtJ • PWK/PhJ • WSB/EiJ (*M. m. domesticus)* • *A/J* • *NOD. B10Sn-H2(b)/J*	N/A	Mice	N/A	2 years	NextGen sequencing Exome-Seq (Illumina)	Dunnick

Arsenite	7784-46-5	Human prostate cell lines	In vitro exposure	30 weeks	NextGen sequencing Exome-Seq (Illumina)	Merrick
2,3-butanedione (diacetyl) 2,3-hexanedione	431-03-8 3848-24-6	Human airway epithelium cell line	In vitro exposure	4 days	High throughput transcriptomics	Gwinn
Bisphenol A and BPA Analogs	80-05-7	Human hepatocyte cell line	In vitro exposure	2 days	High throughput transcriptomics	Devito
Bromodichloroacetic acid Methyleugenol***	5589-96-8 93-15-2	Mice	Gavage	2 years	NextGen sequencing Exome-Seq (Illumina)	Pandiri
DE-71 PCB-126 Phenobarbital***	32534-81-9 57465-28-2 50-06-6	Rats	Gavage	GD** to PND 22	Microarray (Affymetrix)	Dunnick
Phosphate flame retardants: • *tert*-Butylphenyl diphenyl phosphate • 2-Ethylhexyl diphenyl phosphate • Isodecyl diphenyl phosphate • Isopropylated phenol phosphate	56803-37-3 1241-94-7 29761-21-5 68937-41-7	Rats	Gavage	5 days	Microarray (Affymetrix) Metabolomics	Auerbach
Ginkgo biloba extract	90045-36-6	Rats	Gavage	5 days	Microarray (Affymetrix)	Rider/ Auerbach
induced Pluripotent Stem Cells Embryoid bodies Embryonic stem cells	N/A	Human	N/A	N/A	High throughput transcriptomics	Tokar/Devito
Harlan Sprague-Dawley rats	N/A	Rats	N/A	2 years	Targeted resequencing	Pandiri/Kovi
2-Hydroxy-4-methoxybenzophenone	131-57-7	Rats	Feed	90 days	Microarray (Affymetrix)	Auerbach
Methyleugenol extract *Ginkgo biloba* extract***	93-15-2 90045-36-6	Mice	Gavage	2 years	NextGen sequencing Exome-Seq RNA-Seq (Illumina)	Pandiri/Auerbach/Merrick

2,3-Pentanedione	600-14-6	Rats	Inhalation	14 and 28 days	microRNA Microarray (Affymetrix)	Morgan
Polycyclic aromatic compounds: • Acenaphthenequinone • Benzo[b]fluoranthene • Benzo(a)pyrene • Dibenz[a,h]anthracene • 9-Methylanthracene • 1-Methylfluorene • Perinaphthenone Phenanthrene Pyrene	82-86-0 205-99-2 50-32-8 53-70-3 779-02-2 1730-37-6 548-39-0 85-01-8 129-00-0	Human hepatocyte cell line	In vitro exposure	48 hours	Cytotoxicity Gene expression by quantitative polymerase chain reaction (qPCR)	Rider/ Tokar
BDE Toxicogenomics Studies: • 2,2',4,4',5-Pentabromodiphenyl ethers • Pentabromodiphenyl oxide (technical) (DE-71) • 3,3,4,4,5-Pentachlorobiphenyl • 2,2'4,4'-Tetrabromodiphenyl ether (DE-47)	5436-43-1 32534-81- 9 57465-28-8 5436-43-1	Rats, Mice	Gavage	GD** 6 through 3 weeks	Microarray (Affymetrix)	Dunnick
Tetrabromobisphenol A	79-94-7	Rats	Gavage	90 days	Microarray (Affymetrix)	Dunnick/ Merrick
Tetrabromobisphenol A BDE-47 Pentabromodiphenyl oxide-technical (DE-71)	79-94-7 5436-43-1 32534-81-9	Rats	Gavage	GD** 6 through 3 weeks	Microarray (Affymetrix)	Pandiri/Kovi
Tetrabromobisphenol A Pentabromodiphenyl oxide-technical (DE-71) Triclosan alpha, beta-Thujone	79-94-7 32534-81-9 3380-34-5 76231-76-0	Rats	Gavage	5 days	High throughput transcriptomics	Devito/Gwinn
112-Chemical compound test set; pharmaceuticals and environmental compounds	N/A*	Human hepatocyte cell line-HEPARG	In vitro exposure	2 days	High throughput transcriptomics	Ferguson/Ramaiahgari

* Chemical Abstracts Service Registry Number
**GD: gestational day
*** This study will compare toxicogenomic effects among the chemicals listed together.

Project Review Committee Approved

The table below lists studies that were approved by either the internal NIEHS/NTP protocol approval committee or the internal NIEHS/NTP project review committee, but were not started during FY 2016.

Protocol Title	Study Scientist
Developmental immunotoxicology evaluation of bisphenol AF in harlan sprague dawley rats exposed via dosed feed	Germolec/Sutherland
Three-month toxicity studies of 1,2,4-trimethylbenzene in harlan sprague dawley rats (after prenatal exposure, including selected reproductive, developmental, and neurotoxicity endpoints) and B6C3F1/N mice exposed via whole body inhalation	Roberts
Developmental immunotoxicity evaluation of tris(chloropropyl) phosphate (TCPP) in harlan sprague dawley rats exposed via dosed feed	Germolec/Ryan
Subchronic toxicity of sodium metavanadate and vanadyl sulfate in harlan sprague dawley rats (after perinatal exposure) and B6C3F1/N mice exposed via dosed drinking water	Roberts
Immunotoxicology screening study of *Echinacea purpurea* root extract in female harlan sprague dawley rats exposed via oral gavage	Ryan
Toxicokinetic studies of phenolic benzotriazole class chemicals (PBTZs) in male harlan sprague dawley rats via gavage and intravenous administration	Waidyanatha/Blystone
Immunotoxicology screening study of sodium metavanadate in female B6C3F1/N mice exposed via drinking water	Roberts
Prenatal developmental dose range-finding toxicity study of the fixed-dose ratio tri-combination (1:1.5:3) of emtricitabine, tenofovir disoproxil fumarate, and efavirenz in CD-1 mice exposed via gavage	McIntyre
Preliminary toxicokinetic investigation in pregnant CD-1 mice treated via gavage with either emtricitabine, tenofovir disoproxil fumarate, efavirenz; or the fixed-dose ratio tricombination (1:1.5:3)	McIntyre
Immunological evaluation of acenaphthenequinone, dibenzothiophene, and pyrene in B6C3F1/N mice treated for 28 days via gavage: polycyclic aromatic hydrocarbon mixtures assessment program (PAC-MAP) studies	Germolec/Rider
Absorption, distribution, metabolism, and excretion (ADME) of triclocarban in harlan sprague dawley rats and B6C3F1/N mice following gavage, intravenous administration, and dermal application of	Waidyanatha/Sutherland

[14C]triclocarban	
Toxicokinetic studies of bisphenol S in harlan sprague dawley rats and B6C3F1/N mice following gavage, intravenous, and feed exposure	Waidyanatha/Sutherland
Prenatal toxicity study of 2-{[1-(4-phenoxyphenoxy)propan-2-yl]oxy}pyridine in harlan sprague dawley rats exposed via gavage	McIntyre
Immunotoxicity of 2-{[1-(4-phenoxyphenoxy)propan-2-yl]oxy}pyridine in sprague dawley rats exposed via gavage	Germolec
Perinatal dose range-finding study of thallium sulfate in sprague dawley rats and 14-day toxicity study of thallium sulfate in B6C3F1/N mice exposed via dosed drinking water	Shipkowski
Immunotoxicity of N-butylbenzenesulfonamide in B6C3F1/N mice exposed for 28 days via dosed feed	Frawley/Rider

NICEATM

About NICEATM

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

NICEATM Workshops

A summary of workshops held or supported by NICEATM in FY 2016.

NICEATM Support of Tox21

A description of Tox21 projects NICEATM supported in FY 2016.

Additional NICEATM Activities

A summary of other activities NICEATM has conducted and participated in during FY 2016.

About NICEATM

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

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

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

Related Annual Report Pages:

- FY 2016 NICEATM Workshops
- NICEATM Support of Tox21
- Additional NICEATM Activities

Related Links

- Activities and Resources
- Publications
- Reports

NICEATM Workshops

In Vitro to In Vivo Extrapolation for High Throughput Prioritization and Decision Making Workshop

NICEATM and the U.S. Environmental Protection Agency (EPA) presented a webinar series on In Vitro to In Vivo Extrapolation for High Throughput Prioritization and Decision Making. The four webinars, presented monthly from October 2015 through January 2016, reviewed the current science on the use of in vitro data to predict in vivo outcomes of chemical safety testing.

The webinars provided background information for a workshop held on February 17-18, 2016 at the EPA in Research Triangle Park, NC. Workshop participants reviewed the state of the science to form recommendations on best practices for using in vitro to in vivo extrapolation in chemical screening and risk-based decision-making. They also identified areas needing additional data or research, and highlighted examples of how best to apply in vitro to in vivo extrapolation in risk-based decision-making strategies.

Presentations from the workshop and webinar series are available on the NTP website. A report from the workshop will be submitted for publication in FY 2017.

Acute Inhalation Toxicity Webinar Series

NICEATM and the People for the Ethical Treatment of Animals International Science Consortium co-hosted a webinar series on Alternative Approaches for Acute Inhalation Toxicity to Address Global Regulatory and Non-regulatory Data Requirements. The six webinars, held from March to September 2016, explored alternative approaches that could replace, reduce, or refine the use of animals for identifying chemicals that may cause acute systemic toxicity when inhaled. Slides from the webinars are posted on the NTP website.

Related Annual Report Pages:

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

NICEATM Support of Tox21

NICEATM will make curated data from Tox21 and the U.S. Environmental Protection Agency ToxCast program available through its Integrated Chemical Environment resource to be launched in FY 2017. Future resource development plans include the addition of tools such as in vitro to in vivo extrapolation workflows.

The Tox21 and the U.S. Environmental Protection Agency's (EPA) ToxCast programs are investigating the use of the zebrafish model as a screening tool for hazard identification. A Collaborative Workshop on Aquatic Models and 21st Century Toxicology identified the lack of standardized husbandry and testing protocols as a challenge to broader use. These issues will be addressed by the NTP Systematic Evaluation of the Application of Zebrafish in Toxicology initiative supported by NICEATM.

Using the collective results of 16 Tox21 and ToxCast estrogen receptor pathway related assays, NICEATM developed and applied one-compartment or physiologically based pharmacokinetic models to a workflow that quantitatively correlates in vitro and in vivo dosimetry for estrogen receptor reference chemicals. The approach highlighted the importance of pharmacokinetic considerations in assessing and ranking endocrine-active chemicals based on in vitro high throughput screening assays. This work is described in several publications. The first version of the workflow was published in December 2014 in *Applied In Vitro Toxicology*. A manuscript describing the application of an improved approach to a larger chemical set will be submitted to *Environmental Health Perspectives* in FY 2017 and a poster describing open-source workflows to conduct these analyses will be presented at the 2017 Society of Toxicology annual meeting.

Using data from nine Tox21 and ToxCast assays, NICEATM built a model to predict androgen receptor pathway activity and evaluated it using a list of reference chemicals developed from high-quality in vitro data from androgenic activity assays. The model and evaluation are described in a manuscript submitted to *Chemical Research in Toxicology.* From these data and the androgen receptor pathway predictions, NICEATM also developed predictive quantitative structure-activity relationship models for androgen receptor binding and activity. These models were presented in a poster (Zang et al.) at the 2016 Society of Toxicology annual meeting

Related Annual Report Pages:

FY 2016 NICEATM Workshops
Additional NICEATM Activities
About NICEATM

Additional NICEATM Activities

Acute Systemic Toxicity

NICEATM conducted a retrospective analysis to determine if acute oral toxicity data can be used reliably to assign EPA acute dermal hazard classifications, potentially reducing the number of animals needed for pesticide testing. NICEATM obtained high-quality data for 910 pesticide-active ingredients and formulations from EPA toxicity reports, peer reviewed publications, and databases. Oral hazard classifications based on rat oral LD50 values were compared to dermal hazard classifications based on rat dermal LD50 values. Results suggest that acute oral hazard categories are sufficiently protective for acute dermal hazard classification. EPA used these analyses to support guidance for waiving acute dermal toxicity tests required for pesticide formulations. The analysis was described in a poster (Paris et al.) presented at the 2016 Society of Toxicology (SOT) annual meeting, and a manuscript describing this work is in preparation.

Developmental Toxicity

NICEATM is supporting an NTP effort to systematically evaluate the application of zebrafish in NTP toxicology studies (SEAZIT). This effort will provide fundamental knowledge on the use of zebrafish in toxicology. In FY 2016, NICEATM and other SEAZIT team members conducted a series of interviews with researchers considered to be experts in the use of zebrafish in toxicology studies. These interviews identified areas key to development of a harmonized testing protocol for embryonic zebrafish studies and important sources of variability among laboratories. Information from these interviews and from a literature search will be compiled into a manuscript to be submitted for publication in FY 2017. NICEATM will also present a webinar series in February and March 2017 on Using Informatics to Improve Data Analysis of Chemical Screening Assays Conducted in Zebrafish. Information about the webinars is on the NTP website

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

In June 2016, NICEATM requested available data and information on approaches and technologies currently used for identifying potential developmental toxicants. Three responses were received that described assays using stem cells or *C. elegans* with in vitro assays to screen for potential developmental toxicants. Submitted information is being used to assess the state of the science and determine technical needs for alternative methods to evaluate the potential of chemicals to induce adverse effects in offspring.

Endocrine Disruptors

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 androgen receptor agonist and antagonist activity. The study will test 67 reference chemicals to characterize the reliability and relevance of the method, and 30 consumer products to evaluate the utility of the method beyond single chemicals. The study is planned to run through summer 2017.

Skin Sensitization

NICEATM collaborated with ICCVAM scientists to develop integrated testing strategies that use non-animal data to predict skin sensitization hazard. Three manuscripts published or accepted for publication in FY 2016 describe strategies to use non-animal data to predict outcomes of animal skin sensitization tests, human skin sensitization tests, and human or animal tests for skin sensitization potency classification.

NICEATM collaborated with scientists at the University of North Carolina at Chapel Hill to develop quantitative structure-activity relationship (QSAR) models to support identification of potential human skin sensitizers without using animals. A manuscript submitted for publication in FY 2017 describes QSAR models that predict human skin sensitization test results.

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

Ocular Irritation

Optisafe is an in vitro test method that assesses the potential to cause eye irritation by measuring the damage induced by application of a test substance to a semipermeable membrane. NICEATM is coordinating an ICCVAM-sponsored multi-laboratory validation study to determine the reliability and relevance of the OptiSafe test method. Training of participating laboratories is underway with the first phase of chemical testing to begin in FY 2017.

Related Annual Report Pages:

- FY 2016 NICEATM Workshops
- NICEATM Support of Tox21
- About NICEATM

ICCVAM

About ICCVAM

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

ICCVAM Activities

Description of activities NICEATM support in FY 2016.

ICCVAM Test Method Evaluation Activities

A list of NICEATM and ICCVAM test methods evaluation activities in FY 2016.

ICCVAM International Validation Activities

A description and list of international validation activities NICEATM and ICCVAM participated in during FY 2016.

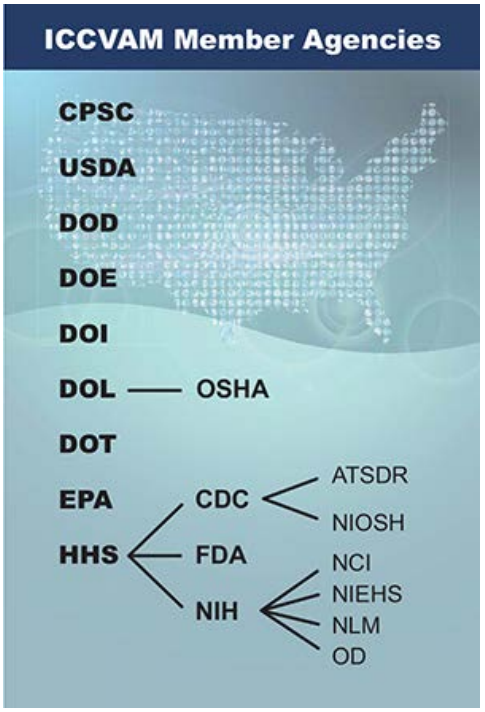
About ICCVAM

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. 285*i*-3), its purpose is "to establish, wherever feasible, guidelines, recommendations, and regulations that promote the regulatory acceptance of new or revised scientifically valid toxicological tests that protect human and animal health and the environment, while reducing, refining, or replacing animal tests and ensuring human safety and product effectiveness."

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

Related Annual Report Pages:

- FY 2016 ICCVAM Activities
- ICCVAM Test Method Evaluation
- International Validation Activities



Related Links

- Information on ICCVAM Activities
- Complete list of articles on ICCVAM activities published in scientific journals

ICCVAM Activities

NICEATM provided support for six teleconferences and two in-person meetings held by ICCVAM in FY 2016. NICEATM also supported three ad hoc ICCVAM working groups focused on acute systemic toxicity, skin sensitization, and identification and characterization of reference chemicals for validation of in vitro endocrine disruptor assays.

The second ICCVAM Communities of Practice webinar was held on January 26, 2016. The webinar focused on applications of methods that use chemical structure, properties, and toxicity data to predict characteristics of untested chemicals. Alex Tropsha, Ph.D., of the University of North Carolina at Chapel Hill discussed how quantitative structure-activity relationship models allow chemical compounds to be characterized mathematically, enabling statistical predictions about the properties of untested chemicals. Louis Scarano, Ph.D., of the U.S. Environmental Protection Agency explained how quantitative tools and models are used to generate predictions about toxic effects of new chemicals. These predictions are then used to conduct occupational risk assessments and identify where further testing might be needed. Slide presentations from the webinar are available on the NTP website.

ICCVAM with NICEATM support held its third public forum on May 25, 2016, at NIH in Bethesda, Maryland. Representatives from 12 ICCVAM member agencies were joined by attendees representing stakeholder groups and over 100 webcast viewers. ICCVAM members provided information about their agency's activities relevant to the development and validation of test methods and approaches that may replace, reduce, or refine animal use. A proposal for a roadmap to replace animal use in U.S. safety testing was highlighted. Representatives from stakeholder groups praised recent progress made by ICCVAM and its member agencies towards replacing required animal tests with non-animal alternatives, and suggested future activities and areas that should receive increased focus. The agenda and presentations are available on the NTP website.

The 15 member agencies of ICCVAM are engaged in additional activities that support replacing, reducing, and refining animal use. Summaries of these activities can be found on the NTP website.

Related Annual Report Pages:

- FY 2016 ICCVAM Activities
- ICCVAM Test Method Evaluation
- International Validation Activities

Related Links

- Information on ICCVAM Activities
- Complete list of articles on ICCVAM activities published in scientific journals

ICCVAM Test Method Evaluation Activities

ICCVAM received no formal test method nominations or submissions in FY 2016. ICCVAM welcomes submissions of innovative test methods, which may be acceptable for specific regulatory use and for which adequate validation studies have been completed. However, to maximize the potential for effective implementation of new test methods or approaches, ICCVAM only conducts evaluations and prepares recommendations on test method submissions proposed for regulatory uses that align with ICCVAM member agencies needs and priorities. More information on ICCVAM test method submissions is available.

NICEATM and ICCVAM test method evaluation activities in FY 2016 are summarized in the table below.

Test Method Evaluation Activities in FY 2016

Test Method	ICCVAM Recommendations/Agency Status
ICCVAM integrated decision strategy for skin sensitization	ICCVAM developed integrated decision strategies using in vitro, in chemico, and in silico information based on an established skin sensitization adverse outcome pathway. A manuscript describing strategies to predict animal and human skin sensitization of test results was published in FY 2016. Another manuscript describing a strategy to predict human skin sensitization potency is in preparation.
Electrophilic allergen screening assay	This test method, nominated by NIOSH, is an in chemico assay intended to identify potential skin sensitizers. A validation study of the method is planned for FY 2017. Laboratories from three ICCVAM agencies will conduct the testing. NICEATM will coordinate the study and members of the ICCVAM Skin Sensitization Working Group will serve on the study management team.
OptiSafe ocular irritation test	NICEATM is coordinating the validation of the in vitro OptiSafe ocular irritation test method. In this method, a test substance is applied to a semipermeable membrane and damage to macromolecules in the membrane is measured to assess the substance's potential to cause eye irritation. Training of participating labs is underway, with the first phase of chemical testing to begin in FY 2017.

Related Annual Report Pages:

- FY 2016 ICCVAM Activities
- ICCVAM Test Method Evaluation
- International Validation Activities

ICCVAM International Validation Activities

NICEATM and ICCVAM participate in international test method validation activities through the Organisation for Economic Co-operation and Development (OECD), and collaborate with countries that are members of the International Cooperation on Alternative Test Methods (ICTAM), including the European Union, Japan, Korea, and Health Canada.

In FY 2016, ICCVAM agencies commented on draft OECD documents through the U.S. National Coordinator for the OECD Test Guidelines Programme, an ex officio ICCVAM member. In FY 2016, NICEATM and ICCVAM collaborated with international colleagues on the following OECD activities:

- Drafted a new proposal for a performance based test guideline regarding defined skin sensitization approaches and test methods to be submitted to OECD in FY 2017.
- Revised the acute dermal toxicity test guideline.
- Drafted a guidance document on integrated approaches to testing and assessment (IATAs) for eye irritation hazard potential.
- Drafted a guidance document on the reporting of defined approaches to be used within IATAs.
- Contributed a case study to a guidance document on IATAs for skin sensitization.

Representatives of NICEATM and ICCVAM will attend meetings of the OECD expert groups on eye irritation and skin sensitization in FY 2017.

International Cooperation on Alternative Test Methods collaborations address three critical areas of cooperation: test method validation studies, independent peer review of validation studies, and the development of formal recommendations on alternative testing methods. Representatives of NICEATM and ICCVAM attended an ICATM coordination meeting in November 2015. A NICEATM scientist served as a liaison member to a European Union Reference Laboratory for Alternatives to Animal Testing Scientific Advisory Committee working group that reviewed the relevance and predictive capacity of two in vitro eye irritation test methods. Representatives of NICEATM and ICCVAM will attend the FY 2017 workshop sponsored by ICATM to develop criteria for evaluating non-animal approaches for skin sensitization potential.

The table below lists ongoing international validation studies led by ICATM member organizations that include NICEATM or ICCVAM participants.

Participation in International Validation Studies

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

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

*Japanese Center for the Validation of Alternative Methods

Related Annual Report Pages:

- FY 2016 ICCVAM Activities
- ICCVAM Test Method Evaluation
- International Validation 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 may be of human concern.

Report on Carcinogens

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

Noncancer Research

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

In FY 2016, NTP published the NTP Monograph on Immunotoxicity Associated with Exposure to Perfluorooctanoic Acid or Perfluorooctane Sulfonate, the first evaluation reaching hazard conclusions using the OHAT Approach to Systematic Review and Evidence Integration. OHAT also published several reports in the new NTP Research Report series, including a pilot study on tin and organotin levels in Danish women and a systematic review of the effects of fluoride on learning and memory in animal studies.

View Research Areas in Noncancer Research

Ongoing Noncancer Health Effects Projects

Show All

Search Projects

Ongoing Noncancer Health Effects Projects

Project & Study Scientist	Project Summary
Evaluation of inflammation-based atherosclerosis associated with environmental exposures Study Scientist: Rooney	There is growing evidence that the environment plays a role in a wide range of diseases that involve inflammation. The extent to which environmental exposures ultimately lead to these adverse health effects through an inflammatory pathway remains unclear. This evaluation will examine the evidence that environmental substances contribute to inflammation, which ultimately leads to atherosclerosis, and identify biomarkers of the inflammation involved. Atherosclerosis was selected for investigation because of the significant public health impact of the disease, and the well-established role for inflammation in the disease process leading to atherosclerosis. The draft concept was reviewed at the December 2014 Board of Scientific Counselors meeting, and the evaluation has been initiated.

Evaluation of immunotoxicity associated with exposure to perfluorooctanoic acid (PFOA) or perfluorooctane sulfonate (PFOS)
Study Scientist: Rooney

Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) are extremely persistent chemicals and are widely distributed in the environment as a result of extensive use over the last 60 years. Although exposures have been dramatically reduced, the persistence and bioaccumulation of both PFOA and PFOS result in detectable levels in the U.S. population. Recent publications have linked PFOA and PFOS exposure in humans to functional immune changes that are consistent with evidence of PFOA- and PFOS-related immunotoxicity reported in animal studies. The NTP conducted a systematic review to evaluate the evidence for an association between exposure to PFOA or PFOS and immunotoxicity or immune-related health effects. The NTP Monograph was finalized in September of 2016 following the Peer-Review Meeting by an ad hoc expert panel on July 19, 2016 in Research Triangle Park, NC. The NTP concluded that both PFOA and PFOS are presumed to be an immune hazard to humans based on a high level of evidence from animal studies that PFOA and PFOS suppressed the antibody response and a moderate level of evidence from studies in humans.

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

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

State of the science for transgenerational inheritance of health effects
Study Scientist: Walker

Transgenerational inheritance is the phenomenon in which an individual's exposures have far-reaching consequences, affecting multiple generations removed from the original insult. The traditional belief suggests that

negative effects of exposure to environmental chemicals are reset in each generation, such that subsequent generations are unaffected by the exposure history of their parents and grandparents. This state-of-the-science evaluation will examine the robustness of the evidence for transgenerational inheritance of health effects associated with exposure to a wide range of stressors, such as environmental chemicals; drugs of abuse, nutrition, and diet; pharmaceuticals; infectious agents; and stress in humans and animals. A Federal Register Notice was published in May 2013 soliciting public comments. The evaluation is nearing completion with a draft manuscript in development.

Evaluation of children's health and traffic-related air pollution
Study Scientist: Howdeshell

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

Evaluation of adverse health effects and occupational exposure to cancer chemotherapy agents
Study Scientist: Howdeshell

Cancer chemotherapy agents are cytotoxic drugs, and many of these agents are known mutagens and developmental toxicants. Occupational exposure to cancer chemotherapy agents may occur in various professions including medical, veterinary, and manufacturing. While improved handling procedures and engineering controls have reduced contamination, surface contamination persists in pharmacy and nursing areas of some hospital-based cancer centers. This evaluation will examine the evidence that occupational exposure to cancer chemotherapy agents is associated with adverse health effects, including genetic toxicity, cancer, reproductive and developmental effects, and acute effects. The draft concept was reviewed at the April 2014 Board of Scientific Counselors meeting, and the evaluation has been initiated.

Biological activity of bisphenol A (BPA) structural analogues and functional alternatives
Study Scientist: Pelch

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

Environmental influences on the epigenome: a scoping report
Study Scientist: Pelch

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

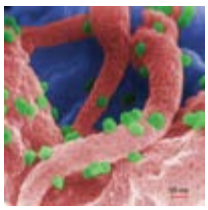
Shift work at night, light at night, and circadian disruption
Study Scientist: Boyd

Circadian disruption occurs when endogenous circadian rhythms, which are daily and predictable variations in biological, physiological, and behavioral processes, are out of phase with the external environment or with each other. People, by virtue of the nature of their work, lifestyle choices, or residence, are subjected to interruptions in the natural light-dark cycles, leading to the potential for circadian disruption. This project is being undertaken in conjunction with an analysis by the Office of the Report on Carcinogens for cancer hazard evaluation. The draft concept was reviewed at the April 2014 Board of Scientific Counselors meeting, and a public workshop/webinar was held at NIEHS in March 2016 to obtain expert opinion to inform potential health hazard assessments. Activity is underway working with the Office of the Report on Carcinogens to finalize the protocol and execute the cancer hazard evaluation.

Report on Carcinogens

About the Report on Carcinogens

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



RoC Activities

A summary of the Office of the Report on Carcinogens activities conducted during FY 2016.

Newly Reviewed Listings for the 14th RoC

A list of newly reviewed substances under consideration for the 14th Report on Carcinogens.

RoC Substances Selected for Evaluation

A list of substances selected for evaluation by the Office of the Report on Carcinogens during FY 2016.

About the Report on Carcinogens

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

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

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

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

Preparation of the RoC is conducted by the Office of the Report on Carcinogens, under the direction of Ruth Lunn, Dr.P.H. Contract support for preparation of the RoC in FY 2016 was provided by Integrated Laboratory Systems Inc. and ICF.

Additional Links for the RoC

- Report on Carcinogens
- RoC Activities in 2016
- Newly Reviewed Listings
- RoC Candidate Substances

RoC Activities

NTP submitted the 14th RoC to the U.S. Department of Health and Human Services (HHS) Secretary for review and approval in FY 2016 and HHS released the 14th RoC on November 3, 2016. This cumulative report contains 248 listings, of which seven were newly reviewed. The newly reviewed listings, include

trichloroethylene, Epstein-Barr virus, human immunodeficiency virus type-1, human T cell lymphotropic virus type-1, Kaposi sarcoma-associated herpesvirus, and Merkel cell polyomavirus, all listed as known to be a human carcinogen; and the class cobalt and cobalt compounds that release cobalt in vivo, listed as reasonably anticipated to be a human carcinogen.

Other RoC activities in FY 2016 were primarily related to conducting the cancer hazard evaluations of several substances that were newly reviewed for the 14th RoC. The RoC Monograph on Cobalt and Cobalt Compounds that Release Cobalt In Vivo was finalized following the December 2015 NTP Board of Scientific Counselors' meeting. On December 17, 2015, NTP convened a panel of experts to peer review five draft RoC monographs on Epstein-Barr Virus, human immunodeficiency virus type-1, human T cell lymphotropic virus type-1, Kaposi sarcoma-associated herpes virus, and Merkel cell. The monographs for these five viruses were finalized following the June 2016 NTP Board of Scientific Counselors' meeting.

Literature-based cancer hazard evaluations are being prepared for (1) shift work at night, light at night, and circadian disruption, (2) haloacetic acids found as disinfection by-products, and (3) *Helicobacter pylori:* Chronic infection. Concepts documents for haloacetic acids and *H. pylori* were presented to the NTP Board of Scientific Counselors at their April 11, 2016 meeting. Goldenseal Root Powder has also selected for review for the RoC. For a table listing RoC ongoing evaluations, go to RoC Substances Selected for Evaluation.

The Office of the Report on Carcinogens, in partnership with the Office of Health Assessment and Translation, convened a workshop titled Shiftwork at Night, Artificial Light at Night and Circadian Disruption and held on March 10-11, 2016. The purpose of the workshop was to obtain external scientific input on topics important for informing the literature-based health hazard assessments, including strategies for integrating data across evidence streams and exposure scenarios, data gaps, and research needs.

Additional Links for the RoC

- Report on Carcinogens
- RoC Activities in 2016
- Newly Reviewed Listings
- RoC Candidate Substances

Newly Reviewed Listings for the 14th RoC

Candidate CASRN* Study Scientist	Primary Uses/Exposures	Listing Status and Rationale
Trichloroethylene 79-01-6 Lunn	Industrial solvent best known for its use as a metal degreaser. Today it is mainly used for the synthesis of hydrofluorocarbon refrigerant.	Known to be a human carcinogen Linked to kidney cancer and possibly non-Hodgkin lymphoma
Epstein-Barr virus N/A Jahnke	Herpesvirus that causes infectious mononucleosis. Infects nine of 10 people worldwide and is transmitted via saliva.	Known to be a human carcinogen Linked to six types of cancer in humans: four types of lymphoma, nasopharyngeal and gastric cancer
Human immunodeficiency virus, type-1 N/A Jahnke	Retrovirus that causes AIDS. Infects 1.2 million people. Transmitted via blood and body fluids.	Known to be a human carcinogen Linked (or potentially linked) to 12 types of cancers
Human T cell lymphotropic virus, type-1 N/A Jahnke	Retrovirus that is usually asymptomatic. Transmitted via body fluids and blood.	Known to be a human carcinogen Linked to adult T-cell leukemia/lymphoma
Kapoosi sarcoma-associated virus N/A Jahnke	Herpesvirus usually causing asymptomatic infections. Transmitted via salvia and from mother to child	Known to be a human carcinogen Linked to Kaposi sarcoma and two types of lymphoma in humans
Merkel cell polyomavirus N/A Jahnke	Polyomavirus whose route of transmission is not clear, but may be transmitted through skin shedding.	Known to be a human carcinogen Linked to Merkel cell carcinoma
Cobalt and cobalt compounds	Naturally occurring metallic element that	Reasonably anticipated to

that release cobalt in vivo 7440-48-4 Lunn	exists in different forms. Used to make alloys for industrial, medical, and military purposes; cemented carbides; as pigments; and for electronics and green energy.	be a human carcinogen Sufficient evidence of carcinogenicity from studies in experimental animals and supporting mechanistic data

* Chemical Abstracts Service Registry Number

Additional Links for the RoC

- Report on Carcinogens
- RoC Activities in 2016
- Newly Reviewed Listings
- RoC Candidate Substances

RoC Substances Selected for Evaluation

Substances Study Scientist	Primary Uses/Exposures	Listing Status and Rationale
Goldenseal Root Powder (Hydrastis canadensis) Office of RoC staff	Herbal remedy (botanical product) used to treat gastrointestinal disturbances, urinary disorders, hemorrhage, skin, mouth, and eye infections and inflammation.	NTP Board of Scientific Counselors review of draft concept, April 2014.
Haloacetic Acids Found as Water Disinfection By-Products Gloria Jahnke	13 individual haloacetic acids or potential class or subclass of these haloacetic acids. People are exposed to these haloacetic acids by ingestion of chlorinated drinking water and by dermal contact or breathing compounds during bathing or using swimming pools and spas that use chlorine for disinfection.	NTP Board of Scientific Counselors review of draft concept, April 2016.
Helicobacter pylori (H. pylori): Chronic Infection Ruth Lunn	Gram negative, multi-flagellated bacterium that colonizes the stomach and causes peptic ulcer. Bacterium is spread by person-to-person contact especially among family member. Routes of exposure include oral-oral, fecal-oral, iatrogenic, and possibly from contaminated water. Risks factors for infection include age, race, socioeconomic status such as crowded living conditions, and poor sanitation/hygiene.	NTP Board of Scientific Counselors review of draft concept, April 2016.
Shift Work at Night, Light at Night, and Circadian Disruption Ruth Lunn	Unnatural (e.g., such as ill-timed) electrical light, especially light-at-night (LAN), may 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 LAN. Shift workers who work at night or evenings starting before 6:00 a.m. can experience an extreme type of LAN exposure, as well as changes in other activities related to LAN, such as changes in daily activities, eating sleeping, lifestyle factors, and social behavior.	Workshop: Shift Work at Night, Artificial Light at Night, and Circadian Disruption workshop, March 2016

Additional Links for the RoC

- Report on Carcinogens RoC
- Activities in 2016
- Newly Reviewed Listings RoC
- Candidate Substances

Partner Agency Research

About 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 the NTP program.

NTP at NIOSH

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

About NTP at NIEHS

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

NIEHS/NTP Staff

Biomolecular Screening

Genetic and epigenetic differences between individuals in the human population are proposed as major factors for individual susceptibility to environmental stressors. Environmental and drug safety assessments are currently conducted with a small number of commonly used animal models, which have limited genetic

diversity. Further, there are many layers of biological regulation that can influence individual genetic susceptibility to chemical and drug toxicity. Animal models have inherent limitations in extrapolating results to human toxicity and disease, and this program is working toward development of more sophisticated analyses in epigenetics to make better use of current animal models, and adopt biological systems that are more appropriate for modeling human toxicity and disease. The NTP Biomolecular Screening Branch conducts in-house projects aimed at understanding individual susceptibility.

In FY 2016, work continued on the mouse methylome project by Alex Merrick, Ph.D., and Paul Wade, Ph.D. Epigenetics involves the study of modifications to DNA, like methylation, and related cellular structures, such as histones, that affect gene expression and an organism's ability to adapt to the environment. NTP designed an epigenetic study to examine DNA methylation and its possible relationship with the susceptibility of mouse strains to develop liver tumors. Male and female C57BL/6N mice were crossed with C3H/HeN mice. Five tissues — brain, liver, cardiac and skeletal muscle, brown and white fat, and epididymal sperm — from the first-generation offspring were collected at the average age NTP starts mice in a subchronic toxicity study, and flash frozen for DNA/RNA isolation and liver sequencing. Progress in FY 2016 involved computational analysis on sites of genomic methylation in relation to known genes and transcriptionally active regions in both parental strains and the resulting first generation offspring. The relationship of DNA methylation to gene expression and possible heredity in offspring is being determined, and the genomic variation between mouse strains, genders, and F1 offspring is being catalogued. The epigenetic landscape is being carefully described in these two mouse strains and offspring to help interpret the contribution of differences in DNA methylation to their differential susceptibility to hepatic malignancy. A manuscript is in preparation to be followed by public release of the methylome data. Additional studies in 2016 have been initiated that will address the impact of sex hormone signaling on DNA methylation at a genome-wide level and the impact of DNA methylation at distal regulatory regions.

NTP Laboratory

The NTP Laboratory, within the NIEHS Division of NTP, conducts in-house, agent-specific, targeted research related to the development and application of modern toxicology and molecular biology tools. These tools are used in the (1) evaluation of specific substances of concern to NTP, (2) issues of central importance to NTP programs, and (3) methods development to advance the NTP mission. The NTP Laboratory also focuses on the study of the developmental origins of adult diseases. The table below includes projects in the NTP Laboratory in FY 2016.

View Research Areas in
NTP Laboratory Projects in FY 2016

Show All

Search Projects

NTP Laboratory Projects in FY 2016

Project & Study Scientist	Project Summary
Application of in vitro assays to evaluate botanicals Study Scientist: DeVito	To determine if in vitro assays and chemical analysis of botanicals can aid in selecting botanicals for in vivo testing. In FY 2016, a workshop on botanical dietary supplement safety was held.

Chemical induced transcriptomic and metabolomic changes in vitro. Study Scientist: DeVito	To evaluate the transcriptomic and metabolomic changes in metabolically active cell lines with 24 chemicals that have been tested in vitro.
Development of in vitro models of metal carcinogenesis Study Scientist: Tokar	To develop in vitro cell transformation models with target relevant cells using arsenic and cadmium. In FY 2016, this project was completed and resulted in multiple publications.
Effects of glyphosate and its formulations on the induction of oxidative stress. Study Scientist: DeVito	To determine if there are differences in the toxicity of glyphosate and its formulations on oxidative stress and other carcinogenic characteristics.
Evaluation of the developmental neurotoxicity of fluoride Study Scientist: Harry	To evaluate fluoride developmental neurotoxicity in rats.
Formaldehyde in p53 knockout mice Study Scientist: Morgan	To define the role of formaldehyde inhalation in hematopoietic tumor induction. This study was completed in FY 2016 and the report is being developed.
Formaldehyde-induced transformation of human myeloid progenitor cells Study Scientist: Morgan	To perform a proof of concept study of in vitro formaldehyde-induced malignant transformation in hematopoietic stem cells. This is a companion study to the formaldehyde in p53 mice study. This study was completed in FY 2016 and the report is being developed.
Incorporating metabolism into high throughput screening assays Study Scientist: DeVito	To develop in vitro methods that incorporate xenobiotic metabolism. A manuscript is in development.
Metalloestrogens and uterine/breast response Study Scientist: Dixon, Fenton	To retest the ability of reported metalloestrogens, like cadmium and arsenic, to cause estrogen receptor stimulation in the uterus as a mode of action towards cancer development.
Method for assessing biological impact of metal particle dissolution Study Scientist: Morgan	(1) To develop an in vitro transwell method with metal particles and macrophages in one well and cells of interest, such as lung epithelium, in the other; and (2) to define the ability of various types of macrophages to release different metals from different particles. In FY 2016, this project was completed and a manuscript was published.

Methods in histopathology of mammary gland development Study Scientist: Fenton	To develop standardized methods to quantitatively assess chemical insult on mammary gland development. This project was completed in FY 2016 and several manuscripts were published.
Refinement of developmental neurotoxicology methods Study Scientist: Harry	To improve methods for various efforts including genetic signatures, stem cells, inflammation, behavior, and conditioning.
Role of microRNAs in malignant transformation Study Scientist: Tokar	To study genes of interest involved in the epigenetics of malignant transformation, using in vitro human model systems of carcinogenesis. MicroRNAs are thought to be a key epigenetic or posttranscriptional gene expression control mechanism.
Stem cells in toxicology and carcinogenesis Study Scientist: Tokar	To perform various in vitro studies on the role of stem cells and cancer stem cells in carcinogenesis and the developmental basis of adult disease.
Toxicants and mammary gland development Study Scientist: Fenton	To determine the effects of different toxicants, including atrazine, on mammary gland development in rats and mice.
Using *Caenorhabditis elegans* for screening mitochondrial toxicants Study Scientist: Boyd	To study the effects of mitochondrial toxicants in *Caenorhabditis elegans*. This project was completed in FY 2016 and a manuscript was published.
Using *Caenorhabditis elegans* as screens for toxicity of flame retardants Study Scientist: Boyd	To study the effects of flame retardants in *Caenorhabditis elegans*. This project was completed in FY 2016, and a manuscript was published.
Using in vitro screens to evaluate potential obesogens Study Scientist: Fenton	To develop orthogonal assays to evaluate findings from Tox21 that identified potential obesogens.
Using in vitro screens to evaluate polyaromatic compounds Study Scientist: DeVito	To apply in vitro assays to assess and categorize the biological effects of polyaromatic compounds.
Utility of a five-day transcriptomic study in adult rats. Study Scientist: Gwinn	To determine the difference in the transcriptomic bone mineral density and adverse effect bone mineral density by examining 20 chemicals that have been tested in vitro at the NTP.

NTP at NCTR

About NTP at the National Center for Toxicological Research

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

NTP at NCTR: Interagency Agreement Projects

A list of projects funded by the NIEHS/NTP interagency agreement with FDA and conducted in FY 2016.

About NTP at the National Center for Toxicological Research

Research in Partnership with NCTR

The National Center for Toxicological Research (NCTR), in partnership with researchers from elsewhere in FDA, other government agencies, academia, and industry, provides innovative technology, methods development, vital scientific training, and technical expertise. The unique scientific expertise of NCTR is critical in supporting FDA product centers and their regulatory roles. NCTR research for NTP is funded by both voluntary allocations and an interagency agreement.

NCTR/NTP Staff

NCTR studies funded by voluntary allocations are listed in the table below. Click the project title for a brief summary.

View Research Areas in

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

Search Projects

Biochemical and Molecular Basis of Toxicology

Project & Study Scientist	Project Summary
Physiologically based pharmacokinetic (PBPK) models for bisphenol A (BPA) Study Scientist: Fisher	(1) To create physiologically based pharmacokinetic (PBPK) models for bisphenol A (BPA) in mouse, rat, and rhesus monkey for multiple life stages: adult; neonate; pregnant, including both mother and fetus; and lactating, both mother and neonate. These PBPK models will be used to calculate internal measures of dose for both aglycone (i.e., active) and conjugated (i.e., inactive) forms of BPA. (2) Human PBPK models for BPA (adult, neonate, pregnant mother and fetus, and lactating mother and infant) will be created using information obtained from the monkey, mouse, and rat, and limited information from humans published in the literature. The human suite of PBPK models will be used to extrapolate the internal doses of BPA associated with toxicity in laboratory animals to humans, and to extrapolate dosimetry from regions of observation to low levels of exposure to BPA for which no experimental data exist. This simulation protocol will help reduce the uncertainty in the assessment of health risks posed by BPA to human populations.
Biologically based dose-response modeling for the thyroid axis in the fetus and neonate Study Scientist: Fisher	(1) To create biologically based dose-response models for the hypothalamic-pituitary-thyroid axis in the developing rat and human as a function of iodide status. (2) To interface the models with physiologically-based pharmacokinetic or toxicokinetic models for thyroid active chemicals to predicted conditions, such as iodide status and chemical exposure, for which brain thyroid hormone homeostasis cannot be maintained in the fetus and neonate. (3) To use the models to evaluate the possible influence of population exposures to thyroid active chemicals on fetal and neonatal thyroid status as a function of iodide intake.
Relationship between liver epigenetic phenotype and susceptibility to nonalcoholic steatohepatitis-induced (NASH) hepatocarcinogenesis in mice Study Scientist: Pogribny	(1) To determine the role of epigenetic dysregulation in the etiology and pathogenesis of dietary nonalcoholic steatohepatitis (NASH)-induced hepatocarcinogenesis in mice. (2) To determine whether or not interstrain-specific susceptibility of mice to NASH-induced hepatocarcinogenesis is associated with differences in individual hepatic epigenetic phenotypes. (3) To determine the role of epigenetic dysregulation in the etiology and pathogenesis of NASH-induced hepatocarcinogenesis in mice induced by tamoxifen administration.

	(4) To determine whether or not aberrant epigenetic markers can be used as targets for prevention of NASH-induced hepatocarcinogenesis in mice.
Sex differences in drug-induced QT prolongation and torsade de pointes: establishing an in vitro model for high throughput screening and risk assessment of torsadogenic drugs Study Scientist: Pang	(1) To establish a model and positive control. (2) To evaluate the sensitivity and specificity of the model, and test the possibility of high throughput screening and ranking of QT-prolonging drugs for the risk of torsade de pointes.
Mechanism of tumorigenic pyrrolizidine alkaloids and development of liquid chromatography-electrospray ionization/multistage mass spectrometry (LC-ES/MS/MS) methodology for detection and quantification of pyrrolizidine alkaloids Study Scientist: Fu	(1) To validate the proposed mechanism by which pyrrolizidine alkaloids induce tumors in rodents. (2) To develop an LC-ES/MS/MS method for detection and quantification of dehaloperoxidase-derived DNA adducts in rodents. (3) To develop an LC-ES/MS/MS method for detection and quantification of genotoxic pyrrolizidine alkaloids in herbal plants and herbal dietary supplements (4) To develop an LC-ES/MS/MS method for detection and quantification of dehaloperoxidase-derived hemoglobin adducts in rodents.
Human biomonitoring for bisphenol A (BPA) Study Scientist: Doerge	(1) To develop and implement sensitive and selective analytical methodology to measure bisphenol A in the blood and urine from humans. (2) To integrate animal exposure data and human biomonitoring data into a physiologically-based pharmacokinetic model for bisphenol A.
Role of peroxisome proliferator-activated receptor alpha (PPARa) and PPARa-mediated species differences in triclosan-induced liver toxicity Study Scientist: Wu	To examine the role of human and mouse peroxisome proliferator-activated receptor alpha (PPARa) in triclosan-induced liver toxicity in vivo.
Evaluation of the effects of black cohosh on risedronate efficacy in peri-menopausal rat model Study Scientist: Hansen	(1) To determine the effect of risedronate or black cohosh individually on bone density, bone turnover and bone histology in a postmenopausal rat model. (2) To determine the effect of the combination of black cohosh and risedronate on bone density, bone turnover and bone histology in a postmenopausal rat model.

Development and evaluation of a novel in vitro epigenomic screening model system for the hazard identification of FDA-regulated products Study Scientist: Pogribny	(1) To determine the dose-dependent in vitro genetic and epigenetic effects of compounds regulated by FDA. (2) To characterize the specific epigenetic changes induced in vitro by genotoxic and non-genotoxic compounds. (3) To characterize the specific genetic and epigenetic effects of compounds regulated by FDA using an in vitro 3-D organotypic liver culture model system.
Relationship between liver epigenetic phenotype and susceptibility to nonalcoholic steatohepatitis-induced (NASH) hepatocarcinogenesis in mice Study Scientist: Pogribny	(1) To determine the role of epigenetic dysregulation in the etiology and pathogenesis of dietary nonalcoholic steatohepatitis (NASH)-induced hepatocarcinogenesis in mice. (2) To determine whether or not interstrain-specific susceptibility of mice to NASH-induced hepatocarcinogenesis is associated with differences in individual hepatic epigenetic phenotypes. (3) To determine the role of epigenetic dysregulation in the etiology and pathogenesis of NASH-induced hepatocarcinogenesis in mice induced by tamoxifen administration. (4) To determine whether or not aberrant epigenetic markers can be used as targets for prevention of NASH-induced hepatocarcinogenesis in mice.
Developing methods for the analysis of brominated vegetable oils and derivatives Study Scientist: Gamboa da Costa	To develop methods for the analysis of the food additive brominated vegetable oil in rat feed and rat tissues.

Neurotoxicology

Project & Study Scientist	Project Summary
The use of computed tomography (CT) combined with positron emission tomography (microPET) to evaluate the neurotoxicity associated with pediatric exposures to the anesthetics sevoflurane and propofol Study Scientist: Wang	(1) To use computed tomography (CT) and positron emission tomography (microPET) to study neurotoxicity in vivo associated with the pediatric use of gaseous anesthetics sevoflurane and propofol. (2) To develop procedures to localize in vivo specific brain areas and structures to evaluate their response to test compounds. (3) To determine the utility of fluorine-18-labeled PET compounds to identify stem cells and apoptotic cells in brain in vivo. (4) To determine cytotoxicity of compounds, including gaseous anesthetics, using embryonic neuralstem cells in vitro.

Assessment of gaseous anesthetics in the developing nonhuman primate Study Scientist: Wang	(1) To determine the dose-response effects of individual or combined gaseous anesthetics nitrous oxide and isoflurane on neuronal cell death in the developing nonhuman primate, using magnetic resonance imaging (MRI) and positron emission tomography (MicroPET). (2) To determine the effect of dose and duration of gaseous anesthetics on nonhuman primate long-term behavior and pathology, using MRI and MicroPET. (3) To evaluate antioxidants in the amelioration of toxicity of gaseous anesthetics.
Developmental neurotoxicity assessment of N-methyl-D-aspartate (NMDA) receptor antagonists in zebrafish Study Scientist: Kanungo	(1) To study wildtype zebrafish embryos exposed to NMDA receptor antagonists (MK-801, dextromethorphan, ketamine and sevoflurane), in order to assess their effects on Rohon-Beard sensory neurons. The effects on the primary and secondary motor neurons and their axons will also be assessed using hb9:GFP transgenic embryos. Postexposure washout experiments will be pursed to determine the effects of these drugs on the nervous system. (2) Certain NMDA receptor antagonists, such as ketamine, are known to modulate hormone levels in mammals and zebrafish. Based on the importance of the neuroprotective nature of neurosteroids, the study will determine estradiol-17' levels in control and treated embryos. Changes in gene expression for the two CYP aromatases/estrogen synthases (brain aromatase cyp19a1b and gonadal aromatase cyp19a1a) will be quantified using quantitative polymerase chain reaction (qPCR). (3) Phenotype-based cell signaling mechanisms, such as MAPK and neuron development-specific gene expression, will be assessed. (4) Reversal of noted adverse effects of these compounds on neurons will be attempted, particularly by treatment with acetyl L-carnitine.
Toxicity assessment of graphene sheets using primary striatal neurons Study Scientist: Ali	(1) To evaluate the toxicity of graphene sheets using in vitro primary cultures of embryonic day 14 (E14) primary rat striatal neurons. (2) To determine pathways involved in graphene toxicity using E14 primary rat striatal neurons.
Identification of protein biomarkers for neurotoxicity assessments using a high throughput antibody microarray approach Study Scientist: Gu	(1) To examine proteomic changes at both the expression and phosphorylation levels using five established in vivo models of neurotoxicity. (2) To identify common changes in protein expression and phosphorylation status in these animal model systems. (3) To confirm the observed alterations in protein expression and phosphorylation status by means of other independent methods. (4) To apply the proteomic findings to a global ischemic animal model to further validate the utility of protein biomarkers for use in neurotoxicity assessments.

Nanotoxicology

Project & Study Scientist	Project Summary
Proteomic assessment of the cytotoxic effects of nanoparticles on the blood-brain barrier Study Scientist: Gu	To 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. The long-term goal is to establish proteomic parameters for toxicity of nanoparticles.
Complement assays for the detection of immune-sensitizing activity of nanomaterials Study Scientist: Leakey	(1) To establish two complement assays for routine evaluation of immune-sensitizing activity of nanomaterials. (2) To validate the assays using nanoparticles with known immunoreactivity. (3) To determine the immune-sensitizing activity of novel nanomaterials.
Physiologically based pharmacokinetic (PBPK) modeling of nanomedicine; building clinically relevant standards for FDA-regulated nanoparticulate drug products Study Scientist: Leakey	(1) To determine in vivo liposomal doxorubicin release kinetics in individual tissues and blood stream by physiologically based pharmacokinetic (PBPK) modeling. (2) To establish quantitative physicochemical property (liposomal size and content of ammonium sulfate) biodistribution relationships of liposomal doxorubicin products by PBPK modeling. (3) To extrapolate the PBPK model to rats and humans. A whole-body PBPK model will be developed to describe and simulate the biodistribution of liposomal vesicles and doxorubicin.
Assessment of size- and shape- dependent toxicity of silver nanoparticles as measured by changes in the permeability at the gastrointestinal surface Study Scientist: Khare	(1) To investigate various cellular components involved in the uptake of nanoparticles in intestine, their accumulation in various cell types, and the effect of nanoparticles on the intestinal microbiome, by determining the effect of nanomaterials on the permeability of intestinal epithelial cells in vitro and ileal mucosa ex vivo. (2) To measure the toxicity of silver nanoparticles as measured by changes in the expression of genes involved in the epithelial integrity of polarized epithelial cells and ileal mucosa.
In vitro genotoxicity of graphene family nanomaterials using FDA recommended short-term genetic toxicity test battery Study Scientist: Mei	To determine (1) the genotoxicity of graphene and derivatives in standard regulatory test battery assays; (2) if any mutagenicity in mouse lymphoma cells is due to loss of heterozygosity in chromosome 11; (3) if genotoxic and mutagenic response is mediated through oxidative pathways; and (4) 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 Study Scientist: Khare	To evaluate the effects of graphene on gastrointestinal homeostasis by determining graphene derivative effects on intestinal bacterial cultures, polarized intestinal epithelial cells, intestinal commensal bacteria in vivo, and gastrointestinal immune responses in vivo.
NCTR/Office of Regulatory Affairs (ORA) Nanotechnology Core Facility Study Scientist: Patri	The goals of the Nanotechnology Core Facility are to (1) provide the expertise and equipment for characterization of nanomaterials used in toxicology studies, (2) provide the expertise and equipment to detect nanomaterials in in vitro and in vivo derived samples, and (3) serve as a resource for U.S. agencies for the design of toxicology studies and generation of standards for analytical methods.
Assessment of whether engineered silver nanomaterials (AG-ENMs) varying by size and coatings behave differently than bulk silver in their ability to induce genetic damage Study Scientist: Chen	(1) To evaluate whether or not the Ames test and mouse lymphoma assay, in addition to the in vitro micronucleus assay, are suitable for detecting the genetoxicity of titanium dioxide nanoparticles, a known rodent carcinogen. (2) To investigate Ag-ENPs of various sizes and to compare the results to those obtained using bulk silver.
Determination of cytotoxicity and genotoxicity of nanomaterials of interest to the FDA and mechanism of action Study Scientist: Fu	(1) To 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. (2) To determine if in the presence of nano-metal materials, endogenous and dietary antioxidants can display pro-oxidative activity.
Assessing epigenetic effects of nanoparticles in human cells Study Scientist: Hammons	(1) To 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). (2) To determine the effect of two types of nanoparticles, silver and titanium dioxide, at various particle sizes, surface coatings, dosages, and durations of exposure on the pattern of global histone modifications, examining the full spectrum of histone modifications, and on genome-wide profiles of histone modifications in four types of human cells (liver, lung, skin, and colorectal). The analysis will include comparisons with disease-associated histone modifications. (3) To correlate the effect on DNA methylation with its effect on DNA methyltransferase expression; correlate the 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.

Bioassay and Biomarker Development and Evaluation

Project & Study Scientist	Project Summary
Development of cancer-relevant biomarkers for identification of potential carcinogens: research to understand the normal background frequencies in rats Study Scientist: McKinzie	(1) To understand the distribution and range of spontaneous oncogene mutant frequencies in the major organs of rats and mice. (2) To provide important basic information for the validation of these oncogene mutant frequencies as biomarkers of chemically induced carcinogenesis.
Development and validation of 3-D quantitative structure-activity relationship (QSAR) models for prediction of the binding affinity of chemicals from the ToxCast database to the estrogen receptor (ER) Study Scientist: Slavov	To develop and validate a 3-D quantitative structure-activity relationship (QSAR) model for estrogen receptor binding and provide estrogen binding affinity for chemicals. (2) To identify structural binding elements. (3) To evaluate the available databases, including EPA EPcat and EPA Endocrine Disruptor Screening Program data for estrogen receptor binding activity.
Validation of a newly developed transgenic, hairless, albino mice Study Scientist: Manjanatha	To evaluate a newly developed transgenic, hairless, albino mouse bearing a gpt-delta reporter construct (THA) for (1) responsiveness of the construct (gpt and spi-red/gam genes) to ultraviolet B radiation (UVB); and (2) examine kinetics of induction of UVB-induced mutations in a reporter construct in the dermis and epidermis, and correlate activity with UVB induction of skin tumors.
Study of translational biomarkers for drug-induce liver injury with next-generation sequencing Study Scientist: Wang	To conduct a comprehensive survey of miRNA using the next generation sequencing technology. The resulting findings will elucidate the molecular pathways and processes modulated by RNAs (including mRNAs, miRNAs and other non-coding RNAs) and their importance in drug-induced liver injury risk and phenotypes.
A comprehensive characterization of iPSC-CMs models for drug-induced arrhythmia using high throughput screening assays Study Scientist: Pang	(1) To develop standard baseline criteria for high throughput readouts of drug-induced arrhythmia in human iPSC-CMs from different suppliers. (2) To assess individual variance and possible sex differences in drug-induced cardiotoxic responses across a panel of non-genetically 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 Study Scientist: Dobrovolsky	To 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 Study Scientist: Guo	To develop and utilize 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.
Evaluation of microRNAs in blood and urine for detection of chemical-induced carcinogenicity Study Scientist: Chen	(1) To determine miRNAs in blood and carcinogenic target tissues that respond to exposure of carcinogens, and the best time for sampling of their expression after the treatments in rats. (2) To determine miRNA profiles from the blood and target tissue samples of rats treated with different mode-of-action carcinogens, such as alkylating agents, aneugens, clastogens, and non-genotoxic carcinogens at the appropriate sampling time. (3) To determine the functions and pathways of the dysregulated miRNAs by the carcinogen treatments and examine whether the miRNA changes can be anchored to the carcinogens with the known mode-of-actions and whether the changes in blood related to those in the target tissues. (4) To establish specific miRNA biomarkers in blood for assessing different types of carcinogens.

NTP at NCTR: Interagency Agreement Projects

NCTR research for NTP is funded by both voluntary allocations and an interagency agreement. Below are FY 2016 projects that were funded through an NIEHS/NTP interagency agreement with FDA. Click the project title for a brief summary.

View Research Areas in

Food Contaminants
Dermal Toxicology Program
Dietary Supplement Program
Enhancing Toxicology Program

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Food Contaminants

Project & Study Scientist	Project Summary
Two-year chronic toxicology study of bisphenol A (BPA) administered by gavage to NCTR Sprague Dawley rats from gestational day 6 until birth and directly to pups from postnatal day 1; continuous and stop-dose exposures Study Scientist: Delclos	To characterize the long-term toxicity of orally administered bisphenol A (BPA), including developmental exposure, in NCTR Sprague Dawley rats over a broad dose range. In addition, animals generated in this study will be assigned to separate protocols for assessment of a range of molecular, morphological, and functional endpoints to determine if these endpoints are predictive of long-term toxic effects or reveal potential effects undetected by standard toxicological evaluations.
Evaluation of molecular, morphological, and functional endpoints in NCTR Sprague Dawley rats treated with bisphenol A (BPA) administered by gavage from gestational day 6 until birth and directly to F1 pups from postnatal day 1; continuous and stop-dose (postnatal day 21) exposures Study Scientist: Delclos	To evaluate a range of molecular, morphological, and functional endpoints in rats dosed orally with a wide range of bisphenol A 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 bisphenol A exposure. Assessments will be conducted at various ages (postnatal days 1, 21, and 90, as well as 6 and 12 months) to determine if any effects observed are predictive of long-term effects evaluated in the companion chronic toxicology study, or if they reveal potential effects undetected by standard toxicological evaluations.

Combined nephrotoxicity of melamine and cyanuric acid in rats – recovery study Study Scientist: Gamboa	To assess the degree of functional and histological recovery after 30- and 90-day recovery periods in rats orally co-exposed with melamine and cyanuric acid for 90 days.
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 Study Scientist: Camacho	(1) 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 subsequent 90-day recovery period. (2) To compare the dose-response 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 Study Scientist: Doerge	To determine serum pharmacokinetics and metabolism of inorganic arsenic at a low dose in adult female CD-1 mice, Sprague Dawley rats, and rhesus monkeys.

Dermal Toxicology Program

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

Dietary Supplement Program

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

Enhancing Toxicology Program

Project & Study Scientist	Project Summary
NTP capability building for microbiome assessment on toxicology studies: assessing the role that the microbiome may play in the toxicity of xenobiotics Study Scientist: Cerniglia	To address critical knowledge gaps in the microbiome field by using the latest advances in microbiome analysis, using in vitro, in vivo, and ex vivo models in toxicity testing risk assessments.

Developing an in vitro system to evaluate the disease-related toxic effects of inhaled test agents in human airway tissue models Study Scientist: Cao	(1) To develop exposure and dosimetry methods for exposing human air-lung interface airway cultures to aerosolized test agents. (2) To 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.
Evaluation of genotoxicity and epigenetic modification of black cohosh extract (BCE) using the modified comet assay Study Scientist: Manjanatha	(1) To perform alkaline single cell gel electrophoresis (Comet) assays to detect both DNA single and double strand breaks using several human cell lines. (2) To perform modified Comet assays using the addition of uracil-DNA glycosylase (UDG) to evaluate the potential underlying mechanism(s) of BCE-associated genotoxicity. (3) To perform recently established modified Comet assays using DNA restriction enzyme, McrBC, which specifically recognizes DNA sites of the form 5'-R(m)C-3' and cuts DNA at methylated Cs for evaluating methylation modification by BCE.

NTP at NIOSH

About NTP at the National Institute for Occupational Safety and Health

NIOSH research projects for NTP to assess the effects of exposures to substances, following its mandate to protect workers' 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 2016.

About NTP at the National Institute for Occupational Safety and Health

In following its mandate to protect workers' health and safety, the National Institute for Occupational Safety and Health (NIOSH) carries out research projects for NTP to assess the effects of exposure to substances, through an interagency agreement with NIEHS. Setting priorities in occupational toxicological research is based upon several sources of information that NIOSH develops and maintains. These include health hazard evaluations, industry-wide studies, gaps in knowledge identified while developing criteria for recommended standards or criteria documents, current intelligence bulletins, hazard reviews and alerts, other technical reports, and information profiles on chemical hazards. NIOSH research for NTP is funded by both voluntary allocations and an interagency agreement focusing on comprehensive assessment of occupationally-relevant exposures and immunotoxicology research.

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

The table below lists NIOSH/NTP projects in FY 2016 funded through voluntary allocations. Click the project title for a brief summary.

View Research Areas in

Biomonitoring, Biomarker Dev. & Health Assessment
Environmental Monitoring
Exposure Assessment
Immunotoxicity and Immunology
Genetics

Show All

Search Projects

Biomonitoring, Biomarker Dev. & Health Assessment

Project & Study Scientist	Project Summary
Exposure assessment research and support Study Scientist: Striley	To support multiple branch and interdivisional projects through (1) the management and planning of field sample

collection, (2) the development of new classical and immunochemical biomonitoring methods, and (3) the validation and adaptation of existing methods. Biological monitoring can assess exposure by analyzing acute and latent metabolites in various biological media. The goal of this project is to develop low-cost, rapid immunochemical and analytical chemistry biomonitoring methods that will be used to identify exposures and evaluate potential interventions. Concurrent with development of exposure assessment methods, this project will identify and develop new multiplex immunochemical methods to evaluate biomarkers of occupational illness or subclinical signs of occupational illness.

Ultraviolet native fluorescence-based monitor for workplace exposures

Study Scientist: Snawder

To develop and evaluate a readily adaptable, next generation, direct reading personal monitor for use in measuring worker exposure to a wide variety of chemicals, including naphthalene and components of asphalt fume. The development of personal monitors for volatile and semivolatile workplace chemicals will be helpful in rapidly assessing chemical exposure and result in more realistic occupational exposure assessments that allow for rapid interventions leading to reduced worker exposures and aiding prevention of occupational illness and disease.

Evaluation of welding fumes as a lung carcinogen in mice exposed by inhalation

Study Scientist: Erdely

To investigate both carcinogenic-metal and non-carcinogenic-metal containing welding fumes as lung carcinogens using a two-stage initiation-promotion mouse model. The findings will establish if welding fume inhalation at relevant occupational exposure levels increases lung tumorigenesis. The project will also generate valuable data regarding the carcinogenic potential of fumes from different types of welding activities that may or may not contain carcinogenic metals. In addition, the project will establish knowledge on which subcomponents of the total welding fume have the greatest carcinogenic potency. The results will be important for the potential reevaluation of welding fume by the International Agency for Research on Cancer.

Systematic assessment of cobalt oxide (CoO) and lanthanum oxide (La2O3) in pulmonary disease

Study Scientist: Qian

To investigate cobalt oxide and lanthanum oxide nanoparticle–induced pulmonary injury in vivo and cellular toxicity in vitro. This project will reveal the toxicological mode of actions for cobalt oxide and lanthanum oxide nanoparticles. Metal oxide nanoparticles are an important class of engineered nanomaterials with a broad application in many industrials. Concerns over potential metal oxide nanoparticle-induced toxicity have emerged,

	particularly due to their ability to induce oxygen radicals and oxidative stress. Results obtained from this study will lead to development of methods for early detection and interventions of cobalt oxide and lanthanum oxide-induced pulmonary diseases, particularly fibrosis, in humans.
Industry-wide studies of workers exposed to carbon nanotubes and nanofibers Study Scientist: Schubauer-Berigan	To collect exposure data from participating pilot-scale or full-scale manufacturers or users of single-walled or multiwalled carbon nanotubes and carbon nanofibers. A study of biomarkers for early pulmonary, cardiovascular, and carcinogenic effect will be carried out among workers at these facilities.
Mortality, cancer incidence, and biomarker studies Study Scientist: Ruder	To elucidate exposure-outcome associations, especially dose-response relationships, for risk assessment and to examine relationships between biomarkers of exposure, susceptibility, and oncogene expression and determine health effects.

Environmental Monitoring

Project & Study Scientist	Project Summary
Analytical research and development infrastructure Study Scientist: Streicher	To provide for administrative needs and analytical instrumentation repair and maintenance in support of Chemical Exposure and Monitoring Branch chemists conducting research on sampling, and analytical methods development for workplace chemicals. Development, evaluation, validation, and use of methods for chemicals such as bisphenol A, manganese speciation, and flame retardants are part of the NIOSH/NTP exposure assessment interagency agreement. In FY 2015, a method developed for bisphenol A was used to analyze field samples. The manganese speciation method used to evaluate field samples has undergone review for formal inclusion in the NIOSH Manual of Analytical Methods. Additionally, sampling and analysis methods for flame retardants were investigated in support of field surveys.
Diacetyl exposure assessment Study Scientist: Streicher	To develop and evaluate sampling and analytical methods for diacetyl and other higher molecular weight alpha dicarbonyl flavoring compounds and enable accurate exposure assessment and evaluation of the effectiveness of control technology. Two sampling and analytical methods are being investigated for measurement of specific flavoring compounds, most notably diacetyl and 2,3-pentanedione. One method measures alpha dicarbonyl compounds present as vapor and the other measures these compounds in airborne particles and bulk powders.

Nanoaerosol monitoring methods Study Scientist: Birch	To develop and apply measurement methods for hazardous aerosols. Globally, exposure to hazardous aerosols remains a serious health concern, with growing attention on fine, ultrafine, and nanomaterial aerosols. New nanomaterials are being developed and used in multiple commercial products, but there is relatively little knowledge regarding their health and environmental impacts. Multiple analytical tools are being utilized, because the properties most responsible for nanoaerosol toxicity are unclear and exposures are often to complex mixtures. This research is providing critical exposure data and information on the widely differing physical and chemical properties of nanoscale aerosols and materials. These properties may have influence on particle toxicity. These methods have general application to exposure monitoring and control studies. Metal contents were determined by inductively coupled plasma atomic emission spectroscopy after microwave digestion in concentrated nitric acid. In addition, all materials were analyzed by thermogravimetric analysis, which gives the onset of oxidation, a measure related to stability, and residual ash content, a measure of purity. High iron content was found in most of the samples, and the residual ash contents of the materials ranged from about 1-10%. In FY 2016, polycyclic aromatic hydrocarbons and transmission electron microscopy analyses will be completed.

Exposure Assessment

Project & Study Scientist	Project Summary
Exposure assessment for toxicologically important chemicals Study Scientist: Curwin	To characterize workplace exposures to chemicals of toxicological concern as identified by NTP and NIOSH. Current studies include welding fumes with emphasis on manganese, occupational exposure to bisphenol A, occupational exposure to carbon nanotubes and nanofibers, flame retardants, and polycyclic aromatic hydrocarbons 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 Study Scientist: Whelan	To support strategic planning and feasibility studies of high priority and emerging problems in occupational health.

Nanotechnology field evaluations Study Scientist: Geraci	To obtain information from as many different facilities in the field as possible, regarding (1) the nature of engineered nanomaterials, (2) the processes involved in their manufacture and use, (3) the potential worker exposures, and (4) the work practices and control procedures where nanomaterials are produced or used. As toxicology studies identify the biologic hazards of nanomaterials, it is important to gain a better understanding of actual workplace exposures.
Dermal permeation of benzene from gasoline and crude oil: current and historical issues Study Scientist: Frasch	To generate and interpret data on the dermal absorption potential of benzene from gasoline. Specifically, (1) to quantify benzene in a sample of gasoline to be used for dermal absorption rate testing; (2) to quantify the dermal absorption rate of benzene in gasoline, both steady state fluxes from “infinite” dose application and non-steady state absorption profiles from finite dose applications; (3) to repeat dermal absorption rates using gasoline fortified with benzene to mimic historically high levels, and undiluted or neat benzene; and (4) to measure the thermodynamic activity of benzene in gasoline. This research will be used in the dermal risk assessment of current and historical benzene exposures.

Immunotoxicity and Immunology

Project & Study Scientist	Project Summary
Immunotoxicological evaluation of occupational chemicals Study Scientist: Anderson	To identify occupational and environmental chemical hazards and evaluate immune function and mechanisms associated with exposure. This research will contribute to better risk assessment and increased identification of immunological hazards encountered in the workplace, which will ultimately establish occupational exposure limits.
Identification of occupational allergens Study Scientist: Noti	(1) To identify exposures to substances that can cause inflammatory or immune reactions in certain work environments. These exposures are important causes of occupational lung diseases, such as asthma and allergic alveolitis. (2) To develop improved techniques for the detection of such immune reactions before adverse clinical outcomes occur. (3) To develop improved techniques for the detection and identification of inciting occupational agents. This project will involve the analyses of clinical samples, environmental bulk samples, and environmental aerosol samples. Successful completion of these investigations should lead to the development of effective prevention strategies for occupational allergies and asthma.

Characterization of in vivo protein haptenation following exposure to aerosolized 4,4'-methylene diphenyl diisocyanate Study Scientist: Hettick	To determine the molecular targets of inhaled diisocyanate particulates and better understand the pathogenic mechanism of isocyanate-induced allergic disease. The project will enhance the overall understanding of the fate of diisocyanate in vivo following occupational exposure by increasing our understanding of disease and identifying potential biomarkers of exposure.
Exosomes as biomarkers and immune modulators of diisocyanate asthma Study Scientist: Hettick	To define mechanisms underlying methylene diphenyldiisocyantate (MDI) associated occupational asthma by identifying biomarkers of MDI exposure and immune regulatory factors that influence the progression and severity of MDI associated occupational asthma. Exposure to MDI, which is used in the manufacturing of glues and polyurethanes, results in occupational asthma in approximately five to 15 percent of workers. Currently, sensitive and reliable markers for MDI exposure and sensitization do not exist, partially due to the lack of specificity of markers commonly associated with asthma. Furthermore, the factors influencing susceptibility and severity of MDI associated occupational asthma have not been elucidated. This project will identify response and legacy biomarkers found in exosomes secreted into the bloodstream that would indicate isocyanate exposure and sensitization. Attempts will be made to distinguish chemical induced biomarkers from high molecular weight allergen induced markers, and determine how exosome genetic content can influence asthma progression. The biomarkers identified in this study can be incorporated into a human exposome database and used in future studies to distinguish MDI associated occupational asthma from general environmental asthmas.

Genetics

Project & Study Scientist	Project Summary
Immunotoxicity of subchronic fungal exposures Study Scientist: Nayak	To determine the pulmonary immunopathological outcomes of subchronic exposures to fungi nominated to the NTP. In FY 2016, subchronic exposure studies with a mycotoxin producing strain of *Stachybotrys chartarum* were completed and a manuscript was published. Future subchronic exposure studies will focus on a low tricothescene producing strain of *S. chartarum*, as well as *Aspergillus versicolor*. 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

Study Scientist: Marshall

To identify the cellular and molecular mechanisms behind the immune-modulating effects of the antibacterial chemical triclosan. This information will provide the basis for evaluating other nonsensitizing antimicrobial chemicals and help identify potentially conserved mechanisms that contribute to allergic disease. This will help determine the need for evaluating these types of workplace chemicals, leading to better risk assessment and establishment of occupational exposure limits.

Highly sensitive and practical biomarkers for nanotoxicity

Study Scientist: Joseph

To develop, validate, and test in a rat model highly sensitive and minimally invasive biomarkers for early detection of pulmonary toxicity, potentially associated with exposure to toxic nanomaterials. Techniques will be employed to develop transcriptomic signatures in blood as surrogate biomarkers for the pulmonary toxicity induced by inhalation exposure to specific nanomaterials. Bioinformatic analysis of the global transcriptomics data will be conducted to gain insights into the molecular mechanisms underlying the pulmonary toxicity of nanomaterials. Determining the molecular mechanisms of pulmonary toxicity and developing highly sensitive and minimally invasive biomarkers for nanotoxicity have implications in monitoring workers for their risk of developing adverse health effects potentially associated with exposure to toxic nanomaterials.

Toxicological investigations of nitrogen-doped multiwalled carbon nanotubes

Study Scientist: Porter

To examine the potential effect of altering the chemical composition of multiwalled carbon nanotubes on their bioactivity in vivo. Knowledge of doping modification may allow for the development and use of less bioactive multiwalled carbon nanotubes. This may reduce the hazard from workplace exposures. Such information may allow material scientists to incorporate a prevention-through-design philosophy into the development of new nanoparticle-based technologies using nanomaterials that pose lower risks to human health. These data will also contribute to NIOSH's effort to develop and implement an evidence-based strategy for recommending occupational exposure limits or occupational exposure bands for carbon nanotubes. These studies will compare two multiwalled carbon nanotubes with different chemical compositions, such as multiwalled carbon nanotubes and nitrogen-doped multiwalled carbon nanotubes. These studies should increase our understanding of the toxicological mechanisms responsible for multiwalled carbon nanotube-induced pathologies, and may also identify extra-pulmonary sites of toxicity resulting from systemic transport of multiwalled carbon nanotubes after pulmonary exposure.

Toxicological evaluation of pulmonary exposure to graphenes Study Scientist: Roberts	(1) To characterize the pulmonary, cardiovascular, and neurological toxicity that may be associated with respiratory exposure to graphenes, using an in vivo, tiered toxicity testing approach that incorporates a dose-response, time-course model with aspiration of nanomaterials as the route of exposure. This will be followed by an inhalation study with a specific particle and dose identified in the first tier of studies. (2) To determine potential mechanisms of pathology, when applicable, and address whether respiratory exposure to graphene nanomaterials, which differ in size and oxidative form, pose a risk for work-related illness. This project is from the Nanotechnology Research Center at NIOSH.
Neurological risks associated with workplace chemicals and nanomaterials Study Scientist: Sriram	To evaluate potential neurotoxicological effects associated with exposure to chemical agents, incidental nanoparticles, and engineered nanomaterials experimental models. This includes hazard identification, evaluating molecular mechanisms of neurotoxicity, and identifying potential biomarkers of neurotoxicity. Findings from this study may contribute toward developing (1) novel biomarkers for monitoring exposures and health effects; (2) pre-job planning protocols, hazard and risk assessment paradigms; and (3) occupational safety standards for neurotoxic exposures.
Mechanism of carbon nanotube-induced carcinogenesis and aneuploidy Study Scientist: Sargent	In vitro exposure of human cells to one to four nanometer diameter single-walled carbon nanotubes disrupts the mitotic apparatus, resulting in errors of chromosome number. Data comparison with 10-20 nanometer diameter multiwalled carbon nanotubes suggests that the diameter of the nanotube is important in the genotoxic response, and that carbon nanotubes are potentially carcinogenic. A study where multiwalled carbon nanotube were inhaled utilizing a two-stage initiation and promotion mouse model demonstrated that multiwalled carbon nanotube are strong promoters of lung adenocarcinoma.
Epigenetic changes in response to nanoparticle exposure Study Scientist: Ding	To investigate potential pulmonary carcinogenesis in response to tungsten carbide-cobalt (WC-Co) particle exposure using cell culture and animal models. Mechanistic investigations, including gene mutation, activation of transcription factors, and reactive oxygen species generation will be conducted to explain the events of WC-Co-induced tumor initiation, promotion, and progression. Determining the mechanisms involved in WC-Co-induced carcinogenesis and elucidating target-

signaling pathways could provide insights for the development of biomarkers and possible prevention strategies for WC-Co-induced diseases.

Nano-Metal Oxide Property Affecting Fibrogenesis or Carcinogenesis
Study Scientist: Rojanasakul

Metal oxide nanoparticles (nMOs), including cerium oxide (nCeO2) and ferric oxide (nFe2O3), are increasingly used in a variety of industrial and commercial applications with the potential of releasing particles into the workplace air. Limited published studies show that pulmonary exposure to nMOs in animal models causes lung inflammation and fibrosis at the human exposure relevant dose. The overall strategy of this project is to determine the effects of physicochemical properties (size and coating) of nMOs and their toxicities using a panel of well characterized nMOs. In vitro study data showed consistent fibrogenic effect of nCeO2 as observed in animal study. This supported the project goal to develop an economic in vitro tool to predict in vivo toxic potential of nMOs. Sub-chronic exposure of nFe2O3 induced neoplastic transformation of primary human small airway epithelial cells. The mechanism of this effect is under investigation. By utilizing such in vitro/in vivo models, key physicochemical properties of nMOs affecting their toxic responses were identified, which may support potential safe-by-design strategies.

Hydraulic Fracturing: toxicological effects of silica and diesel exhaust exposure
Study Scientist: Fedan

The toxicities of inhaled hydraulic fracturing sand dust, alone and in combination with inhaled diesel exhaust that mimic worker exposures during hydraulic fracturing operations, are being studied. Effects on several organ systems are being investigated using a battery of in vivo and in vitro animal model tests. The initial exposures to hydraulic fracturing sand dust, using two exposure doses, is nearly finished. Effects of exposure on the lung, cardiovascular system, immune systems, brain, skin, and blood have been examined. The next set of exposures will be to diesel exhaust, where organ effects will be investigated.

Pulmonary function and nanoparticle inhalation: in vivo and in vitro effects
Study Scientist: Fedan

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

Health effects of inhaled crude oil
Study Scientist: Fedan

To design and build an inhalation exposure system that delivers crude oil vapor to rats. This system will be used to study the effects of crude oil vapor inhalation on the

	lung, cardiovascular system, immune system, brain, skin, and blood. Surrogate oil from the Gulf of Mexico, and oil from the Macondo well, has been obtained. The exposure system for delivering oil vapor to rats is completed and awaits calibration gases before the exposures can begin.
Toxicity assessment of carbon nanotubes and carbon nanofibers from U.S. facilities Study Scientist: Erdely	To evaluate the toxicity 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. This study will assess general pulmonary and systemic toxicity, pathology, biodistribution, and genotoxicity.
Toxicity associated with the life cycle of carbon nanotubes Study Scientist: Erdely	In vivo and in vitro data suggests exposure to carbon nanotubes has significant adverse health effects. There is little data defining the toxicity of carbon nanotubes at each stage of their production life-cycle (as produced, post-production modification, and incorporation into composites), although the numbers of potential exposed workers increases with each stage. This project will evaluate the pulmonary response and genotoxicity of carbon nanotubes at different stages of production.
A translational in vitro approach to assess cardiovascular risk Study Scientist: Erdely	Respiratory exposure to particulates has been associated to increased mortality from cardiovascular diseases. This project will develop and test an in vitro model to assess cardiovascular risk following a pulmonary exposure to engineered nanomaterials. If successful, these studies will have direct impacts on future toxicological assessment methods, as the cardiovascular system appears more sensitive than typical pulmonary toxicity measurements.

NTP at NIOSH: Immunotoxicology Research

Interagency Agreement on Immunotoxicology Research

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

The table below lists NIEHS and NIOSH Interagency Agreement on Immunotoxicology Studies in FY 2016. Click the project title for a brief summary.

View Research Areas in
Immunotoxicology Studies

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Immunotoxicology Studies

Project & Study Scientist	Project Summary
Identification and characterization of cross-reactive fungal biomarkers Study Scientist: Green	To develop monoclonal species-specific antibodies to recombinant fungal biomarker antigens. The utility of these antibodies will be important for the quantification of occupationally-relevant fungal biomarkers, particularly to those fungi that have been nominated to the NTP.
Toxicity of subchronic fungal exposures Study Scientist: Green	To characterize the toxicological and pulmonary immune responses associated with subchronic fungal exposures using a model that replicates human exposure. This model utilizes an acoustical generator system, and nose-only exposure chamber to characterize toxicological endpoints following subchronic exposures to spores derived from fungi nominated to the NTP. In FY 2016, subchronic exposure studies with a mycotoxin producing strain of *Stachybotrys chartarum* were completed and two

manuscripts are in preparation. Future subchronic exposure studies will focus on a low tricothescene producing strain of *S. chartarum*, as well as *Aspergillus versicolor*. Proposed studies will provide further insight into the mechanisms of pulmonary toxicity to fungi encountered in the workplace. *Alternaria alternata*, mixed fungal exposures, and other occupationally relevant fungi identified in concurrent NTP funded diversity studies will be evaluated in the future. These toxicological studies will provide novel datasets that will be used to characterize the hazards that fungal exposure may represent to human and occupational health.

Identification and characterization of fungal exposures

Study Scientist: Green

To investigate and characterize the diversity of mold in indoor and occupational environments using ribosomal RNA 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. These methodological approaches have 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

Study Scientist: Park

To examine potential roles of exposure to fungal toxins on occupants' health in water-damaged buildings. Cost-effective and robust methods have been developed using ultra-performance liquid chromatography-tandem mass spectrometry for simultaneous analysis of 30 fungal secondary metabolites, including mycotoxins in environmental samples. The accuracy of the method was increased by using isotopically labeled (C13) mycotoxin internal standards to compensate for extraction loss and matrix effects. Methods to examine stability of mycotoxins in floor dust stored in different temperature conditions by analyzing them at different points of time for two years are being used. Next steps include: (1) quantifying fungal secondary metabolites including mycotoxins in floor dust samples collected from a school study conducted in FY 2015 and previous epidemiologic studies of water-damaged buildings; (2) continuing to collaborate with a research group in Austria to screen more than 550 microbial metabolites in the dust samples from the school study; and (3) examining the effect of exposure to fungal secondary metabolites including mycotoxins on occupants' health using statistical models adjusted for exposures to other microbial agents that were also measured in the epidemiologic 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. FY 2016 efforts listed in the table below address worker exposures to welding fumes, nanosized materials, food flavorings, bisphenol A, indium compounds, and other industrial chemicals.

NIOSH mobile lab for field studies

The table below lists NIEHS and NIOSH Interagency Agreement Projects on Occupationally Relevant Exposures in FY 2016. Click the project title for a brief summary.

View Research Areas in
Occupationally Relevant Exposures

Show All

Search Projects

Occupationally Relevant Exposures

Project & Study Scientist	Project Summary
Administrative support Study Scientist: Whelan	To enable NIOSH scientists to (1) participate in review and oversight of NTP activities, and (2) attend NTP-related meetings in Research Triangle Park, North Carolina and Washington, D.C.
Occupational exposure assessment of welding fume with emphasis on manganese compounds Study Scientist: Hanley	(1) To identify industries, such as construction, shipbuilding, railroad, manufacturing companies, and unions involved in welding operations for exposure assessments where the potential for substantial manganese exposure exists; (2) develop methods to identify manganese compounds and different valence states, based on selective solubility with various welding fumes matrices; and (3) characterize welding fume exposures based on welding-associated jobs, tasks, and processes.
Exposure assessment of engineered nanoparticles Study Scientist: Geraci	(1) To identify workplaces engaged in the synthesis, manufacture, and use of engineered nanomaterials; and (2) characterize workplace exposure to selected engineered nanoparticles.
Durability of nanoscale cellulose fibers in artificial human lung fluids Study Scientist: Stefaniak	To investigate the in vitro durability of nanocellulose materials in artificial lung fluids. Data generated from this study will be used to inform larger in vivo inhalation studies.
Occupational exposure to bisphenol A (BPA) in the U.S. Study Scientist: Hines	(1) To understand bisphenol A (BPA) use in industry, including processes, jobs, and tasks with potential BPA exposure; (2) develop air, hand wipe, and surface wipe sampling, and analytical methods for BPA, using liquid chromatography-tandem mass spectrometry and liquid chromatography with ultraviolet detection; and (3) assess exposure to BPA among workers through air, hand wipe, and urine sample collection.

Assessment of occupational exposures to flame retardants.

Study Scientist: Estill

To assess exposure to nine alternative flame retardants plus a panel of polybrominated diphenyl ethers. Exposure will be assessed among workers involved in the manufacture, installation, or use of goods containing these nine alternative flame retardants. Worksite categories included in the study are manufacture of products that use flexible polyurethane foams, plastics, or resins; fabrication and manufacture of rigid polystyrene foam; cutting, installing, or spraying polyurethane foam insulation at construction sites; using gymnasiums; manufacture of wire harnesses or printed circuit boards; and the fire service industry. This study will compare exposures among industries, processes, and tasks; determine the route of exposure; and make recommendations to reduce exposures. These data will be used to determine exposure levels of workers in different occupations and how they relate to the general population by comparison to the National Health and Nutrition Examination Survey data. The results will aid in the design of toxicological studies, understanding and use of toxicological studies, and risk assessment.

Assessment of occupational exposure to polycyclic aromatic hydrocarbons (PAHs) in coal tar sealant applications

Study Scientist: Hanley

To evaluate the levels of occupational chemical exposure among workers who are using coal tar-based pavement sealants. Coal tar is sometimes used as a base material for blacktop pavement sealants, accounting for as much as 35 percent of the formulation in some of these products. Coal tar is a byproduct of the production of coke, which is needed for steel production. Coal tar pitch volatiles are a mixture of chemicals that can evaporate into air from products containing coal tar, including coal tar pavement sealants. These coal tar pitch volatiles contain several chemicals known as polycyclic aromatic hydrocarbons (PAHs). The focus of this study is on the assessment of occupational exposure to PAHs among coal tar sealant workers. This study will provide data regarding levels of exposure to airborne chemicals that will be compared to current NIOSH recommended exposure limits for coal tar pitch volatiles, and will report results for specific PAH chemicals using NIOSH analytical methods. PAHs will be measured in dermal wipe samples, and PAH metabolites will be measured in biological samples collected from workers to characterize levels present in this workforce.

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