National Toxicology Program

U.S. Department of Health and Human Services

Annual Report

National Toxicology Program

ANNUAL REPORT
For
Fiscal Year 2011

National Institute of Environmental Health Sciences
National Institutes of Health

National Center for Toxicological Research
Food and Drug Administration

National Institute for Occupational Safety and Health
Centers for Disease Control and Prevention

September 2012

Department of Health and Human Services

National Toxicology Program

NIH Publication No. 12-5971

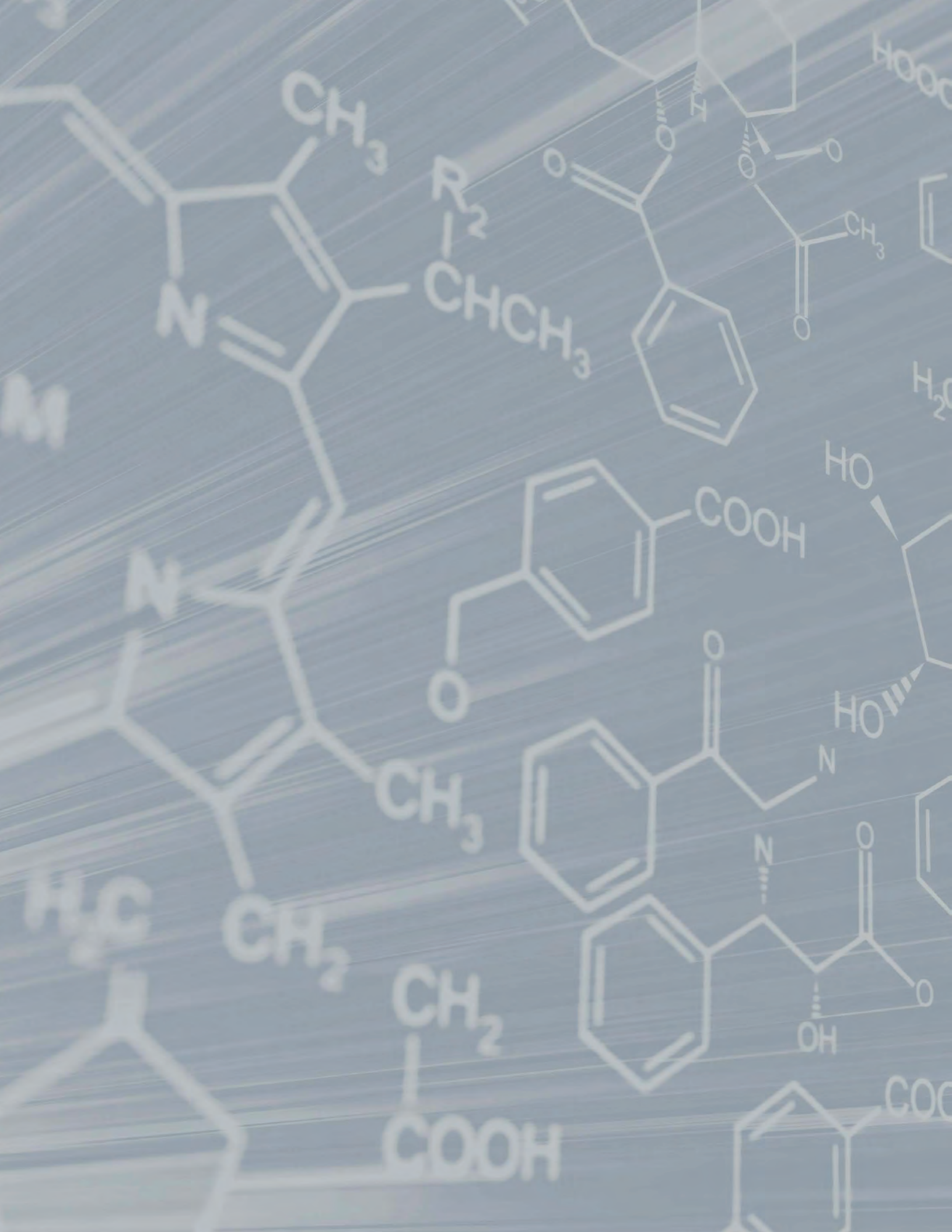


Table of Contents

Frequently Used Abbreviations

2M4N	2-methoxy-4-nitroaniline
3TC	lamivudine
ACB	allele-specific competitive blocker
ACD	allergic contact dermatitis
ADME	absorption, distribution, metabolism, and excretion
Ag	silver
ATSDR	Agency for Toxic Substances and Disease Registry
AZT	zidovudine, 3'-Azido-3'-Deoxythymidine
BPA	bisphenol A
BSC	Board of Scientific Counselors
BALF	bronchoalveolar lavage fluid
CASRN	Chemical Abstracts Service Registry Number
CDC	Centers for Disease Control and Prevention
CDMA	code division multiple access
CEBS	Chemical Effects in Biological Systems
CERHR	Center for the Evaluation of Risks to Human Reproduction
CNS	central nervous system
CNT	carbon nanotube
CPSC	U.S. Consumer Product Safey Commission
CYP	cytochrome P450
DCA	dichloroaniline
DEHP	di(2-ethylhexyl) phthalate
DGE	differential gene expression
DHHS	Department of Health and Human Services
DILI	drug-induced liver injury
DNMT	DNA methyltransferases
DRPM	direct reading, personal monitors
DTBBA	dithiobisbenzanilide
DO	diversity outbred
ECVAM	European Centre for the Validation of Alternative Methods
EDTA	ethylenediaminetetraacetate
EGEHE	ethylene glycol 2-ethylhexyl ether
ENU	N-ethyl-N'-nitrosourea
EPA	U.S. Environmental Protection Agency
ESR	electron spin resonance
FDA	U.S. Food and Drug Administration
FFPE	formalin fixed, paraffin embedded
FY	fiscal year
GABA	gamma-aminobutyric acid
GC/MS	gas chromatography/mass spectroscopy
GD	gestational day
GEMM	genetically engineered mouse model
GMM	genetically modified model
GSM	global system for mobile communication
HHE	Health Hazard Evaluations
HPLC	high performance liquid chromatography
HPRT	hypoxanthine-guanine phosphoribosyltransferase
HTS	high throughput screening
IAG	interagency agreement
IARC	International Agency for Research on Cancer
ICATM	International Cooperation on Alternative Test Methods
ICD	irritant contact dermatitis
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
IgE	immunoglobulin E
IRIS	EPA's Integrated Risk Information System
JaCVAM	Japanese Center for the Validation of Alternative Methods
KoCVAM	Korean Center for the Validation of Alternative Methods
LC/MS/MS	liquid chromatography/tandem mass spectrometry
LCM	laser capture microdissection
LLNA	Local Lymph Node Assay
LOH	loss of heterozygosity
mAb	monoclonal antibody

MiRNA	microRNA
MLA	Mouse Lymphoma Assay
Mn	manganese
MOC	Memorandum of Cooperation
MOU	Memorandum of Understanding
MRI	magnetic resonance imaging
MS	mass spectrometry
N/A	not applicable
NASH	nonalcoholic steatohepatitis
NCGC	NIH Chemical Genomics Center
NCI	National Cancer Institute
NCTR	National Center for Toxicological Research
NICEATM	NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
NHGRI	National Human Genome Research Institute
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NMDA	N-methyl-D-aspartic acid
NMR	nuclear magnetic resonance
NNLA	NTP Nonneoplastic Lesion Atlas
NTP	National Toxicology Program
NVP	Nevirapine
OECD	Organisation for Economic Co-operation and Development
OEHHA	Office of Environmental Health Hazard Assessment
OPA	ortho-phthalaldehyde
ORA	Office of Regulatory Affairs
OSHA	Occupational Safety and Health Administration
PAH	polycyclic aromatic hydrocarbon
PBPK	physiologically based pharmacokinetic
PBPK/PD	PBPK/pharmacodynamic
PCB	polychlorinated biphenyl
PCBTF	chloro-4-(trifluoromethyl) benzene
PCR	polymerase chain reaction
PET	Positron Emission Tomography
PFAA	perfluoralkyl acid
PFOA	perfluorooctanoic acid
PIG-A	phosphatidylinositol glycan – complementation group A
PND	postnatal day
PPAR	peroxisome proliferator-activated receptor
PWG	pathology working group
qHTS	quantitative high throughput screens
qNPA	quantitative nuclease protection assay
qPCR	quantitative polymerase chain reaction.
QSDAR	quantitative spectrometric data-activity relationship
RACB	reproductive assessment by continuous breeding
RBC/RET	red blood cell/reticulocyte
RFR	radiofrequency radiation
RoC	Report on Carcinogens
ROS	reactive oxygen species
RP	retinyl palmitate
SACATM	Scientific Advisory Committee on Alternative Toxicological Methods
SD	Sprague Dawley
SOT	Society of Toxicology
SSL	simulated solar light
STL	Special Techniques Laboratory
STP	Society of Toxicologic Pathologists
TCAB	tetrachloroazobenzene
TiO2	titanium dioxide
TK	toxicokinetics
TOX	NTP Toxicity Report
TR	NTP Technical Report
UDP	uridine diphosphate
UGT	UDP glucuronosyltransferases
UV	ultraviolet
U.S.	United States
VOC	volatile organic compound

Letter from the NIEHS/NTP Director

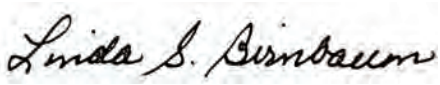
In 2011, Health and Human Services (HHS) Secretary Sebelius and Congress approved reorganization of the National Institute of Environmental Health Sciences (NIEHS), creating the Division of the National Toxicology Program (DNTP) within NIEHS. This reorganization enhances NTP's visibility and recognizes its unique mission and goals within the National Institutes of Health and the unique capabilities and talents of its staff. The DNTP retained four previous branches and established the NTP Laboratory where staff will carry out important targeted in-house research. In addition, the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR) was transformed into the Office of Health Assessment and Translation (OHAT), which will now expand the focus of its evaluations, grounded in reproduction and development assessments, to a broader range of human health effects.

The NTP carried out a number of significant, widely attended workshops this past year. OHAT held a timely workshop on the *Role of Environmental Chemicals in the Development of Diabetes and Obesity* in January 2011. Two workshops in the Series on Best Practices for Regulatory Safety Testing were held in January 2011, *Assessing the Potential for Chemically Induced Eye Injuries* and *Assessing the Potential for Chemically Induced Allergic Contact Dermatitis*. In September 2011, the NTP and NIEHS held a joint workshop on *Advancing Research on Mixtures: New Perspectives and Approaches for Predicting Adverse Human Health Effects*.

NTP's research and testing program continually aims to provide a safer tomorrow by studying substances in our environment. Reports on studies of a number of dietary supplements, AIDS therapeutics, skin care products, and widely used industrial chemicals were disseminated by NTP in FY 2011. These included publication of nine NTP Technical Reports and two NTP Toxicity Reports, and drafts of 10 reports for which we held two public peer review meetings. We were pleased to provide important information on substances that pose a cancer risk through publication of the *12th Report on Carcinogens* in June. This edition added eight newly reviewed substances to the report for a total of 240 listings, including some classes of related chemicals or agents.

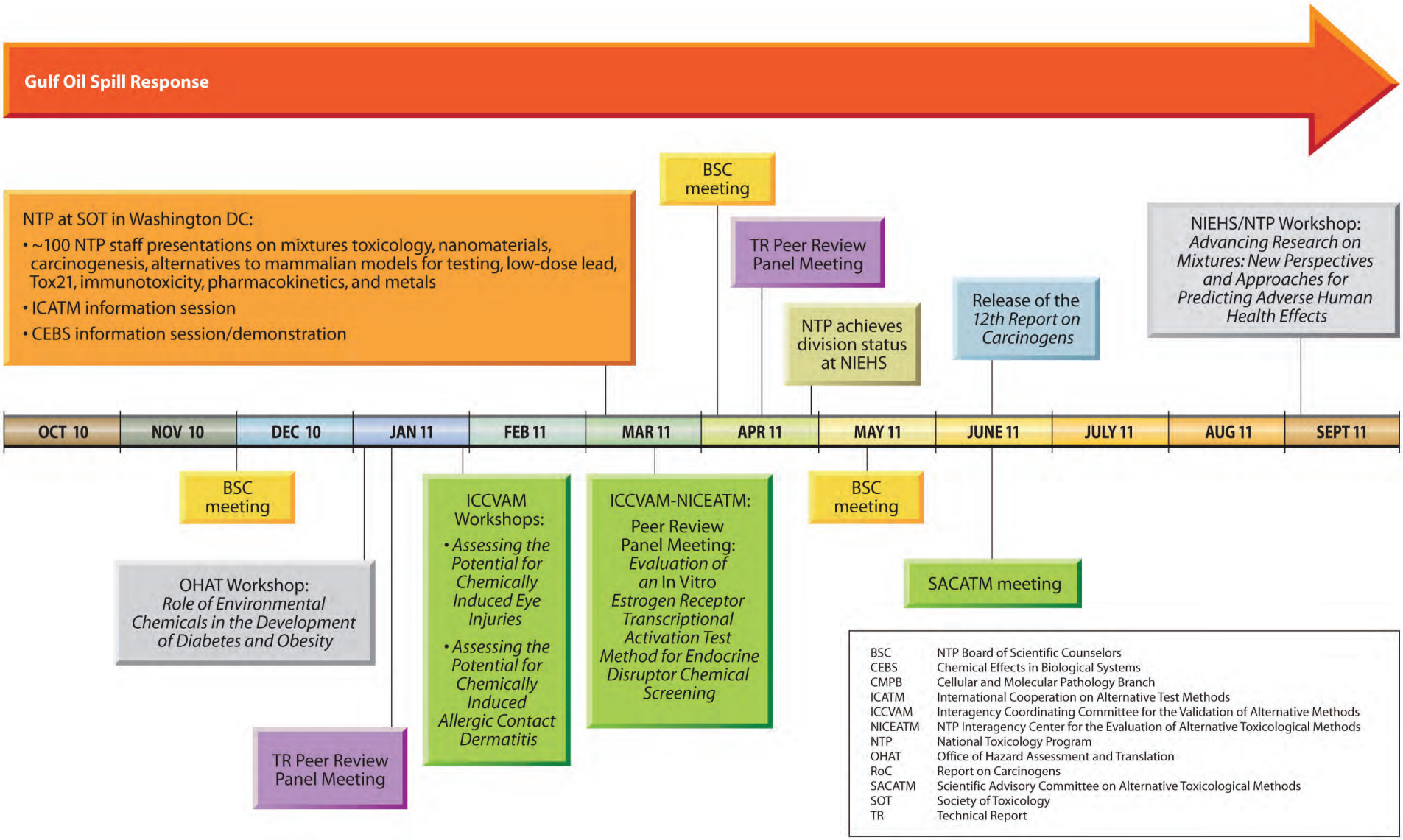
The NTP continued its efforts to address health concerns associated with the Deepwater Horizon oil spill in the Gulf of Mexico. NTP research, together with that of other federal agencies and academic investigators, has given us a better understanding of the chemical hazards created during this incident. A primary focus for the NTP is to increase our knowledge of the toxicity of components of oil that persist in the environment. We will continue to tackle lingering concerns regarding the safety of Gulf seafood, hazards to offshore and onshore cleanup workers, and potential long-term health impacts of residual oil in the environment.

All of these efforts, by teams of NTP scientists and through collaborations with other NIEHS divisions and Federal agency scientists, were successful in translating and communicating important scientific findings to advance human health protection. We will continue to proactively address complex new public health issues as they emerge.



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

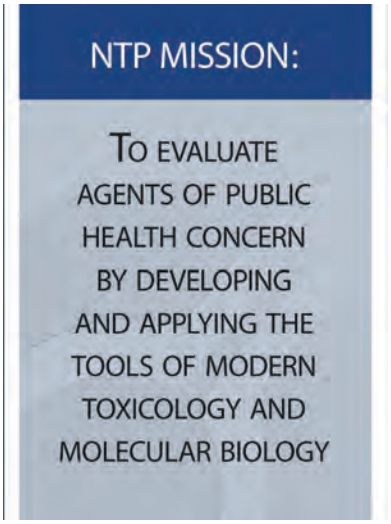
FY 2011 Highlights, Public Meetings, and Events



Overview of the National Toxicology Program

Mission and Goals

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



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

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

Organizational Structure and Oversight

Three agencies, the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health, the National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention, and the National Center for Toxicological Research (NCTR) of the Food and Drug Administration (FDA), form the core for the NTP (Figure 1). The NTP is located at the NIEHS, and the Director of the NIEHS serves as the NTP Director. Questions and inquiries about the NTP can be directed to the NTP Office of Liaison, Policy and Review (919-541-7539) or *CDM@niehs.nih.gov*.

NTP Management

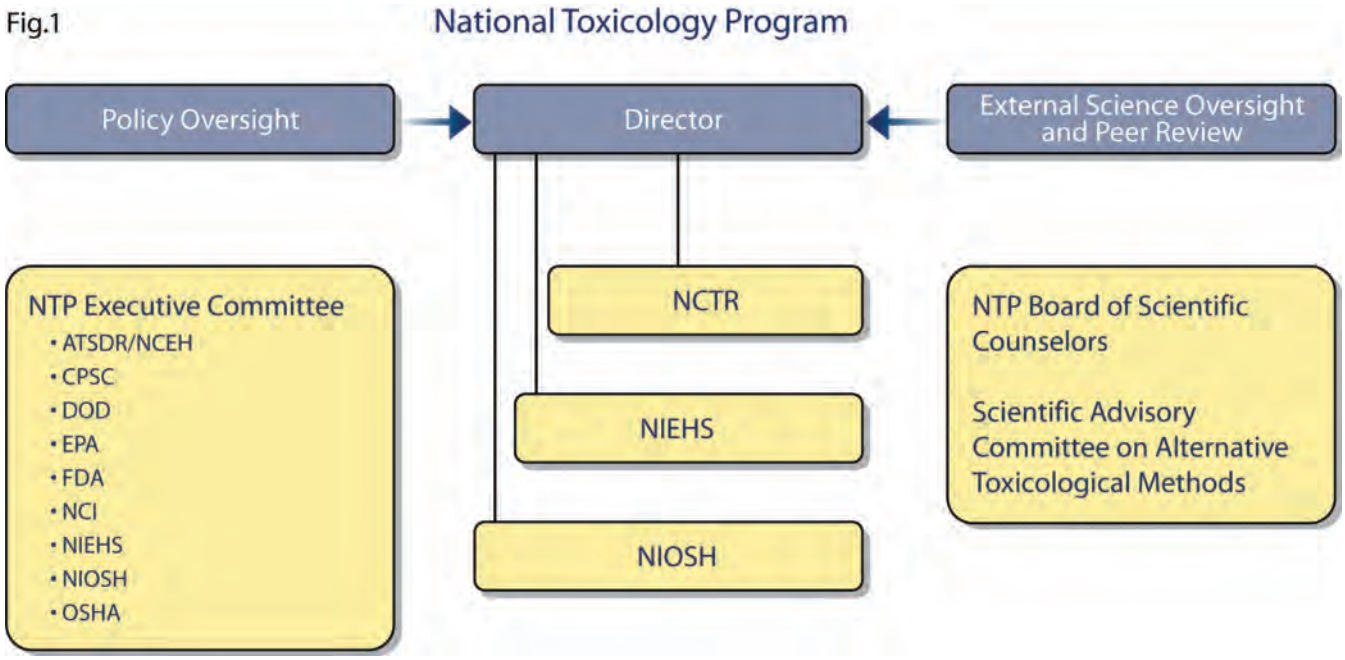
Dr. Linda Birnbaum, Director of NIEHS and NTP

Agency Program Management

NCTR: Dr. Paul Howard, Associate Director, Office of Scientific Coordination
NIEHS: Dr. John Bucher, Associate Director, NTP
NIOSH: Dr. Mark Toraason, Senior Fellow, Division of Applied Research and Technology and Dr. Gayle Debord, Chief, Biomonitoring and Health Assessment Branch

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

Fig.1



Addressing Scientific and Regulatory Needs

The NTP is flexible and innovative in its approach toward addressing public health concerns related to exposures to chemical and physical agents at home, in the workplace, and in the environment. Over the years since taking over the National Cancer Institute's (NCI's) cancer bioassay program, the NTP has expanded its scope beyond cancer to include examining the impact of substances on non-cancer outcomes, such as those affecting reproduction and development and the immune, respiratory, nervous, cardiovascular, and endocrine systems.

The NTP recognizes that initiatives addressing critical gaps in knowledge needed to evaluate environmental toxicants offer the best opportunities for preventing environmentally mediated diseases. Therefore, the NTP's testing of substances continues to evolve to include more mechanism-based toxicology studies that focus on understanding the modes of action of agents under study. In recent years, the NTP has placed a greater emphasis on providing human relevance in interpreting and understanding toxicological information created from animal or *in vitro* cell models. This is important if we are to be at the forefront in research efforts to improve methods to assess risk that account for the entire sequence of events from initial chemical exposure to ultimate toxicity.

Examples of activities it covers include:

- Increased use of both information on mechanisms of action and scientific judgment in deliberations for listings in the Report on Carcinogens
- Increased efforts to examine alternative testing methods that may provide better information than current models while using fewer animals or causing less pain or distress, and may provide better data for risk assessments
- Increased efforts to collect information on (1) a broader variety of both environmental and occupational exposures, (2) potentially toxic mixtures of compounds, and (3) susceptibilities based on life stages (e.g., neonatal, elderly)

Internationally, the NTP rodent bioassay is recognized as the standard for identifying carcinogenic agents; however, the NTP continues to work to reduce, refine, and/or replace the use of experimental animals and to develop and validate alternative testing methods. This effort led to the creation of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) in 1998. The NTP continues to work with the Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM) through NICEATM in promoting the development, validation, and regulatory acceptance of new and revised alternative toxicological methods.

Strengthening existing partnerships and forging new ones are important to achieve NTP goals. Partnerships with other sister Federal agencies are in place (interagency agreements [IAGs] are presented on page 67). The NTP continues to support an effort to evaluate the phototoxicity of various compounds through the NTP Center for Phototoxicology at the NCTR. The NTP is also contributing to toxicological assessments of emerging issues, such as nanotechnology, radiofrequency radiation emissions from cellular phones, herbal medicines/dietary supplements, water disinfection by-products, mold, and phthalates, and will provide this information to other agencies.

Regulatory agencies make decisions to protect public health based on scientific information from several sources (e.g., toxicology, human studies, and basic research). The NTP plays a critical role in providing needed scientific data, interpretation, and guidance in the appropriate uses of these data to regulatory agencies as well as other groups involved in health-related research. The NTP is committed to using the best science available in setting priorities for future studies and in designing, conducting, and interpreting the findings of those studies. The American people and government agencies at state and Federal levels rely on the NTP to provide a strong scientific basis for making credible decisions that will protect public health. The NTP maintains an objective, science-based approach in dealing with critical issues in toxicology and is recognized by many groups for its scientific rigor, objectivity, and open approach in the continuing dialogue on appropriately applying scientific advances to toxicology research and testing.

Communication and Public Outreach

Maintaining open communications and ensuring dialogue with Federal and state agencies, industry, nongovernment groups, academia, and the public are goals of the NTP. NTP advisory groups (see page 8) provide regular scientific and public peer review and input. NTP conferences and workshops remain a priority and are designed to bring researchers, regulators, policy makers, and the public together to examine issues and achieve consensus on future directions in toxicology and risk assessment.

Distribution of NTP study results, program plans, initiatives, announcements, press advisories, and publications is accomplished in several ways to communicate as much as possible with the public. Information is routinely

distributed to interested parties through Federal Register announcements and the NTP website (*http://ntp.niehs.nih.gov*). The website offers access to information about the program that details and highlights ongoing and future initiatives, announcements, NTP centers, NTP publications, and study data. The public can subscribe to the NTP Listserv on the website to receive news and updates. Currently the Listserv has more than 4000 subscribers. The NTP publishes the quarterly newsletter, *NTP Update*, which can be downloaded from the NTP website. NTP actively participates in the annual Society of Toxicology (SOT) meeting. At the 2011 SOT meeting in Washington DC, NTP staff participated in approximately 100 workshop/symposium/platform sessions, education/information sessions and posters.

The NIEHS/NTP Central Data Management Office oversees distribution (upon request) of specific chemical study information and printed NTP documents – NTP study status reports, final and draft copies of NTP Technical Report Series, and background documents for substances nominated to the NTP for study. On-line, searchable access is available for the Report on Carcinogens (RoC) and the NTP Technical, Toxicity, and Genetically Modified Models series reports (*http://ntp.niehs.nih.gov*).

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

NTP Office of Liaison, Policy and Review

NIEHS/NIH
MD K2-03
111 TW Alexander Drive, RTP, NC 27709
Phone: (919) 541-7539
wolfe@niehs.nih.gov

Central Data Management

NIEHS/NIH
MD K2-05
111 TW Alexander Drive, RTP, NC 27709
Phone: (919) 541-3419
cdm@niehs.nih.gov

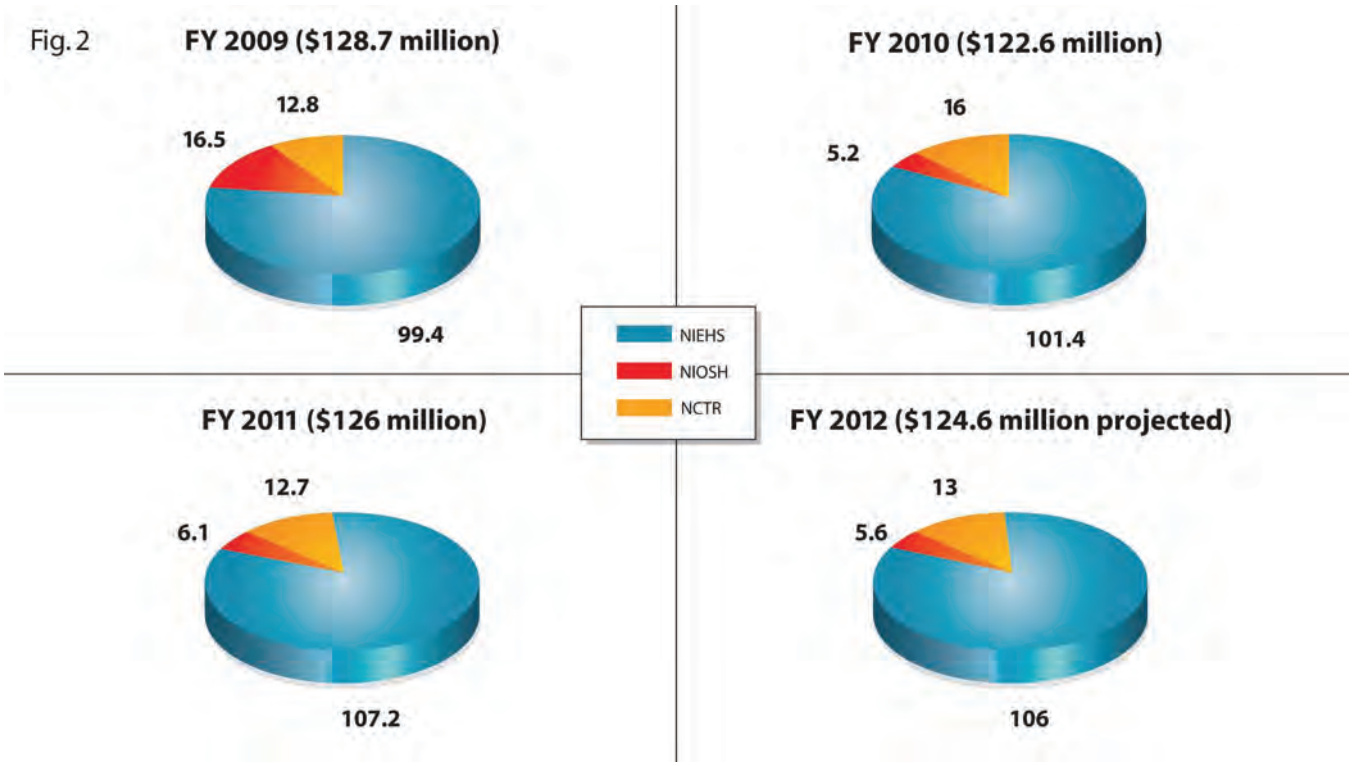
Resources and Planning

Current and Projected Research Capacity

The NTP relies on voluntary allocations from the program's three core agencies (NIEHS, NCTR, and NIOSH) to support its various programs and initiatives. These allocations are specified after yearly appropriations are determined. As shown in Figure 2, the total NTP budget for FY 2011 was $126 million.

The NTP conducts its research studies mainly through contract laboratories or in-house at the core agencies, but also supports IAGs with other Federal agencies. Funds are used to sponsor workshops and conferences and to produce and distribute printed programmatic materials. In FY 2011, the NIEHS funded 33 contracts and held four workshops and three expert-panel meetings for the NTP. The NIEHS also funded IAGs with NIOSH, NCTR, EPA, and the NIH Chemical Genomics Center (NCGC) and held five scientific advisory meetings.

Fig. 2



The NTP maintains an objective, science-based approach in dealing with critical issues in toxicology and continually sets priorities to improve the nation's ability to evaluate the human health effects caused by environmental exposures.

In summary, the NTP is a comprehensive research program spanning several agencies committed to providing resources to support the NTP's research and to communicating the knowledge learned to all stakeholders, public and private. The NTP's efforts in testing, research, and assessing health hazards work to obtain the best scientifically valid data for health regulatory and research agencies to use to make appropriate decisions about potential human risks from exposure to environmental toxicants. Toward that end, the NTP is continually evolving to remain at the cutting edge of scientific research and development and application of technology.

Advisory Boards and Committees

As shown in Figure 1 (page 4), the NTP relies on a number of external boards and committees for science and policy oversight and peer review. As needed, the program convenes Special Emphasis Panels and Working Groups to address specific topics.

NTP Board of Scientific Counselors

The NTP Board of Scientific Counselors (BSC), a federally chartered advisory group, provides scientific oversight to the NTP on the scientific merit of its programs and activities. The Secretary of DHHS appoints members to the BSC. The BSC can consist of up to 35 scientists, primarily from the public and private sectors, with scientific expertise relevant to the NTP's activities. The BSC charter and current roster are available at *http://ntp.niehs.nih.gov/go/164*. Dr. Lori White, Designated Federal Officer, manages the BSC. A list of members during FY 2011 is provided in Table 1.

The BSC met twice in FY 2011. The first BSC meeting was held on November 30 – December 1, 2010. The BSC voted unanimously to approve the concept for a contract, NTP Sperm Count and Vaginal Cytology Evaluation. The BSC reviewed the activities of the Biomolecular Screening Branch and prepared a report (available at *http://ntp.niehs.nih.gov/go/9741*). The BSC provided input on four concepts for the NTP testing program: (a) *Exposure Characterization and Reproductive Health of Men Working with Bisphenol A in the United States,* (b) *Cholesterol and Lipid Modulating Agents: Toxicological Approaches to Assessing Complex Mixtures,* (c) *N-butylbenzenesulfonamide, and* (d) *Selected Flame Retardants – Update.* The NIEHS/NTP Director and NTP Associate Director provided reports, updating the BSC on NTP progress since the June 2010 meeting.

BSC members and NTP staff at the December 2011 BSC meeting.

The second BSC meeting was held on April 13, 2011. The BSC voted unanimously to approve the concept for a contract, Potential for Environmental and Therapeutic Agents to Induce Immunotoxicity. The BSC was provided overviews of several NTP initiatives including a Modified One-Generation Reproduction Study Design and New Statistical Methods for Analyzing NTP's 2-year Cancer Bioassay Data. The BSC provided input on three concepts for the NTP testing program: (a) *Nanomaterials Exposure Assessment,* (b) *Biospecimen Repository and Analysis Capabilities to Support NTP Exposure Assessment Projects, and* (c) *the Center for the Evaluation of Risks to Human Reproduction Folic Acid Workshop*. The NIEHS/NTP Director and NTP Associate Director provided reports, updating the BSC on NTP progress since the November/December 2010 meeting. Additional information about the BSC, including minutes from its meetings, is available on the NTP website (*http://ntp.niehs.nih.gov/go/164*) or from Dr. White (*whiteld@niehs.nih.gov*).

Table 1. NTP Board of Scientific Counselors Membership Roster FY 2011		
Name and Title	**Affiliation**	**Term Ends**
Tracie E. Bunton, DVM, PhD, DACVP Toxicology Consultant	Eicarte LLC Fairfield, PA	12/27/10
Edward W. Carney, PhD Technical Leader Developmental, Reproductive and General Toxicology	The Dow Chemical Company Midland, MI	12/27/10
Russell C. Cattley, VMD, PhD Executive Director Pathology	Amgen Thousand Oaks, CA	12/27/10
David A. Eastmond, PhD (chair beginning 1/11) Professor and Chair Department of Cell Biology and Neuroscience	University of California Riverside, CA	12/27/12
Janan T. Eppig, PhD Senior Staff Scientist	The Jackson Laboratory Bar Harbor, ME	04/15/11
Elaine M. Faustman, PhD Professor and Director Institute for Risk Analysis and Risk Communication Department of Environmental and Occupational Health Sciences	University of Washington Seattle, WA	12/27/12
William P. Janzen, Professor Division of Medicinal Chemistry and Natural Products; Director, Assay Development and Compound Profiling	University of North Carolina at Chapel Hill Chapel Hill, NC	12/27/10
Dana Loomis, PhD Professor and Chair Department of Epidemiology	University of Nebraska Medical Center Omaha, NE	12/27/12
Stephen W. Looney, PhD Professor, Department of Biostatistics Department of Oral Health and Diagnostic Science	Georgia Health Sciences University Augusta, GA	06/30/12
Melissa A. McDiarmid, MD, MPH Professor of Epidemiology and Preventive Medicine Director Occupational Health Program	University of Maryland School of Medicine Baltimore, MD	06/30/13
Lisa Minor, PhD In Vitro Strategies	*In Vitro* Strategies, LLC Flemington, NJ	06/30/13
Richard Miller, DVM, PhD Vice President, Safety Assessment	GlaxoSmithKline Research Triangle Park, NC	06/30/13
Mitzi Nagarkatti, PhD Professor and Chair Department of Pathology, Microbiology and Immunology	University of South Carolina School of Medicine Columbia, SC	12/27/11
Raymond F. Novak, PhD (chair 1/10 – 12/10) Director, Institute of Environmental Health Sciences	Wayne State University Detroit, MI	12/27/10
Ruthann A. Rudel, MS Senior Scientist Toxicology and Environmental Health Risk Assessment	Silent Spring Institute Newton, MA	12/27/11
James L. Sherley, MD, PhD Senior Scientist, Boston Biomedical Research Institute	Boston Biomedical Research Institute Watertown, MA	06/30/11
Gina M. Solomon, MD, MPH Senior Scientist	Natural Resources Defense Council San Francisco, CA	12/27/11
Justin G. Teeguarden, PhD Senior Scientist Fundamental and Computational Sciences Directorate	Pacific Northwest National Laboratory Richland, WA	12/27/11
Judith Zelikoff, PhD Professor Environmental Medicine Director, Community Outreach	New York University School of Medicine Tuxedo, NY	12/27/12

NTP Technical Reports Peer Review Panels

The NTP convened two Technical Reports (TRs) Peer Review Panels in FY 2011 at the NIEHS. The meetings were open to the public with time scheduled for oral public comment. The panels were charged to (1) peer review the scientific and technical elements of the study and their presentation and (2) determine whether the study's experimental design and conduct supported the NTP's conclusions regarding the carcinogenic activity of the substance tested. The panels consisted of experts in general pathology, carcinogenesis, dermal toxicology, gastrointestinal pathology, and environmental toxicology. The panels reviewed the draft TRs for kava kava extract, retinoic acid/retinyl palmitate, methyl *trans*-styryl ketone, styrene-acrylonitile trimer, and *alpha*,*beta*-thujone at the January 26, 2011 meeting and the draft TRs for senna, AIDS therapeutics, acrylamide, and a nondecolorized whole leaf extract of *Aloe vera* at the April 5, 2011 meeting. Dr. White served as Designated Federal Official for the January peer review meeting and Ms. Danica Andrews for the April peer review meeting.

Additional information about past TR review panels is available at *http://ntp.niehs.nih.gov/go/36144* and information about upcoming TR review panels is available at *http://ntp.niehs.nih.gov/go/36051*.

Scientific Advisory Committee on Alternative Toxicological Methods

Members of SACATM and ICCVAM and NIEHS/NTP staff at the June 2011 SACATM meeting.

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) is a federally chartered advisory committee established on January 9, 2002, in response to the ICCVAM Authorization Act of 2000 (42 U.S.C. 285*l*-3(d)). SACATM advises ICCVAM, NICEATM, and the Director of the NIEHS regarding statutorily mandated duties of ICCVAM and activities of NICEATM (see page 36). SACATM provides advice on priorities and activities related to the development, validation, scientific review, regulatory acceptance, implementation, and national and international harmonization of new, revised, and alternative toxicological test methods. The SACATM charter and current roster are available at *http://ntp.niehs.nih.gov/go/167*. A list of members during FY 2011 is provided in Table 2. SACATM typically meets once a year and members serve rotating terms of up to four years. Dr. Lori White, Designated Federal Officer, manages SACATM.

SACATM met once during FY 2011 at the Hilton Arlington, Arlington, Virginia, on June 16-17, 2011. At that meeting, SACATM voted unanimously to give a high priority to validation efforts for botulinum *in vitro* assays and a high priority to further discussions for an *in vitro* pyrogen test. SACATM also agreed with the conclusions of the Peer Review Panel Report on the *Evaluation of an* In Vitro *Estrogen Receptor Transcriptional Activation Test Method for Endocrine Disruptor Chemical Screening*. ICCVAM agency representatives presented updates on the NIH-FDA Regulatory Science Initiative and Small Business Innovation Research grants, and reports on the workshops on *Best Practices for Regulatory Safety Testing and Alternative Methods to Reduce, Refine, and Replace the Use of Animals in Vaccine Potency Testing: State of the Science and Future Directions*. Liaisons from the European Center for the Validation of Alternative Methods, the Korean Center for the Validation of Alternative Methods, the Japanese Center or the Validation of Alternative Methods, and Health Canada presented updates on the activities of their groups. Additional information about SACATM, including minutes from its meetings, is available at *http://ntp.niehs.nih.gov/go/167* or from Dr. Lori White (*whiteld@niehs.nih.gov*).

Table 2. Scientific Advisory Committie on Alternative Toxicological Methods Roster FY 2011		
Name and Title	**Affiliation**	**Term Ends**
Laura Andrews, PhD, DABT Vice President Pharmacology and Toxicology	Genzyme Corporation Framington, MA	06/30/12
Karen K. Brown, PhD President	Pair O' Docs Enterprises Parkville, MO	06/30/11
Joy Cavagnaro, PhD, DABT, RAC, ATS, RAPS President and Founder	Access BIO, L.C. Boyce, VA	11/30/14
George B. Corcoran, PhD, ATS Professor and Chairman Department of Pharmaceutical Sciences	Wayne State University Detroit, MI	06/30/11
Eugene L. Elmore, PhD Senior Project Scientist Department of Radiation Oncology	University of California Irvine, CA	11/30/12
Steven R. Hansen, DVM, MS, MBA, DABT, ABVT Senior Vice President, Animal Health Services	ASPCA Animal Poison Control Center Urbana, IL	11/30/12
Gwendolyn Y. McCormick, DVM, MS, DACLAM Attending Veterinarian and Distinguished Research Fellow, Animal Resources Department	Boehringer Ingelheim Pharmaceuticals, Inc Ridgefield, CT	11/30/12
Sharon A. Meyer, PhD Associate Professor, Department of Toxicology	The University of Louisiana at Monroe Monroe, LA	06/30/11
Steven M. Niemi, DVM Director, Center for Comparative Medicine	Massachusetts General Hospital Charlestown, MA	06/30/13
Ricardo Ochoa, DVM, PhD, ACVP President and Principal	Pre-Clinical Safety, Inc. Niantic, CT	11/30/14
Michael J. Olson, PhD, ATS Director, Occupational Toxicology Corporate Environment, Health, Safety and Sustainability	GlaxoSmithKline Research Triangle Park, NC	06/30/13
Linda A. Toth, DVM, PhD Associate Dean for Research and Faculty Affairs Professor, Department of Pharmacology	Southern Illinois University School of Medicine Springfield, IL	06/30/13
Daniel M. Wilson, PhD, DABT Mammalian Toxicology Consultant Toxicology and Environmental Research and Consulting	The Dow Chemical Company Midland, MI	11/30/14
Gary Wnorowski, MBA, LAT President	Eurofins/Product Safety Laboratories Dayton, NJ	06/30/11

NTP Executive Committee

The NTP Executive Committee provides programmatic and policy oversight to the NTP Director. The Executive Committee meets once or twice a year in closed forum. In FY 2011 the Department of Defense joined the Executive Committee. Members of this committee include the heads (or their designees) from the following Federal agencies:

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

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

Interagency Coordinating Committee on the Validation of Alternative Methods

ICCVAM is a permanent interagency committee of the NIEHS under NICEATM. The committee was formally established by the ICCVAM Authorization Act of 2000 (42 U.S.C. 285*l*-3). The purpose of ICCVAM is to establish, wherever feasible, guidelines, recommendations, and regulations that promote the regulatory acceptance of new or revised scientifically valid toxicological tests that protect human and animal health and the environment while reducing, refining, or replacing animal tests and ensuring human safety and product effectiveness (see *http://iccvam.niehs.nih.gov/about/process.htm*). Members of this committee include representatives from the following Federal agencies:

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

NIOSH/NTP

NIOSH/NTP: Division of Surveillance, Hazard Evaluations, and Field Studies

NIOSH/NTP: Division of Applied Research and Technology and Education and Information Division

NIOSH/NTP: Health Effects Laboratory Division

The National Institute for Occupational Safety and Health (NIOSH) is the Federal agency responsible for conducting research and making recommendations for the prevention of work-related injury and illness. The mission of NIOSH is to generate new knowledge in the field of occupational safety and health and to transfer that knowledge into practice for the betterment of workers. To accomplish this mission, NIOSH conducts scientific research, develops guidance and authoritative recommendations, distributes information, and responds to requests for workplace Health Hazard Evaluations (HHEs).

NIOSH's participation in the NTP is consistent with its mandate to protect workers' health and safety under the Occupational Safety and Health Act and the Federal Mine Safety and Health Act. Setting priorities in occupational toxicological research is based upon several sources of information that are developed and maintained by NIOSH. These include HHEs, industry-wide studies, gaps in knowledge identified while developing criteria for recommended standards or Criteria Documents, Current Intelligence Bulletins, hazard reviews or alerts, other technical reports, and information profiles on chemical hazards. Toxicological research on important occupational chemicals is conducted in genetic toxicology, carcinogenesis, toxicological characterization, chemical disposition, biological monitoring, reproductive and developmental toxicology, dermal toxicology, and exposure assessment. NIOSH research projects are conducted by the:

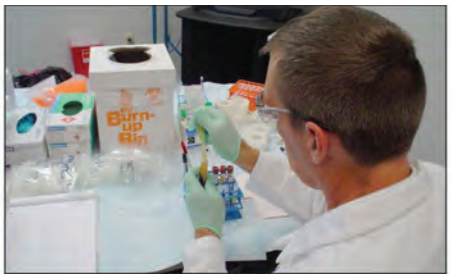
- Division of Applied Research and Technology – Cincinnati, Ohio
- Division of Surveillance, Hazard Evaluations, and Field Studies – Cincinnati, Ohio
- Education and Information Division – Cincinnati, Ohio
- Health Effects Laboratory Division – Morgantown, West Virginia

NIOSH/NTP studies funded by NIOSH voluntary contributions are listed in Table 3.

Table 3. NIOSH/NTP Projects FY 2011	
NIOSH/NTP Project Project Officer	**Objective and/or Summary**
Reproductive Health Assessment of Male Workers *[Schrader]*	To evaluate reproductive health hazards using a health profile consisting of biomarkers for assessing male fecundity. Current efforts will focus on completing the Longitudinal Investigation of Fertility and the Environment (LIFE) project, a collaborative effort between NIOSH and the NICHD/NIH. This work includes development of new biomarkers to include in the male reproductive health profile.
Immunochemical Biological Monitoring for Occupational Exposure and Disease *[Striley]*	To evaluate industrial chemicals with known acute and chronic toxicities that present a significant exposure risk for workers. Biological monitoring can assess exposure by analyzing acute and latent metabolites in various biological media. The goal of this project is to develop low-cost, rapid immunochemical and analytical chemistry biomonitoring methods that will be used to identify exposures and evaluate potential interventions. This project will identify and develop new multiplex immunochemical methods to evaluate biomarkers of occupational illness or subclinical signs of occupational illness.
Orthophthalaldehyde (OPA) Hazard Assessment *[Toraason]*	To conduct an assessment of occupational exposures to OPA and to determine if healthcare workers are experiencing adverse effects associated with exposure. This study will also develop analytical methods for environmental monitoring of OPA and determine the feasibility of an OPA biomarker. Because of the absence of published toxicological data on OPA, testing will be conducted in experimental animals. The toxicological testing will focus on dermal and respiratory irritation and sensitization. Dose-response data will be obtained for hazard identification risk assessment, which, along with health assessments, will serve as the basis for establishing exposure limits.
UV Native Fluorescence Based Monitor for Workplace Exposures *[Snawder]*	To develop and evaluate a readily adaptable, next generation, direct reading, personal monitors (DRPMs) for use in measuring worker exposure to a wide variety of chemicals including naphthalene and components of asphalt fume. The development of DRPMs for volatile and semi-volatile workplace chemicals will be helpful in rapidly assessing chemical exposure and will result in more realistic occupational exposure assessments and allow for rapid interventions leading to reduced worker exposures and thus preventing occupational illness and disease.
Analytical Research and Development Infrastructure *[Streicher]*	To provide for the administrative needs and analytical instrumentation repair and maintenance in support of Chemical Exposure and Monitoring Branch chemists conducting research on sampling and analytical methods development for workplace chemicals. New methods needed to assess chemicals being investigated as part of the NIOSH/NTP exposure assessment interagency agreement are developed in this project.
Diacetyl Exposure Assessment *[Streicher]*	To develop and evaluate sampling and analytical methods for diacetyl and other flavoring compounds to enable accurate exposure assessment and evaluation of the effectiveness of control technology. Two sampling and analytical methods are being investigated for measurement of specific flavoring compounds, most notably diacetyl and 2,3-pentanedione in airborne particles and bulk powders. Broader gas chromatography-mass spectrometry method(s) will be developed for a range of compounds present in flavorings.
Chemical Exposure Monitoring with Indoor Positioning *[Brown]*	To investigate a direct reading exposure method that uses a personal photo ionization detector chemical monitor with telemetry and an indoor positioning system to provide remote monitoring of a worker's exposure to volatile organic chemicals (VOCs) with position and time. The personal monitor continuously samples and analyzes the workers breathing zone air for VOCs while recording their position and time of exposure. Indoor positioning is accomplished using a radio transmitter attached to the personal monitor and receivers placed in the ceiling corners of the room. The positioning receivers communicate with each other and a remote laptop using wireless local area network technology. The remote laptop calculates and visualizes the worker position and exposure level. Once developed, this technology will be applied to analyze workplace exposures to diacetyl.
Exposure Assessment for Toxicologically-Important Chemicals *[Estill]*	To characterize workplace exposures to (1) welding fumes with emphasis on manganese (Mn), (2) indium and indium compounds, (3) diacetyl, (4) 2-methoxy-4-nitroaniline, (5) 2′,2‴-dithiobisbenzanilide, and (6) bisphenol A (BPA). These chemicals have been nominated by various groups to the NTP. NIOSH will identify possible candidate industries, labor unions, workplaces, and uses and users; determine if there is relevance for occupational health; estimate number of workers exposed; and perform limited workplace exposure sampling.

NIOSH/NTP Project Project Officer	Objective and/or Summary
Exposures and Engineering Controls in the Flavoring Industry *[Curwin]*	To conduct a complete exposure assessment, evaluate potential engineering controls within the flavoring industry, and create appropriate work practice advice to reduce occupational exposures in these industries. Although a dose response curve for various flavoring compounds and associated health effects has not been established, improved work practices and engineer control advice can minimize occupational exposures. Data from initial research efforts have been very useful in preliminary rulemaking efforts for both OSHA and Cal-OSHA.
Immunotoxicological Evaluation of Occupational Chemicals *[Anderson]*	To identify occupational and environmental chemical hazards and evaluate immune function and mechanism associated with exposure. The Immunotoxicology and Hazard Identification Lab will achieve this goal through both individual projects and collaborations. This research will contribute to increased identification of immunological hazards encountered in the workplace. Further evaluation of these compounds will allow for better risk assessment, which will ultimately establish occupational exposure limits.
Evaluation of Perfluoralkyl acids (PFAAs) Immunotoxicity *[Franko]*	To investigate the immunotoxicity of perfluorooctanoic acid (PFOA), no longer used in manufacturing, but still persistent in the environment, which has been shown in a murine model to be both immunosuppressive and to have a potential role in asthma and allergy. Due to the potential health effects linked to PFOA exposure, replacement perfluoralkyl acids (PFAAs) are now being used in the manufacturing process but little is known about what effects these compounds will have on immune function. This project will evaluate the immunotoxic effects associated with individual PFAAs that are still in use, and investigate the mechanism mediating the identified immunological alterations associated with PFOA exposure.
PFOA and PFOS-induced Oxidative Stress *[Qian]*	To investigate whether exposure to PFOA and perfluorooctane sulfonate (PFOS) induces an oxidative stress response in a mouse model and in human cells. PFOA and PFOS are widely known man-made fluorocarbon-based acids, which have been used in various industrial processes in the aircraft, automotive, chemical, building material, and personal care products industries. They are non-biodegradable and persistent in the human body and environment. Surveillance data suggests that PFOA and PFOS may cause adverse health effects, but no consistent association between exposure and health effects has been proven.
Airway Fungal Exposure and Allergic Sensitization in Mice *[Templeton]*	To compare the immunological health effects of lung exposure to fungal spores or to hyphal fragment preparations. Agriculture, as well as construction and remediation workers, are exposed to elevated levels of fungi and can experience rhinitis, respiratory allergic symptoms and/or asthma as a result of their exposure. This project will have two major areas of study (1) determination of the health effects following aspiration of hyphal fragments from *Stachybotrys chartarum* and *Alternaria alternata* in the absence of intact spores in mice, and (2) comparison of the ability of aspirated spores or hyphal suspensions from *Aspergillus* spp, *S. chartarum*, and *A. alternata* to exacerbate respiratory allergy to ovalbumin.
Immune and Inflammatory Aspects of Occupational Rhinitis *[Johnson]*	To investigate occupational asthma in workers who often exhibit concurrent occupational rhinitis with the likelihood that rhinitis developed first. Understanding the mechanisms of occupational rhinitis is an important area of research in occupational safety, health and medicine. A combined study design utilizing human and animal research will be employed to identify the orthologously-conserved pathways and gene networks that characterize the pathobiology of occupational rhinitis induced by diisocyanates. The outcomes of this research will benefit occupational safety and health through improved diagnosis and prevention of allergic airways disease caused by diisocyanates.
Genetics in Occupational Diseases *[Yucesoy]*	To investigate susceptibility gene variants that contribute to the development and severity of occupational irritant contact dermatitis (ICD) and asthma using high-density and high throughput genotyping platforms. Previous and on-going studies showed that cytokine polymorphisms have a major influence on silicosis, dementia, accelerated decline in lung function and vaccine efficacy. Understanding the genetic contribution to the development, progression and outcomes of complex occupational diseases will help improve the accuracy of risk assessment and improve safe exposure levels for genetically susceptible groups in the workforce.

NIOSH project to collect personal breathing zone and dermal samples to assess worker exposures to paving asphalt emissions



NIOSH researcher processing worker blood and urine samples at a field site for biomonitoring studies

NIOSH researcher collecting a surface wipe sample for possible antineoplastic drug contamination

NIOSH/NTP Project Project Officer	Objective and/or Summary
Genetic Fingerprint of Mouse Lung Cancer *[Reynolds]*	To determine if there are different carcinogen-specific chromosomal (genetic) markers in spontaneously-occurring and chemically-induced mouse lung adenocarcinomas using *in vitro* and *in vivo* animal models. Mice were exposed by inhalation to vanadium pentoxide, nickel oxide, or cumene (a benzene derivative). Workers in the construction and manufacturing sectors are exposed to these compounds. NIOSH is also planning to analyze mouse lung tumors induced by single-wall carbon nanotubes. If these experiments are successful the plan is to extend these findings to tumors from occupationally-exposed human populations. Results from these studies will be used to establish biomarkers for early detection and therapeutic intervention of lung cancer in worker populations.
Workplace Exposure, Inflammation, and Cardiovascular Toxicity *[Erdely]*	To investigate the role of ultrafine/nanoparticle-induced cardiopulmonary inflammation and to identify specific markers of lung inflammation that directly correlate to systemic effects. This laboratory-based research will evaluate novel molecular mechanisms involved in the link between occupational exposures to ultrafine/nanosize particulates and the development of cardiovascular diseases. Planned studies will help to identify potential risk factors, biomarkers, and specific targets for prevention and therapeutic intervention of occupational-related cardiovascular diseases.
Cutaneous Bioactivation of Xenobiotics: Hapten vs. Pro-hapten *[Siegel]*	To develop an *in vivo* model of allergic skin sensitization that can discriminate between chemicals requiring metabolic activation for sensitization (pro-haptens) and those that can sensitize without biological activation (pro-haptens). The model will involve the dermal application of various pharmacological inhibitors of the cytochrome P450 (CYP) pathway prior to performing either the local lymph node assay (LLNA) or/and mouse ear swelling test. Selective inhibition of the CYP pathway should distinguish between direct-acting haptens and metabolically-activated pro-haptens. Validation of the models will be done using known direct acting haptens and pro-haptens. Successful development of these models will produce data that strengthen *in silico* hazard predictive models and allows for substitution or modification of allergenic chemicals and drugs.
Identification of Occupational Allergens *[Beezhold]*	To identify exposures to substances that can cause inflammatory or immune reactions in certain work environments. These exposures are important causes of occupational lung diseases such as asthma and allergic alveolitis. This project is intended to address these concerns through the development of improved techniques for the detection of such immune reactions before adverse clinical outcomes occur, and through the development of improved techniques for the detection and identification of inciting occupational agents. The project will involve the analyses of clinical samples, environmental bulk samples, and environmental aerosol samples. Successful completion of these investigations should lead to the development of effective prevention strategies for occupational allergies and asthma.

NCTR/NTP

NCTR/NTP

The National Center for Toxicological Research (NCTR), the FDA's research center, plays a critical role in carrying out the agency's mission. 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 conducts an array of studies that reflect the NTP mission statement. These NCTR/NTP studies, funded by NCTR voluntary allocations, are listed in Table 4.

Table 4. NCTR/NTP Projects in FY 2011

NCTR/NTP Project Project Officer	Objective and/or Project Summary
Physiologically-based Pharmacokinetic (PBPK) Models for Bisphenol A [Fisher]	(1) To create PBPK models for BPA in three species of adult, neonatal, and pregnant (mother and fetus) and lactating (mother and neonate) laboratory animals (mouse, rat, and rhesus monkey); (2) to use PBPK models to calculate internal measures of dose for both aglycone (i.e., active) and conjugated (i.e., inactive) forms of BPA; (3) to create PBPK models for BPA exposure in humans (adult, child, and pregnant mother and fetus, and lactating mother and infant); (4) to extrapolate the internal doses of BPA associated with toxicity in laboratory animals to humans using the human suite of PBPK models; and (5) to extrapolate dosimetry from regions of observation to low levels of exposure to BPA for which no experimental data exist.
Relationship between Liver Epigenetic Phenotype and Susceptibility to Nonalcoholic Steatohepatitis (NASH)-Induced Hepatocarcinogenesis in Mice [Pogribny]	(1) To determine the role of epigenetic dysregulation in the etiology and pathogenesis of dietary NASH-induced hepatocarcinogenesis in mice, (2) to determine whether or not interstrain-specific susceptibility of mice to NASH-induced hepatocarcinogenesis is associated with differences in individual hepatic epigenetic phenotypes, (3) to determine the role of epigenetic dysregulation in the etiology and pathogenesis of NASH-induced hepatocarcinogenesis in mice induced by tamoxifen administration, and (4) to determine whether or not aberrant epigenetic markers can be used as targets for prevention of NASH-induced hepatocarcinogenesis in mice.

NCTR/NTP Project Project Officer	Objective and/or Project Summary
Development of a Physiologically-based Pharmacokinetic/ Pharmacodynamic (PBPK/PD) Model for Acrylamide [Fisher]	(1) To develop a PBPK/PD model for acrylamide and glycidamide, (2) to determine mutagenicity of acrylamide and its metabolite glycidamide in Big Blue® rats, and (3) to determine the DNA adduct levels and the extent of mutagenicity of furan and its metabolite cis-2-buten-4-dial in neonatal B6C3F1/Tk $^{+/-}$ mice.
Global and Locus-Specific DNA Hypomethylation: A Common Mechanism Involved in Genotoxic and Non-Genotoxic Rat Hepatocarcinogenesis [Pogribny]	(1) To determine if the temporal alterations in genomic methylation profile in preneoplastic liver tissue observed in the folate/methyl-deficient model of rat endogenous hepatocarcinogenesis also occur in other carcinogenesis model; (2) to identify genes that are consistently up-regulated or down-regulated in target tissue during the promotion stage of carcinogenesis; and (3) to evaluate whether or not the global and locus-specific DNA hypomethylation, along with aberrant expression of related genes and changes in chromatin conformation is specific only to target tissues and may be used for early detection of chemicals with carcinogenic potential.
Further Evaluation of the Types of Genetic Events Detected by the Mouse Lymphoma Assay (MLA) and the Role of the Assay in Mechanistically Based Risk Assessment [Moore]	(1) To determine if the L5178Y/TK+/- MLA adequately detects both aneuploidy and mitotic recombination, (2) to determine if the L5178Y mouse lymphoma cells have active recombinase functions which lead to a large proportion of mutants that result from recombinase-mediated rearrangements, and (3) to determine the fundamental genetic mechanism(s) causing the small and large colony thymidine kinase mutant phenotypes.
Effect of p53 Genotype on Gene-Expression Profiles in Mice Exposed to the Model Mutagen, N-Ethyl-N'-Nitrosourea (ENU) [Morris]	(1) To determine the effect of mutation in the p53 tumor suppressor gene on gene-expression profiles in young and aged mice, and (2) Determine the effect of mutation in p53 tumor-suppressor gene on gene-expression profiles in young and aged mice exposed to the model mutagen ENU.
Development of Cancer-relevant Biomarkers for Identification of Potential Carcinogens: Research to Understand the Normal Background Frequencies in Rats [McKinzie]	To understand the distribution and range of spontaneous oncogene mutant frequencies in the major organs of rats and mice.
Assessment of Interindividual Variability in Expression of DNA Methyltransferases (DNMTs), DNMT3a, and DNMT3b, in Liver and Identification of Factors Influencing Expressions [Hammons]	(1) To determine levels of expression of DNMT3a and DNMT3b in liver samples from a pool of donors selected according to smoking status, gender, and age; (2) to determine the effect of tobacco smoke on DNMT1, 3a, and 3b expression in liver cell systems; and (3) to assess the polymorphism frequency identified in DNMT3b in the sample pool included in the study and assess whether it is correlated with expression.
Assessment of Ketamine in the Developing Nonhuman Primate [Wang]	(1) To determine, using neurohistochemical approaches, if, and at what developmental stages, ketamine exposure increases neuronal apoptosis/proliferation; (2) to determine, using neurohistochemical approaches, the dose-response for ketamine to produce apoptosis at the most sensitive developmental stage; (3) to determine the reversibility or permanence of the response using behavioral, imaging, and neurohistochemical approaches; and (4) to determine, at the most sensitive stage and dose, genomic and proteomic responses to ketamine treatment.
Phosphatidylinositol Glycan – Complementation Group A (PIG-A) Mutagenesis: Development of Methods for the Identification and Molecular Characterization of Mutations in the PIG-A Gene in Human Lymphoblastoid Cells and C57Bl/6 Mice [Dobrovolsky]	(1) To develop flow-cytometric methods for the detection of cells with mutations in the PIG-A gene using wild-type and mutant human lymphoblastoid cells, TK6, and WTK1, as a model, and (2) to develop flow cytometric methods for the detection of hematopoietic cells with mutations in the PIG-A gene in C57Bl/6 mice.

NCTR/NTP Project Project Officer	Objective and/or Project Summary
PIG-A Mutagenesis: Development of Methods for the Identification and Molecular Characterization of Mutations in the PIG-A Gene of F344 Rats [Heflich]	(1) To develop methods for measuring PIG-A mutant frequencies in lymphocytes cultured from rats; (2) to develop flow cytometric methods for measuring PIG-A mutant/variant frequencies in both the lymphocytes and red blood cells of rats; (3) to treat rats with either ENU or 7,12-Dimethylbenz(a)anthracene and measure PIG-A mutant manifestation in lymphoctyes and compare with PIG-A variant manifestation in red blood cells and hypoxanthine-guanine phosphoribosyltransferase (HPRT) mutant manifestation in lymphocytes; and (4) to determine the spectra of the PIG-A and HPRT mutations induced in the mutant lymphocytes detected in Objectives 1, 2, and 3
Phytoestrogens and Aging: Dose, Timing, and Tissue [Doerge]	(1) To evaluate the potential benefits or detrimental effects of dietary phytoestrogens on breast cancer progression, adipose tissue, and the brain, using well-established laboratory animal models; and (2) to determine bioavailability of soy isoflavones in neonatal and adult male non-human primates.
Interagency Collaboration on Identification of *In Vitro* and Omics Biomarkers for Liver Toxicity [Tong]	(1) To characterize uridine diphosphate (UDP) glucuronosyltransferases (UGT) mRNA expression in normal and malignant human-breast tissues isolated from the same donor and from different donors; (2) to identify polymorphisms in those UGT genes that show significant inter-individual differences in UGT mRNA expression in all breast tissues; (3) to determine the methylation profile of those UGTs identified in objective 2 and correlate it to UGT expression; and (4) to determine the effects of polymorphisms in UGT genes on glucuronidation of estradiol, 4-hydroxyestrone, and 4-hydroxy-tamoxifen using glucuronidation-activity assay and tetrazolium salt (MTT)-cytotoxicity assays.
Evaluation of the Genetic Toxicity and Behavioral Effects of Chronic Methylphenidate Exposure in Juvenile Male Rhesus Monkeys *(Macaca mulatta)* [Morris]	(1) To determine the baseline frequency of measures of genetic damage in a population of juvenile rhesus monkeys; (2) to determine the frequency of these measures of genetic damage in a population of juvenile rhesus monkeys at defined intervals during a chronic exposure to methylphenidate; (3) to determine if chronic exposure to methylphenidate results in measurable effects on the behavior of juvenile rhesus monkeys utilizing the NCTR Operant Test Battery; and (4) to determine the plasma concentration of methylphenidate and its major metabolite, ritalinic acid, during the chronic exposure of juvenile rhesus monkeys to the drug.
Molecular Mechanisms Underlying Gender-associated Differences in the Adverse Reactions to the Antiretroviral Agent, Zidovudine (AZT): Role of Mitochondrial Toxicity [Desai]	(1) To to elucidate molecular mechanisms of mitochondrial dysfunction that will address gender-based differences in adverse effects of antiretroviral drugs, such as AZT; and (2) to provide critical information to the FDA for the development of guidelines to plan new treatment strategies to reduce the frequency and severity of antiretroviral-related toxic effects in women, particularly in pregnant women.
Neurotoxicity Assessment of Mn Nanoparticles in PC-12 Cells and in Mice [Ali]	(1) To evaluate the neurotoxicity of different size Mn nanoparticles using PC-12 cultured cells; (2) to determine if *in vitro* exposure to Mn nanoparticles selectively induces specific genomic changes in PC-12 cultured cells using oligonucleotide microarrays; (3) to determine if multiple doses of Mn nanoparticles produce reactive oxygen species (ROS), alterations in lipid peroxidation and/or changes in antioxidant enzymes (catalase, superoxide dismutase, glutathione peroxidase), and levels of glutathione in various regions of the mouse brain; (4) to determine if single or multiple doses of Mn nanoparticles induce specific genomic changes in various regions of the mouse brain using oligonucleotide microarrays; (5) to determine if single or multiple doses of Mn nanoparticles produce significant changes in neurotransmitter concentrations in various regions of the mouse brain; and (6) to determine if single or multiple doses of Mn nanoparticles produce significant changes in the formation of 3-nitrotyrosine, an *in vivo* biomarker for oxidative stress, in various regions of the mouse brain.
Methods Development for High-Resolution Dedicated Positron Emission Tomography (microPET) to Rodent Neuroplasticity and Toxicity During Development [Wang]	To use the microPET to screen and evaluate *in vitro* and *in vivo* measurements from a broad range of pathophysiological or pharmacological parameters using specific tracers in the developing rat, using three different age groups of developing rats (pregnant gestational day (GD)18 female rats; postnatal day (PND)7 rat pups; PND35 rats).

NCTR/NTP Project Project Officer	Objective and/or Project Summary
Cancer Mutations as Biomarkers of Cancer Risk: Human Studies with Implications for Personalized Medicine [Parsons]	(1) To develop the information necessary for the rational use of oncogene mutations as quantitative biomarkers of cancer risk, specifically; (2) to determine normal and pathological levels of relevant oncogene mutations in multiple human tissues and tumors using allele-specific competitive blocker polymerase chain reaction (ACB -PCR); (3) to compare the information derived from human tissues with data generated in a parallel rodent protocol as an approach for incorporating carcinogenesis-relevant data into the rodent-to-human extrapolation necessary in cancer risk assessment; (4) to validate a streamlined ACB-PCR methodology and to develop the methodology necessary to measure oncogene mutation frequency in cell-free DNA isolated from plasma; and (5) to convey to the regulatory risk assessment community, through a series of publications, the regulatory significance of the data regarding tumor-associated mutations which have and will be generated.
Development of a New Safety Evaluation Method Using MicroRNA (miRNA) Expression Analysis as a Biomarker for Detecting Carcinogens [Chen]	(1) To determine miRNA expression profiles of the tumor target tissues of rats and mice treated with genotoxic carcinogens aristolochic acid, riddelliine and comfrey, and non-genotoxic carcinogens, propiconazole, and triadimeforn, and non-carcinogen myclobutanil using microarray technologies; (2) to develop a PCR array containing the primers that are specifically used to amplify carcinogensis-related miRNAs and use the PCR array to conduct time-course and dose-response studies for miRNA expression alterations in tissues of rats treated with carcinogens; and (3) to define the miRNA biomarker genes that are associated with carcinogen exposure by prediction of their target genes and determination of their biological functions.
Neurotoxicity Assessment of Silver (Ag) Nanoparticles in PC-12 Cells and in Rats [Ali]	(1) To evaluate the neurotoxicity of different sizes of Ag nanoparticles using cultured PC-12 cells; (2) to determine if *in vitro* exposure to Ag nanoparticles selectively induces specific genomic changes in cultured PC-12 cells using microarrays; (3) to determine if single or multiple doses of Ag nanoparticles produce ROS, alterations in lipid peroxidation and/or changes in antioxidant enzymes (catalase, superoxide dismutase, glutathione peroxidase) and glutathione levels in the rat brain; (4) to determine if single or multiple doses of Ag nanoparticles induce specific genomic changes in the rat brain as indicated with microarrays; (5) to determine if single or multiple doses of Ag nanoparticles produce significant changes in neurotransmitter concentrations in the brain in rat; (6) to determine if single or multiple doses of Ag nanoparticles produce significant changes in the formation of 3-nitrotyrosine, an *in vivo* biomarker for oxidative stress, in the rat brain; and (7) to determine if multiple doses of Ag nanoparticles produce morphological alterations in blood-brain barrier, brain, or other visceral organs of the rat.
Development of High Throughput Methodology for Detection of *In Vivo* Mutation in the Endogenous PIG-A Gene of Human Blood Cells Using Flow Cytometry [Dobrovolsky]	(1) To design high throughput methods for detecting PIG-A mutant human red and white blood cells by flow cytometric detection of cells lacking cell surface protein markers anchored by glycosyl phosphatidyl inositol (e.g., CD59, CD48); (2) to establish a normal range of PIG-A mutant frequencies in red and white blood cells and compare these ranges with those of different groups of human subjects hypothesized to have increased mutational loads (patients with the disease paroxysmal nocturnal hemoglobinurea, patients undergoing radiation treatment or chemotherapy with DNA reactive drugs, and patients predisposed to cancer due to inherited deficiencies in endogenous pathways); (3) to compare red blood cell PIG-A mutant frequencies determined in objective 2 with PIG-A mutant frequencies in white blood cells from these samples determined by limiting-dilution cloning, and (4) to determine the PIG-A DNA sequence changes responsible for the white blood cell mutants.
Evaluation of the Ability of Both the Agar and Microwell Versions of the MLA to Optimally Detect the Mutagenic Potential and Potency of Complex Chemical Mixtures [Moore]	To develop science-based best practice standards and tools to incorporate translational and applied toxicological advancements into the regulatory science process to create a seamless bench-to-bedside continuum.
Assessment of Gaseous Anesthetics in the Developing Nonhuman Primate [Wang]	(1) To evaluate dose-response effects of gaseous anesthetics to determine if prolonged exposure to nitrous oxide or isoflurane alone will result in an increase in neuronal cell death, and determine if combinations of nitrous oxide and isoflurane will prevent or enhance each other's effects on the developing nonhuman primate; (2) to determine if a relative high dose or prolonged exposure of the developing nonhuman primates to nitrous oxide or isoflurane alone, or their combination will induce long-term behavioral deficits, as well as long-lasting pathological changes; (3) to determine, using noninvasive imaging techniques (microPET and MRI), if a high dose or prolonged exposure of the developing nonhuman primates to nitrous oxide or isoflurane alone, or in combination will induce long-lasting pathological changes; and (4) to identify potential underlying mechanisms that could link alteration of mitochondrial function and elevation of ROS to gaseous anesthetic-induced neuronal cell death.

NCTR/NTP Project Project Officer	Objective and/or Project Summary
Development of Methods for Evaluating DNA Damage using Single Cell Gel Electrophoresis (Comet Assay) in Rodents [Aidoo]	To evaluate and establish methods and conditions that enhance the sensitivity and reproducibility of the *in vivo* alkaline-comet assay for use in preclinical-hazard identification and genotoxicity testing of food ingredients and chemicals for regulatory purposes.
Gene Expression Responses by Avirulent *Bacillus anthracis* and Human Epithelial Cells During Initial Host-Pathogen Contact [Khan]	(1) To compare the gene expression profiles of the bacteria and cell lines with and without co-culture, focusing on differences that relate to pathogenesis; and (2) to identify key signal transduction pathways and immune system interaction genes involved in epithelial cell stimulation by *B. anthracis*.
Development and Application of a Mitochondria-Specific Gene Array (Mitochip) for the Investigation of Clinical and Non-Clinical Predictive Biomarkers of Toxicity [Desai]	(1) To develop MitoChips for various mammalian species, including rat, non-human primate, and human; (2) to do transcriptional profiling of mitochondria-related genes using mitochondria-specific gene arrays to investigate the mechanisms of drug toxicities and degenerative diseases associated with mitochondrial dysfunction in different mammalian species; and (3) to characterize species-specific transcriptional profiles to predict risk of drug toxicity or disease onset in different mammalian species
Inactivation of UGT in Human Breast Tissue: Accessing Cancer Risk, Tamoxifen Safety and Toxicity [Starlard-Davenport]	(1) To characterize UGT mRNA expression in normal and malignant human breast tissues isolated from the same donor and different donors; (2) to identify polymorphisms in the UGT genes that show significant inter-individual differences in UGT mRNA expression in all breast tissues; (3) to determine the methylation profile of the UGTs identified in objective 2 and correlate with UGT expression; and (4) to determine the effects of polymorphisms in UGT genes on glucuronidation of ethinyl estradiol, hydroxy-ethinyl estradiol and 4-hydroxy tamoxifen.
Method Development for Study of Antioxidant Properties in Dietary Supplement [Fu]	(1) To determine whether or not the studied herbal dietary supplements can enhance or inhibit free radical formation or lipid peroxidation, mediated by microsomal metabolism, in a dose dependent manner; (2) to determine the toxic effects including mitochondrial dehydrogenase activity, intracellular ROS concentration, and mitochondrial membrane potential, and (3) to use electron spin resonance (ESR) oximetry technique to determine the inhibition/induction of lipid peroxidation, of the herbal dietary supplements in cells, including A549 human lung carcinoma cells and rabbit brain rBCECs cells.
Use of ESR Spectroscopy to Characterize the Interactions Between Nanoscale Materials and Model Biological Systems [Fu]	(1) To determine whether nanomaterials can catalyze Fenton reaction to initiate hydroxyl radical formation in a nanoparticle size dependent manner, or reduced by natural reducing agents, such as ascorbic acid and glutathione, leading to the formation of reactive oxygen species; (2) to determine whether nanomaterials enhance or inhibit free radical formation mediated by microsomal metabolism or inhibit microsomal metabolism mediated by lipid peroxidation, in a nanoparticle size dependent manner; (3) to determine the toxic effects, including mitochondrial dehydrogenase activity, intracellular ROS concentration, and mitochondrial membrane potential, and (4) to use ESR oximetry technique to determine the inhibition/induction of lipid peroxidation of nanomaterials of different particle size in cells (A549 human lung carcinoma cells and rabbit brain rBCECs cells).
Neurotoxicity Assessment of Carbon Nanotubes (CNTs) and Gold Nanoparticles using a Brain Microvascular Endothelial Cell System, PC-12 Cultured Cells, and a Whole Animal Model (Rats or Mice) [Ali]	(1) To evaluate the neurotoxicity of single and multiple wall and different sizes of CNTs in brain microvascular endothelial cells system and PC-12 cultured cells; (2) to determine, using microarrays, if the *in vitro* exposure to these CNTs (single and multiple walls) selectively induce specific genomic/proteomic changes; (3) to determine if acute or chronic exposure of CNTs in the mouse brain produce (a) ROS, alterations in lipid peroxidation and/or changes in antioxidant enzymes (catalase, superoxide dismutase, glutathione peroxidase) and glutathione levels, (b) specific genomic/proteomic changes indicated with microarrays, or (c) changes in neurotransmitter concentrations, formation of 3-nitrotyrosine, an *in vivo* biomarker for oxidative stress; and (3) to determine if acute or chronic exposure of CNTs produce morphological alterations in the brain or visceral organs of the mice.

NCTR/NTP Project Project Officer	Objective and/or Project Summary
Assessment of the Nephrotoxicity of a Seven-Day Combined Exposure to Melamine and Cyanuric Acid [Gamboa da Costa]	To investigate the nephrotoxic effect of a seven-day co-exposure to melamine and cyanuric acid in Fischer 344 rats.
Studies Comparing the Neurotoxicology of Amphetamine with Methamphetamine and Methylphenidate (Ritalin) [Levi]	(1) To determine the appropriate dose range and plasma levels of methylphenidate that produce hyperthermic profile similar to that produced by neurotoxic doses of amphetamine and methamphetamine and (2) to evaluate the hyperthermic profiles resulting from the selected dose.
Methylphenidate (Ritalin) Exposure during Pregnancy: Assessment of Neurotoxicity in Offspring [Ferguson]	To quantify the neurobehavioral toxicity associated with pre- and early postnatal treatment with methylphenidate in rats, measuring a wide range of behaviors at preweaning, adolescent, and adult ages.
Biomarkers of Liver Toxicity [Salminen]	(1) To determine biomarkers of hepatotoxicity in preclinical studies that are more predictive of adverse effects in humans and (2) to qualify biomarkers (e.g., via the FDA/EMEA qualification process) and assess their potential translation for clinical use.
Development of a FDA Resource and Knowledge Base for Sex Difference in Drug-Induced Liver Injury (DILI) [Tong]	To develop a knowledge base for the sex differences in drug-induced liver injury (DILI) through analyzing and modeling the molecular data in public domain, specifically through: (a) collection of the genomic data from public resources and through collaborations; (b) development of a standard data curation model for the sex-biased DILI in ArrayTrack to manage the collected data; (c) meta-analysis, text mining, and network analyses to develop a relationship between drugs, molecular signatures, liver-specific biomarkers, genes/proteins functions, pathways and sex-biased liver toxicity.
3D- and 4D- Quantitative Spectrometric Data-activity Relationship (QSDAR) Modeling Applied to Various Toxicological Endpoints [Beger]	(1) To develop 3D- and 4D- QSDAR models for endocrine disruptors, lowest-observed-adverse-effects level, and no observed-adverse-effects level, and other relevant toxicological endpoints; and (2) to determine how the technique used to predict ^{13}C or ^{15}N NMR spectra affects on 3D-QSDAR modeling.
Methods Development for Toxicity Assays using the Zebrafish Embryo as a Model System: Whole Animal High Throughput Assays for Chemical Testing [Kanungo]	(1) To use the established high throughput assay system with zebrafish embryos for morphological and behavioral endpoints of toxicity, and subtle organ-specific toxicities to study the effect of methamphetamine on Zebra fish embryos, especially relating to sensory and motor neuron development; (2) to determine if CNTs pass through the blood brain barrier in zebrafish embryos and have any toxic effects on early development, and if so, determine if these nanomaterials generate ROS, cause the depletion of dopamine and its metabolites, dihydroxyphenylacetic acid and homovanillic acid, and alter markers of oxidative stress;and (3) to study the effect of nicotine on zebrafish embryos, especially relating to sensory and motor neuron development and the mechanism of action.
In Vitro Assay to Predict Developmental Neurotoxicity of Pediatric Anesthetics [Wang]	(1) To use rodent *in vitro* organotypic and primary culture models to examine effects of propofol (gamma-aminobutyric acid [GABA] A agonist), baclofen (GABA B agonist), diazepam (GABA A agonist), pentobarbital (GABA A agonist and 2-amino-3-(5-methyl-3-oxo-1, 2- oxazol-4-yl) propanoic acid antagonist), etomidate (GABA A agonist), sevoflurane (N-methyl-D-aspartic acid [NMDA] antagonist and GABA agonist), fentanyl (opiate agonist) and anesthetic combinations commonly used in pediatric surgical procedures; (2) to determine the utility of *in vitro* culture systems to predict *in vivo* outcomes in subsequent studies; (3) to determine the dose and time-course over which the potential neurotoxic effects of anesthetics are expressed in the developing brain; (4) to determine effective ways to protect against anesthetic-induced developmental neurotoxicity that have potential clinical utility; (5) to identify mechanisms that link altered NMDA receptor function and/or elevation of ROS to anesthetic-induced neuroapoptosis; and (6) to identify biomarkers such as genomic pathway signatures and determine their validity for predicting *in vitro* outcomes of pediatric anesthetic exposure.

NCTR/NTP Project Project Officer	Objective and/or Project Summary
PIG-A Mutagenesis; An International Validation Study Comparing PIG-A Mutation in Rats With Other Biomarkers of Genetic Toxicity [Heflich]	(1) To generate data using a standardized protocol that, in combination with results from other investigators, will be used to determine the sensitivity, specificity, and portability of the rat red blood cell/reticulocyte (RBC/RET) PIG-A gene mutation assay; and (2) to perform the *in vivo* Comet, micronucleus, and the PIG-A and HPRT lymphocyte gene mutation assays in conjunction with the RBC/RET PIG-A assay, to determine how the RBC/RET PIG-A assay compares in terms of sensitivity and specificity with these other *in vivo* assays that have been used or considered for use as regulatory assays.
Effect of Soy-containing Diets on Ammonium Perchlorate-induced Thyroid Toxicity in Sprague-Dawley (SD) Rats (II) [Doerge]	To determine the effect of dietary whole soy and purified genistein, the principal soy isoflavone, on the dose-response characteristics for perchlorate-induced thyroid toxicity in male SD rats.
Study of Drug Induced Liver Toxicity Using Primary Rat and Mouse Hepatocytes [Guo]	To obtain signature gene and protein expression patterns for mouse and rat primary hepatocytes following xenobiotic induced toxicity.
The Sequencing Quality Control Project [Shi]	(1) To assess the technical performance of the next-generation sequencing platforms that will be used in toxicology studies, by using reference RNA samples analyzed at multiple times; (2) to use one next-generation sequencing platform to sequence RNA samples from a toxicogenomic study; and (3) to use reference DNA samples to assess technical performance for exome sequencing.
Identification of New Mechanistic Biomarkers of Adverse Responses to Acetaminophen [Beger]	To provide pharmacokinetics data for acetaminophen and acetaminophen/N-acetylcysteine, in addition to metabolomics analyses of metabolites, involved in one carbon metabolism and energy metabolism such as those of the citric acid cycle in blood and urine samples from children and adolescents who have adverse reactions to acetaminophen.
Genotyping of Transporter Genes Associated with Gender Differences and Promoter Methylation of UGT1A1 in Human Liver: A Means of Assessing Safety and Toxicity of Chemotherapeutic Drugs [Lyn-Cook]	(1) To identify polymorphisms in drug transporter genes identified to be differentially expressed according to gender in human liver samples, (2) to correlate polymorphism frequencies in male and female to gene expression, (3) to evaluate the methylation profile of UGT1A1 promoter in human liver samples from male and female and correlate it to expression of UGT and its activity, and (4) to evaluate effects of polymorphisms in transporter genes on uptake and clearance of chemotherapeutic drugs in a functional assay using the B-CLEAR human *in vitro* model.
Proteomic Approaches to Elicidate Biodegradative Pathways [Wang]	To use a proteomic approach to isolate putative catabolic proteins that are over-expressed when microorganisms are grown in the presence of toxic polycyclic aromatic hydrocarbons.
NCTR/Office of Regulatory Affairs (ORA) Nanotechnology Core Facility [Howard]	(1) To support the needs of NCTR research projects to characterize nanoscale materials used in toxicology tests and to detect these materials in biological samples, (2) to support the needs of ORA to detect and characterize nanoscale materials in FDA regulated products, and (3) to develop methods and approaches to anticipate needs of the research community.
Analytical Assay for Photochemical Generation of Hydroxyl Radical [Howard]	(1) To provide support for analysis of the photoactivation of nanomaterials using the coumarin-3-carboxylic acid oxidation assay, (2) to provide particle-size analysis for all nanomaterials being analyzed; and (3) to improve the assay using ultraviolet light diode laser as a replacement to the existing broad band ultraviolet light A source.

NIEHS/NTP

NIEHS/NTP staff at the NIEHS building, Research Triangle Park, NC

Highlighted Activities

Division of the National Toxicology Program

In FY 2011 the Division of the National Toxicology Program (DNTP) was established within the NIEHS. The NTP was formerly a program within DIR and the change was in recognition of the unique mission of NTP and the unique training requirements and capabilities of its staff. Secretary Sebelius signed the reorganization documents following a review by the Office of Management and Budget. Congress was notified of the change in spring of 2011 and a *Federal Register* notice (*http://ntp.niehs.nih.gov/go/frn*) announcing the reorganization was published on April 28, 2011.

The new structure affords greater efficiency at NIEHS, by making a clear staffing and budgetary demarcation between the components of the NIEHS carrying out work dedicated solely to the pursuit of the goals and initiatives of the NTP, and the principal investigator-initiated efforts carried out by staff in the DIR. Dr. John Bucher serves as director of the DNTP. Information about the DNTP is available at *http://www.niehs.nih.gov/research/atniehs/dntp/index.cfm*.

NIEHS Strategic Planning

In 2011 NIEHS initiated a strategic planning process, which will guide the institute's activities over the next five years. The process was designed with three phases, the first of which was soliciting stakeholder input. A Stakeholder Community Workshop was held in July 2011, with more than 180 participants. It employed a Modified Open Space format, which ultimately yielded a slate of 13 "big topics" for further development. The strategic planning process will continue in FY 2012 to develop the mission statement, vision statement, and supporting pillars. Information about the strategic plan is available at *http://www.niehs.nih.gov/strategicplan*.

Gulf Oil Spill Response

Immediately following the Deepwater Horizon explosion on April 20, 2010, and the ensuing massive oil spill in the Gulf of Mexico, NTP and NIEHS began coordinated efforts with other federal agencies (including FDA, OSHA, NHGRI, NIOSH, ATSDR, EPA, National Oceanographic and Atmospheric Administration, United States Fish and Wildlife Service, U.S. Geological Survey, and U.S. Coast Guard) to limit the adverse impacts of the oil and dispersants on human health, ecological health, and food sources.

Early efforts by NTP focused upon assembly and distribution of information on characteristics and toxicity of oil and oil dispersants. The NTP is pursuing several lines of research to address concerns regarding the safety of Gulf seafood, hazards to offshore and onshore cleanup workers, and potential long-term health impacts of residual oil in the environment. NIEHS/NTP obtained samples of source oil, tar balls, and the dispersant COREXIT® EC9500A. The NTP is conducting analytical chemistry studies to better understand the composition of the source oil and tar balls and oiled sediment collected along the shoreline. The focus of these analyses is on components that are more likely to persist in the environment and potentially lead to residual human exposures. These analytical chemistry efforts will help understand exposures to response workers and inform exposure assessments in the Gulf Long-term Follow-up Study (GuLF STUDY, see below). The NTP will also use this information to develop a toxicology research program on polycyclic aromatic hydrocarbons (PAHs). The aim of this program is to further characterize the hazard of PAHs

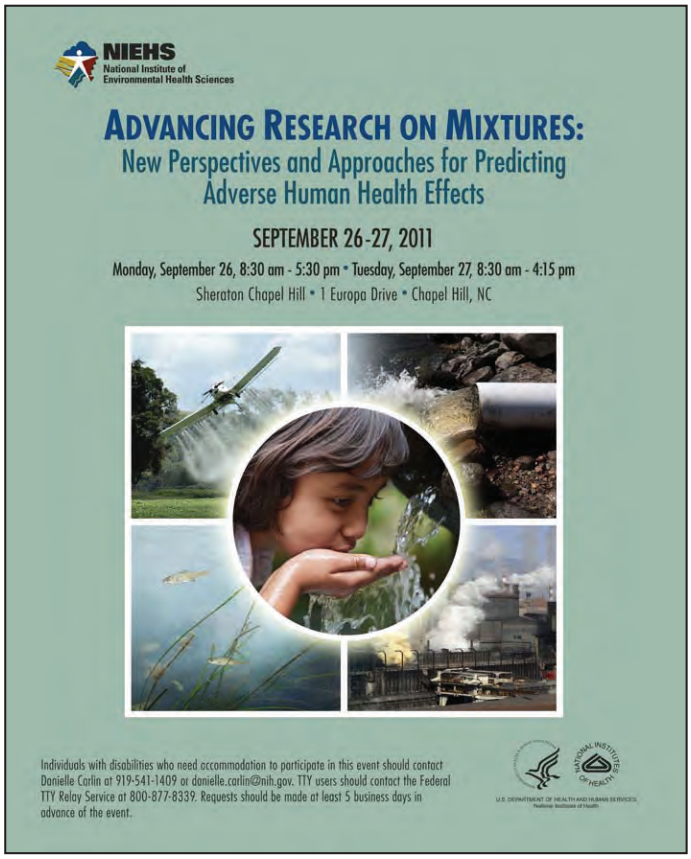
present in oil to determine if those PAHs routinely monitored in environmental media adequately capture the hazard of crude oil exposures, and to better understand whether there are combinations of individual PAHs that require they be considered in aggregate when establishing safe exposure levels.

The NTP's toxicology assessments will inform the ongoing GuLF study, which will assess the possible health effects of the oil spill on up to 55,000 cleanup workers and volunteers in coastal towns across Louisiana, Mississippi, Alabama, and Florida. This longitudinal cohort study, coordinated by the NIEHS, is the largest health study of its kind ever conducted, and is an important component of the comprehensive federal response to the oil spill. Information about the GuLF STUDY is available at *http://nihgulfstudy.org/*. NIEHS also led the creation of a trans-NIH funded network of community and university partnerships that will investigate personal and community health effects stemming from the Deepwater Horizon oil spill and enhance community resiliency to potential disasters.

Information about NIEHS oil spill response efforts is available at *http://www.niehs.nih.gov/about/od/programs/gulfspill* and information about the overall federal oil spill response efforts is available at *http://www.restorethegulf.gov/*.

Contact Information: Dr. Scott Masten, *masten@niehs.nih.gov*

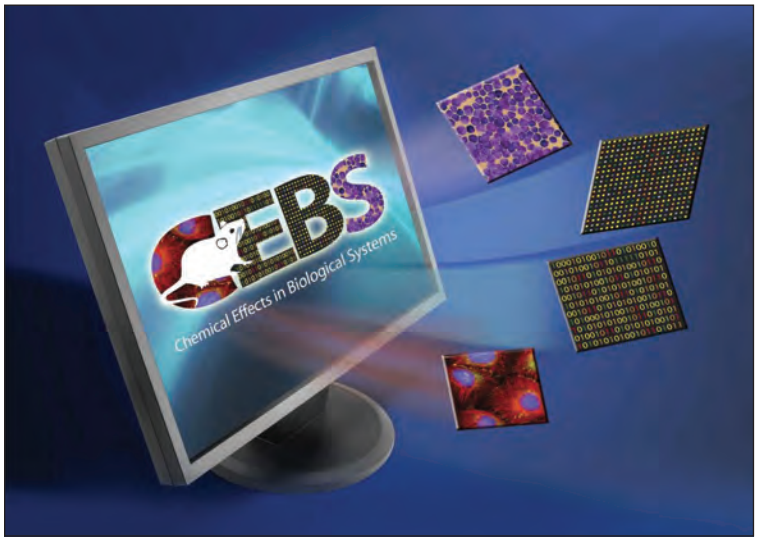
Workshop: Advancing Research on Mixtures: New Perspectives and Approaches for Predicting Adverse Human Health Effects



A collaborative effort between Division of Extramural Research and Training and the NTP culminated in a workshop on September 26-27, 2011, in Chapel Hill, NC, that brought together experts from diverse disciplines (exposure science, epidemiology, toxicology, statistics, and risk assessment) to focus on mixtures. The purpose of the workshop was to identify and address key issues presented in research on mixtures. The workshop goals were to (1) identify and prioritize the knowledge gaps and challenges in mixtures research in toxicology, epidemiology, exposure science, risk assessment, and statistics; (2) obtain advice on integrating multidisciplinary capabilities to address critical topics in mixtures research; (3) provide recommendations for research on key topics; (4) inform the development of a long-term NIEHS mixtures research agenda; and (5) foster collaborations between extramural and NIEHS scientists. The NIEHS will use the results from the workshop to inform the development of an intramural and extramural mixtures research strategy and to provide input to the scientific community for advancing mixtures research.

Contact Information: Dr. Cynthia Rider, *cynthia.rider@nih.gov*

Chemical Effects in Biological Systems (CEBS): A Publicly Accessible NTP Integrated Data Management System



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

An important feature of the database is its flexibility — CEBS can house "any" type of biological measurements from "any" type of study design. This flexibility in CEBS allows data from different sources to be integrated into one place, to permit data mining and analysis. In addition, any one study can have different types of data associated with it such as blood chemistry, histopathology, and microarray — all viewed together under one study name. The investigator does not have to access different databases, each housing one specific type of data.

In 2011, the NTP added over 9000 studies to CEBS. Many of these additions were legacy NTP genetic toxicology, immunotoxicology, and carcinogenicity/toxicology studies. The legacy studies investigated the potential of many different chemicals to cause genetic damage or mutations, adverse effects on the immune system, tumor formation, or toxicity in *in vitro* or *in vivo* models. The high throughput toxicological screening Phase I Tox21 studies, which use *in vitro* biochemical and cell-based assays, were also added to CEBS.

The NTP is continuing to add legacy NTP data to CEBS and will be adding Phase II Tox21 data. When this project is completed, all the public NTP data will be accessible in CEBS for reference and for data mining.

CEBS consists of a database, a user interface, and tools for loading data and managing it for display. Testing has also begun on analytical tools and incorporating graphical displays of data. The user is able to download raw data from a single study or batch files of many studies using the new File Transfer Protocol (FTP) site. Study conclusions are also shown and can be searched.

CEBS captures the details of the study design and execution plus the biological responses of subjects in a way that permits searching, filtering, and sub-setting of the data. The user can view the details of each study, search for particular studies or study subjects of interest based on treatment, response, or other characteristics, and then either analyze the data within CEBS or download for import into other tools. CEBS can be accessed at *http://cebs.niehs.nih.gov*.

Contact information: Dr. Jennifer Fostel, *fostel@niehs.nih.gov*

Use of NTP Products by Other Agencies

Federal and state regulatory agencies use NTP study data and recommendations in considering the need to regulate and test specific chemicals to protect human health. Table 5 lists NTP data and recommendations used in FY 2011.

Table 5. Use of NTP Study Data or Reccomendations by Federal and State Regulatory Agencies in FY 2011

Agency, *Title*, Additional Information	Information Cited
California EPA Office of Environmental Health Hazard Assessment (OEHHA): Chemical Listed as Known to the State of California to Cause Reproductive Toxicity: Acrylamide [79-06-1]	NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Acrylamide (2005)
California EPA OEHHA: Proposition 65 - Notice of Intent to List: Androstenedione [63-05-8]	NTP Toxicology and Carcinogenesis Studies of Androstenedione in F344/N Rats and B6C3F1 Mice (Gavage Studies). TR-560 (2010)
California EPA OEHHA: Proposition 65 - Notice of Intent to List: Dibromoacetonitrile [3252-43-5]	NTP Toxicology and Carcinogenesis Studies of Dibromoacetonitrile in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). TR-544 (2010)
California EPA OEHHA: Proposition 65 - Notice of Intent to List: Malonaldehyde, Sodium Salt [24382-04-5]	NTP Toxicology and Carcinogenesis Studies of Malonaldehyde, Sodium Salt (3-Hydroxy-2-propenal, Sodium Salt) in F344/N Rats and B6C3F1 Mice (Gavage Studies). TR-331 (1988)
Department of Defense: Defense Federal Acquisition Regulation Supplement; Minimizing the Use of Materials Containing Hexavalent Chromium (DFARS Case 2009–D004)	The RoC first listed hexavalent chromium compounds as known human carcinogens in 1980
Department of Transportation: Revision to the List of Hazardous Substances and Reportable Quantities – removing saccharin [81-07-2] and its salts	RoC, Appendix B: saccharin and its salts do not pose a present or potential risk of causing carcinogenic effects on humans.
Department of Transportation: Greenhouse Gas Emissions Standards and Fuel Efficiency Standards for Medium- and Heavy-Duty Engines and Vehicles	RoC has listed: • benzene [71-43-2] and 1,3-butadiene [106-99-0] as known human carcinogens (1980 and 1989) • acetaldehyde [75-07-0] as reasonably anticipated to be a human carcinogen (1991) • naphthalene [91-20-3] as reasonably anticipated to be a human carcinogen (2004)
EPA: Testing of Certain High Production Volume Chemicals; Second Group of Chemicals	NICEATM studies (2003): Test Method Protocol for Solubility Determination, *In Vitro* Cytotoxicity Validation Study — Phase III; Test Method Protocol for the BALB/c 3T3 Neutral Red Uptake Cytotoxicity Test, a Test for Basal Cytotoxicity for an *In Vitro* Validation Study — Phase III ; Test Method Protocol for the NHK Neutral Red Uptake Cytotoxicity Test, a Test for Basal Cytotoxicity for an *In Vitro* Validation Study — Phase III
EPA: (S,S)-Ethylenediamine Disuccinic Acid Trisodium Salt [178949–82–1] Exemption From the Requirement of a Tolerance	Bioassay of Trisodium ethylenediaminetetraacetate trihydrate (EDTA) for Possible Carcinogenicity in mice and rats showed no carcinogenic potential. TR-11 (1977). Since (S,S)-ethylenediamine disuccinic acid trisodium salt ((S,S)-EDDS) is similar to EDTA, (S,S)-EDDS is not likely to be carcinogenic to humans at low doses.
EPA: Sodium Ferric EDTA [178949–82–1]; Exemption From the Requirement of a Tolerance	Bioassay of Trisodium ethylenediaminetetraacetate trihydrate (EDTA) for Possible Carcinogenicity in mice and rats showed no carcinogenic potential. TR-11 (1977).

Agency, *Title*, Additional Information	Information Cited
EPA: National Emission Standards for Hazardous Air Pollutants From Coal- and Oil-Fired Electric Utility Steam Generating Units and Standards of Performance for Fossil-Fuel-Fired Electric Utility, Industrial-Commercial-Institutional, and Small Industrial-Commercial-Institutional Steam Generating Units	RoC has listed: • benzene [71-43-2] as known human carcinogens (1980) • acetaldehyde [75-07-0] as reasonably anticipated to be a human carcinogen (1991)
EPA:Agency Information Collection Activities; Submission to OMB for Review and Approval; Proposed Collections; Toxic Chemical Release Reporting; Request for Comments on Proposed Renewal of Form R and Form A, Including Minor Form Revisions and the Ratio-Based Burden Methodology	RoC
EPA: Ethylene Glycol; Exemption from the Requirement of a Tolerance	Toxicology and Carcinogenesis Studies of Ethylene Glycol in B6C3F1 Mice (Feed Studies). TR-413 (1993)
EPA: Diethylene Glycol MonoEthyl Ether (DEGEE); Exemption From the Requirement of a Tolerance	Toxicology and Carcinogenesis Studies of Ethylene Glycol in B6C3F1 Mice (Feed Studies). TR-413 (1993)
EPA: Testing of BPA [80-05-7]	NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A (2008)
EPA: Carboxymethyl Guar Gum Sodium Salt and Carboxymethyl-Hydroxypropyl Guar; Exemption From the Requirement of a Tolerance	Carcinogenesis Bioassay of Guar Gum in F344 Rats and B6C3F1 Mice (Feed Study) TR-229 (1982)
EPA: Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Request for Comments	RoC has identified constituents in tobacco products and tobacco smoke as human carcinogens or reasonably anticipated to be human carcinogens (2000)
EPA: Greenhouse Gas Emissions Standards and Fuel Efficiency Standards for Medium- and Heavy-Duty Engines and Vehicles	RoC has listed: • benzene [71-43-2] and 1,3-butadiene [106-99-0] as known human carcinogens (1980 and 1989) • acetaldehyde [75-07-0] as reasonably anticipated to be a human carcinogen (1991) • naphthalene [91-20-3] as reasonably anticipated to be a human carcinogen (2004)
FDA: Labeling and Effectiveness Testing; Sunscreen Drug Products for Over-the-Counter Human Use	RoC indicates that UVA and UVB radiation across the spectrum are known human carcinogens, but either UVA or UVB radiation alone is reasonably anticipated to be a human carcinogen. Cited in the National Toxicology Program's Report on Carcinogens (2002).
U.S. Forest Service: Information Collection; Qualified Products List for Long-Term Retardant for Wildland Firefighting	The Forest Service evaluates and approves commercial wildland firefighting chemicals. Products must not contain chemicals listed as a Chemical of Concern. To create their list, they include chemicals appearing in the RoC.

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

Report on Carcinogens

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

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

The 12th RoC, the latest edition, was published on June 10, 2011. The 12th RoC contains 240 listings, including some classes of related chemicals or agents. There are six new listings and two revised listings in this edition (see Table 6 or the website *http://ntp.niehs.nih.gov/go/roc12)*.

Table 6. New or Revised Listing in the 12th Report on Carcinogens, published in FY 2011

Candidate Substance [CASRN]	Primary Uses/ Exposures	Listing Status
Aristolochic Acids (AA)	A family of nitrophenanthrene carboxylic acids that occurs naturally in plants in the Aristolochiaceae family, primarily of the genera *Aristolochia* and *Asarum*. Botanical products from plants containing aristolochic acids are used in traditional folk medicines, particularly in Chinese herbal medicine, and have been used inadvertently as part of a weight-loss regimen.	Known to be human carcinogens
Captafol [2425-06-01]	A broad-spectrum fungicide that has been widely used since 1961 for the control of fungal diseases in fruits, vegetables, and some other plants. Use of captafol in the United States was banned in 1999.	Reasonably anticipated to be a human carcinogen
Cobalt–Tungsten Carbide: Powders and Hard Metals	Composites of tungsten-carbides with a metallic cobalt, used to make cutting and grinding tools, dies, and wear products for a broad spectrum of industries, including mining and oil and gas drilling.	Reasonably anticipated to be a human carcinogen
Formaldehyde [50-00-0] (nominated formaldehyde for reclassification)	Primarily used to produce resins for the production of many different products, including plastics, adhesives and binders for wood products, pulp and paper, and synthetic fibers, and in textile finishing. It is also used as a disinfectant and preservative and as an intermediate for many industrial chemicals.	Known to be a human carcinogen
Certain Glass Wool Fibers (inhalable) (nominated glass wool (respirable size) for delisting)	Glass wool fibers, which are a type of synthetic vitreous fibers, are an inorganic fibrous material manufactured primarily from glass and processed inorganic oxides. The major uses of glass wool are in thermal, electrical, and acoustical insulation, weatherproofing, and filtration media. Some special-purpose glass wool fibers are used for high-efficiency air filtration media and acid battery separators.	Glass wool (respirable) was first listed in the 7th RoC as *reasonably anticipated to be a human carcinogen*, but the scope of the listing changed and now certain glass wool fibers (inhalable) are listed as *reasonably anticipated to be human carcinogens*.
ortho-Nitrotoluene [88-72-2]	A chemical intermediate used in the synthesis of azo dyes. It is also used (either directly or as an intermediate) in the production of other dyes, agricultural chemicals, rubber chemicals, pesticides, petrochemicals, pharmaceuticals, and explosives.	Reasonably anticipated to be a human carcinogen

Candidate Substance [CASRN]	Primary Uses/ Exposures	Listing Status
Riddelliine [2346-96-0]	Found in a class of plants growing in the western United States. Some common names for Senecio plants are ragwort and groundsel. These plants are not used for food in the U.S., but have been used in medicinal herb preparations.	Reasonably anticipated to be a human carcinogen
Styrene [100-42-5]	Used worldwide in the production of polymers, which are incorporated into products such as rubber, plastic, insulation, fiberglass, pipes, automobile parts, food containers, and carpet backing.	Reasonably anticipated to be a human carcinogen

During FY 2012, the NTP will make revisions to the multi-step process used to review nominations for the RoC. Public input on and BSC review of the proposed process will be sought and used to update the process. Information is available at *http://ntp.niehs.nih.gov/go/rocprocess*.

Also during FY 2012, the 13th RoC will be under development. Substances nominated for possible review for future editions of the RoC are in Table 7 (*http://ntp.niehs.nih.gov/go/rocnom*).

Table 7. Substances Nominated to the Report on Carcinogens at the end of FY 2011

Candidate Substance [CASRN]	Primary Uses/Exposures
Alkenylbenzenes (selected dietary): estragole [140-67-0] myristicin [607-91-0] isosafrole [120-58-1]	Naturally occurring organic chemicals used primarily as an additive, flavoring, or fragrance in food products, but may also be in other products such as cosmetic and cleaning agents.
1- Bromopropane [106-94-5]	Primarily used as a solvent for fats, waxes, or resins and in some spray adhesives and aerosol propellant applications. Also used as an intermediate in the synthesis of pharmaceuticals, insecticides, quarternary ammonium compounds, flavors and fragrances.
Carbon black [1333-86-4]	Family of products consisting of elemental carbon in the form of colloidal particles that rapidly form aggregates. The products are used primarily for rubber reinforcement, but are also used as black pigments and for electrical conductivity purposes.
Cumene [98-82-8]	An alkylated benzene used primarily to produce phenol and acetone.
Diesel exhaust particulates (currently listed as *reasonably anticipated to be a human carcinogen*)	A mixture of combustion products of diesel fuel; the exact composition of the mixture depends on the nature of the engine, operating conditions, lubricating oil, additives, emission control system, and fuel composition. Occupational exposure occurs primarily among miners (who use diesel power equipment), railroad workers and transportation workers such as truck drivers.
Ethylbenzene [100-41-4]	An alkylated benzene used primarily for the manufacture of styrene.
Helicobacter pylori	Bacteria responsible for most ulcers and many cases of stomach inflammation (chronic gastritis).
Indium compounds	Indium compounds are chemicals that include the metal indium. Indium phosphide is used primarily in the semiconductor industry; however, most of the semiconductor industry in the U.S. is silicon based. Other indium compounds (such as indium tin oxide) are primarily used in optoelectronics and flat panel display technology.
Iron (excess) or iron overload [7439-89-6] (elemental iron)	Iron is a transition metal that exists mainly in the ferrous (2+) and ferric (3+) oxidation states in biological systems. It is used for medical treatment, as well as for other consumer and industrial needs. It is also found naturally in food. Iron overload disorders can be hereditary, acquired or iatrogenic.

Candidate Substance [CASRN]	Primary Uses/Exposures
Pentachlorophenol [87-86-5]	General biocide that has been used extensively as a fungicide, bactericide, herbicide and insecticide by agriculture and other industries. In 1987, over-the-counter use was banned and other uses restricted. The only current use of pentachlorophenol in the United States is defined as a 'heavy duty' wood preservative that is used primarily in the treatment of utility poles and cross arms.
Shiftwork involving light at night	Shift work is synonymous with irregular, odd, flexible, variable, unusual, non-standard working hours. Shift work can be with or without night work.
ortho-Toluidine [95-53-4] (currently listed as *reasonably anticipated to be a human carcinogen*)	Arylamine used as an intermediate to manufacture herbicides, dyes, pigments and rubber chemicals.
Trichloroethylene [79-01-6] (currently listed as *reasonably anticipated to be a human carcinogen*)	Halogenated alkene used mainly as an intermediate for hydrofluorocarbon production (67%) and as a degreaser for metal parts (30%). It is a major ingredient in many consumer products and has been found in food and drinking water, and the environment (ambient air, ground and tap water).
Uranium (depleted)	A byproduct of the production of enriched uranium for use in nuclear reactors. It has a lower content of the isotope U-235 and emits fewer alpha particles than natural uranium. Used by the military for armor-piercing munitions and armor plates. Used as counterbalance weight in aircraft, and radiation shielding in medical radiation therapy.
Viruses (selected): Kaposi's sarcoma – associated herpesvirus, Epstein-Barr virus, human T-cell lymphotropic virus type 1, human immunodeficiency virus (HIV), and Merkel cell polyomavirus	Epstein-Barr virus and Kaposi's sarcoma – associated herpesvirus are members of the herpesvirus family, which are double stranded DNA viruses with a capsid, and cause characteristic lesions. Epstein-Barr virus causes infectious mononucleosis. HIV is a retrovirus that causes acquired immunodeficiency syndrome. Human T-cell lymphotropic virus type 1 is a retrovirus that causes multiple disorders including an inflammatory neurological disease. Merkel cell polyomavirus is a non-enveloped, double-stranded DNA virus.

Contact Information: Dr. Ruth Lunn, Director, ORoC, *lunn@niehs.nih.gov*. RoC website: *http://ntp.niehs.nih.gov/go/roc*

Office of Health Assessment and Translation

In FY 2011, NIEHS/NTP established the Office of Health Assessment and Translation (OHAT), formerly the Center for the Evaluation of Risks to Human Reproduction (CERHR), to serve as an environmental health resource to the public and to regulatory and health agencies. This office conducts evaluations to assess the evidence that environmental chemicals, physical substances, or mixtures (collectively referred to as "substances") cause adverse health effects and provides opinions on whether these substances may be of concern given what is known about current human exposure levels.

NTP's CERHR focused on effects on reproduction and development, which was appropriate at the time because of a strong interest in these health outcomes by the public, regulatory and health agencies, and the scientific community. Using approaches developed for CERHR evaluations, OHAT extends them to other important heath outcomes, using a more flexible scientific analysis program that allows the exploration of linkages between toxicity pathways and disease outcomes (see Environmental Health Perspectives, 119(5) May 2011). OHAT accepts nominations of substances considered potential health hazards from individuals and from non-profit, commercial, governmental or other organizations. OHAT organizes workshops and state-of-the-science evaluations to address issues of importance in environmental health sciences. OHAT assessments are published as NTP Monographs.

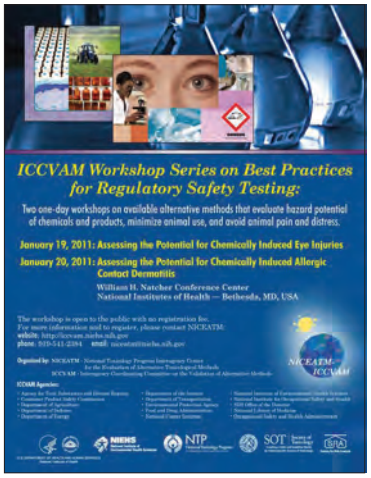
NTP Workshop: Role of Environmental Chemicals in the Development of Diabetes and Obesity

To address the concept that environmental chemicals may be contributing factors to the epidemics of diabetes and obesity, the NTP held a workshop in Raleigh, NC on January 11–13, 2011. The workshop evaluated the science associating exposure to certain chemicals or chemical classes with the development of diabetes and obesity in humans. Goals of the workshop were to (1) evaluate strength/weaknesses, consistency, and biological plausibility of findings reported in humans and experimental animals for certain environmental chemicals including arsenic and cadmium, persistent organic pollutants, pesticides, bisphenol A, phthalates, and organotins; (2) identify the most useful and relevant endpoints in experimental animals and *in vitro* models; (3) identify relevant pathways and biological targets for assays for the Toxicology Testing in the 21st Century high throughput screening initiative ("Tox21"); and (4) identify data gaps and areas for future evaluation/research. Preliminary conclusions of the workshop included (1) plausibility of "obesogen" hypothesis, (2) linkage of type 2 diabetes to certain chemical exposures (3) common mechanistic basis for certain chemical classes, (4) utilization of Tox21 approaches to identify substances of potential interest, and (5) refinement of endpoints examined using high throughput screening approaches. OHAT will publish an NTP workshop report based on the discussions at the workshop. Complete information about the workshop is found at *http://ntp.niehs.nih.gov/go/36433*.

During FY 2011 two important OHAT evaluations were in progress, Potential Developmental Effects of Cancer Chemotherapy during Pregnancy (*http://ntp.niehs.nih.gov/go/36495*) and Heath Effects of Low-level Lead (*http://ntp.niehs.nih.gov/go/36443*). Expert panel meetings are anticipated in FY 2012 for both of these evaluations.

Contact Information: Dr. Kristina Thayer, OHAT Director, *thayer@niehs.nih.gov*. OHAT website *http://ntp.niehs.nih.gov/go/ohat*

NTP Interagency Center for the Evaluation of Alternative Toxicological Methods



NIEHS established ICCVAM in 1997 to advance the regulatory acceptance of scientifically valid alternative testing methods. Alternative methods are those methods that reduce, refine (enhance animal well-being and lessen or avoid pain and distress), or replace the use of animals. NICEATM was established in 1998 to administer ICCVAM, provide scientific support for ICCVAM activities, and conduct independent validation studies on promising test methods. Dr. William Stokes (Rear Admiral, U.S. Public Health Service) is the NICEATM Director and Executive Director of ICCVAM. Integrated Laboratory Systems, Inc., provided contract support for NICEATM in FY 2011. Information about ICCVAM and NICEATM is available at *http://iccvam.niehs.nih.gov*). ICCVAM has contributed to the approval or endorsement of 44 alternative safety or potency testing methods by Federal regulatory agencies since its first test method evaluation in 1998.

NICEATM-ICCVAM organized two workshops in the ICCVAM Workshop Series on Best Practices for Regulatory Safety Testing (*http://iccvam.niehs.nih.gov/meetings/Implement-2011/ImplmtnWksp.htm*) at the Natcher Conference Center in Bethesda, MD. The specific goals of these workshops were to (1) provide an overview of the available methods in each area, including the applications, strengths and weaknesses of each method; (2) provide information on the procedures for conducting and interpreting data in accordance with regulatory testing requirements and guidelines; (3) give participants an opportunity to become familiar with data generated by each test method; (4) provide a forum for scientists to share information on the appropriate use of results in regulatory safety testing; (5) discuss challenges of incorporating alternative test methods into regulatory safety testing guidelines; and (6) identify and discuss new methods in the development and validation pipeline for each safety testing area, and ways to increase the availability of high quality data necessary for validating new methods. The *Assessing the Potential for Chemically Induced Eye Injuries* workshop was held on January 19, 2011, and the *Assessing the Potential for Chemically Induced Allergic Contact Dermatitis* workshop was held on January 20, 2011. Over seventy scientists from industry, academia, research and regulatory agencies, and animal welfare organizations attended each workshop, which was also made available to remote participants via a live webcast.

On March 6 – 10, 2011, NICEATM-ICCVAM participated in the 50th annual meeting of the Society of Toxicology (SOT) in Washington, DC. Dr. Stokes and former ICCVAM Chair Dr. Marilyn Wind co-chaired the platform session *The International Cooperation on Alternative Test Methods (ICATM): Translating Science to Provide Improved Public Health Safety Assessment Tools*. NICEATM-ICCVAM presented posters in sessions titled *Alternatives to Mammalian Models for Testing, Risk Assessment and Regulatory Policy Applications, Safety and Risk Assessment: Critical Characterizations for Chemicals and New Concerns,* and *Disease Prevention*.

During the SOT meeting, ICATM welcomed a new member, the Korean Center for the Validation of Alternative Methods (KoCVAM), at a signing ceremony on March 8 (see *http://www.niehs.nih.gov/news/newsletter/2011/april/science-agreement/index.cfm*). ICATM is a voluntary international cooperation of national organizations including Canada, the European Union, Japan, South Korea, and the United States.

Information about NICEATM-ICCVAM activities at the 2011 SOT Meeting can be found at *http://iccvam.niehs.nih.gov/meetings/SOT11/sotablst.htm*; more information about ICATM can be found at *http://iccvam.niehs.nih.gov/about/icatm.htm*.

On March 29-30, 2011, NICEATM and ICCVAM held a Peer Review Panel Meeting: Evaluation of an *In Vitro* Estrogen Receptor Transcriptional Activation Test Method for Endocrine Disruptor Chemical Screening at the William

H. Natcher Conference Center, Bethesda, MD. The panel was charged to review a draft background review document that evaluated the validation status of the B G1Luc estrogen receptor (ER) transcriptional activation (TA) test method (also known as the LUMI–CELL® ER test method) for identification of potential endocrine disruptor activity. The BG1Luc ER TA test method is an *in vitro* assay used to identify chemicals that can interact with human estrogen receptors. Meeting information is available at *http://iccvam.niehs.nih.gov/methods/endocrine/PeerPanel11.htm*.

On August 21-25, 2011, NICEATM-ICCVAM participated in the *8th World Congress on Alternatives and Animal Use in the Life Sciences* in Montreal, Canada. At the meeting NICEATM staff and ICCVAM members delivered a total of 20 platform and poster presentations in the themes of Safety and Efficacy Testing of Chemicals, Pharmaceuticals and Biologicals; Policy/Law on Animal Use, Public Engagement and Ethics Review; Animal Welfare for Refinement and High Quality Science; and Replacement and Reduction in Basic Research. ICCVAM members also chaired or co-chaired eight platform presentation sessions. Information about NICEATM–ICCVAM activities at the 8th World Congress can be found at *http://iccvam.niehs.nih.gov/meetings/8WC/8WCablst.htm*.

In FY 2012, NICEATM-ICCVAM has scheduled the *International Workshop on Alternative Methods for Human and Veterinary Rabies Vaccine Testing: State of the Science and Planning the Way Forward* (*http://iccvam.niehs.nih.gov/meetings/RabiesVaccWksp-2011/RabiesVaccWksp.htm*) at the U.S. Department of Agriculture (USDA) Center for Veterinary Biologics, National Centers for Animal Health, Ames, Iowa. This October 2011 workshop will bring together international scientific experts from government, industry, and academia to (1) review the available methods and approaches that reduce, refine, and replace animals used in human and veterinary rabies vaccine potency testing and (2) develop an implementation strategy to achieve global acceptance and use of these alternatives. Workshop information is available at *http://iccvam.niehs.nih.gov/meetings/RabiesVaccWksp-2011/RabiesVaccWksp.htm*.

NICEATM–ICCVAM will present seven poster presentations at the 51st annual meeting of the Society of Toxicology in March 2012. The posters will report on evaluations of test methods to identify substances with the potential to affect endocrine function, cause allergic contact dermatitis, or produce systemic toxicity due to skin exposure. Information on NICEATM–ICCVAM presentations at the 2012 SOT meeting will be available at *http://iccvam.niehs.nih.gov/meetings/SOT12/sotablst.htm*.

In FY 2012, NICEATM-ICCVAM will also convene an *International Workshop on Alternative Methods for Leptospira Species Vaccine Potency Testing: State of the Science*. This workshop will be held at the USDA Center for Veterinary Biologics in Ames, Iowa in September 2012. Workshop information will be available at *http://iccvam.niehs.nih.gov/meetings/LeptoVaccWksp-2012/LeptoVaccWksp.htm*

Recent NICEATM-ICCVAM publications, test methods currently under review, and project status are presented in Tables 8, 9, and 10, respectively.

Table 8. NICEA TM-ICCVAM Publications in FY 2011

Date	Title
October 23, 2010	Safety assessment of allergic contact dermatitis hazards: an analysis supporting reduced animal use for the murine local lymph node assay (published in *Regulatory Toxicology and Pharmacology*)
February 20, 2011	Informational Brochure: "NICEATM-ICCVAM: Advancing Public Health and Animal Welfare"
February 20, 2011	Informational Brochure: "Nominations and Submissions to ICCVAM: A Guide for Test Method Developers and Sponsors"
May 18, 2011	Independent Scientific Peer Review Panel Report: Evaluation of the LUMI-CELL ER® (BG1Luc ER TA) Test Method. An evaluation of an *in vitro* estrogen receptor transcriptional activation test method for endocrine disruptor chemical screening
June 30, 2011	ICCVAM Test Method Evaluation Report: Usefulness and Limitations of the Murine Local Lymph Node Assay for Potency Categorization of Chemicals Causing Allergic Contact Dermatitis in Humans (NIH Publication No. 11-7709)
July 1, 2011	Using fewer animals to identify chemical eye hazards: revised criteria necessary to maintain equivalent hazard classification. (Published in *Regulatory Toxicology and Pharmacology*)

A list of all NICEATM-ICCVAM publications is available at http://ntp-apps.niehs.nih.gov/iccvampb/searchDoc.cfm. A list of articles published by NICEATM-ICCVAM in scientific journals is available at http://iccvam.niehs.nih.gov/articles/publications.htm.

Table 9. Nominations or Submissions to NICEA TH-ICCVAM in FY 2011

Test Method Nomination or Submission	Nominator or Sponsor/Activity Status
Submission of the BoTest™, BoTest™ Matrix, and BoCell™ Botulinum Neurotoxin Activity assays for interlaboratory validation studies by ICCVAM and NICEATM	BioSentinel Pharmaceuticals/ Final ICCVAM priority: high, in conjunction with a review of other botulinum toxin test methods
Nomination of an *in vitro* test method for assessing pyrogenicity of pharmaceuticals and other products for further evaluation in order to expand its applicability domain to non-endotoxin pyrogens	Biotest AG/ Final ICCVAM priority: high, with a recommendation of further discussion

Further information on the status of nominations and submissions is available at http://iccvam.niehs.nih.gov/SuppDocs/submission.htm.

Table 10. NICEA TH-ICCVAM Recomendations in FY 2011

Test Method	ICCVAM Recommendations/Agency Status
Routine Use of Topical Anesthetics, Systemic Analgesics, and Humane Endpoints for Ocular Safety Testing	Pain management procedures should always be used to avoid or minimize pain and distress when it is determined necessary to conduct the Draize rabbit eye test for regulatory safety assessments. These procedures include the routine use of topical anesthetics, systemic analgesics, and humane endpoints. Agency responses received FY 2011. http://iccvam.niehs.nih.gov/methods/ocutox/Transmit-2010.htm
Cytosensor Microphysiometer (CM) Ocular Test Method	CM can be used as a screening test to identify some types of substances that may cause permanent or severe eye injuries. CM can be used to determine if a limited range of substances will not cause sufficient injury to require hazard labeling for eye irritation. Agency responses received FY 2011. http://iccvam.niehs.nih.gov/methods/ocutox/Transmit-2010.htm
Proposed *in vitro* testing strategy that uses three *in vitro* test methods to assess the eye irritation potential of antimicrobial cleaning products	Further studies recommended. Agency responses received FY 2011. http://iccvam.niehs.nih.gov/methods/ocutox/Transmit-2010.htm
Proposed low volume rabbit eye test	Proposed low volume rabbit eye test should not be used for regulatory testing due to performance issues when compared to the current standard rabbit eye test. Agency responses received FY 2011. http://iccvam.niehs.nih.gov/methods/ocutox/Transmit-2010.htm
Nonradioactive versions of the murine Local Lymph Node Assay (LLNA) and expanded applicability domain for the LLNA	Two nonradioactive LLNA methods can be used to identify substances that may cause allergic skin reactions. The LLNA may be used to test most chemicals and products for their potential to cause allergic contact dermatitis. Agency responses received FY 2011. http://iccvam.niehs.nih.gov/methods/immunotox/llna.htm
Use of the BG1Luc ER TA test method for endocrine disruptor chemical screening	Draft recommendations made available January 24, 2011; reviewed by independent peer review panel March 29-30, 2011. http://iccvam.niehs.nih.gov/methods/endocrine/end_eval.htm#agencyresponses
Using Fewer Animals to Identify Chemical Eye Hazards: Revised Criteria Necessary to Maintain Equivalent Hazard Classification	Draft recommendations made available August 3, 2011 http://iccvam.niehs.nih.gov/ methods/ocutox/reducenum.htm
Report and Recommendations on the Usefulness and Limitations of the Murine Local Lymph Node Assay for Potency Categorization of Chemicals Causing Allergic Contact Dermatitis in Humans	ICCVAM test method recommendations to U.S. Federal agencies in June 2011 http://iccvam.niehs.nih.gov/methods/immunotox/LLNApotency.htm

NICEATM and ICCVAM prepared, commented on, or otherwise contributed to the development of new test guidelines, revisions of existing test guidelines, and guidance documents considered by the Organisation for Economic Co-operation and Development (OECD). An ICCVAM working group supported by NICEATM developed a guidance document for optimizing the value of data generated by *in vitro* ocular test methods, and an ICCVAM working group provided comments on draft Test Guideline 488 for transgenic rodent *in vivo* gene mutation assays. OECD adopted both of these in 2011. ICCVAM working groups developed or provided comments on test guidelines or guidance documents currently being considered by OECD in the areas of ocular safety testing, acute systemic toxicity, dermal corrosivity and irritation, and endocrine disruptor testing. Dr. Warren Casey, Deputy Director of NICEATM, is a member of the OECD Validation Management Group for Non-animal Testing (VMG-NA), and attended the VMG-NA meeting that took place in FY 2011.

Representatives from NICEATM and ICCVAM participated as liaison members at meetings of the scientific advisory committee of the European Center for the Validation of Alternative Methods that took place in October 2010 and February 2011.

Ongoing collaborations on validation studies between NICEATM-ICCVAM and their ICATM partners are summarized in Table 11.

Table 11. NICEATM Participation in International Validation Studies

Test Method	Type of Test	Lead Organization	NICEATM-ICCVAM Involvement
BG1Luc estrogen receptor transcriptional activation test method	Endocrine disruption	NICEATM	NICEATM coordinated an international validation study that included participating laboratories in the United States, European Union, and Japan.
CertiChem MCF-7 cell proliferation test method	Endocrine disruption	NICEATM	NICEATM coordinated an international validation study that included participating laboratories in the United States, Korea, and Japan.
EpiOcular™ (MatTek) and SkinEthic™ (L'oreal)	Ocular irritation	ECVAM	NICEATM and ICCVAM liaison members served on the validation management team and provided comments on study design, chemical selection, and test method performance criteria.
Human cryopreserved HepaRG and cryopreserved hepatocytes CYP induction test methods	Acute toxicity	ECVAM	NICEATM and ICCVAM liaison members served on the validation management team and provided comments on study design, chemical selection, test method protocols, and study reports.
In vitro tests for assessing skin sensitization potential of chemicals	Allergic contact dermatitis	ECVAM	NICEATM and ICCVAM liaison members served on the validation management team and provided comments on study design, chemical selection, and test method protocols.

Nomination, Selection, Evaluation, and Review

Nominations for Study

The NTP maintains a balanced research and testing program that provides data addressing a wide variety of issues important to public health. The NTP actively seeks to identify and select for study chemicals and other substances for which sufficient information is not available to adequately evaluate potential human health hazards. The NTP accomplishes this goal through a formal open nomination and selection process. Substances considered appropriate for study generally fall into two broad, yet overlapping, categories:

1. Substances judged to have high concern as a possible public health hazard based on the extent of human exposure and/or suspicion of toxicity.
2. Substances for which toxicological data gaps exist and additional studies would help assess potential human health risks, e.g., by extrapolating data across species or by evaluating dose-response relationships.

Input is also solicited regarding the nomination of studies that test hypotheses to enhance the predictive ability of future NTP studies, address mechanisms of toxicity, or fill significant gaps in the knowledge of the toxicity of classes of chemical, biological, or physical substances. Increased efforts continue to focus on:

- Improving the quality of the nominations of chemicals, environmental agents, or issues for study so that public health and regulatory needs are addressed.
- Broadening the base and diversity of nominating organizations and individuals.
- Increasing nominations for studying non-cancer toxicological endpoints.

The nomination process is open to the public. The NTP routinely solicits nominations at conferences and workshops; through the NTP newsletter, *Federal Register* notices, NTP website (*http://ntp.niehs.nih.gov*); and from interested individuals and groups. Also, NCI, FDA, NIOSH, and NIEHS routinely identify and forward nominations to the NTP. The NTP also reviews environmental occurrence and human exposure databases and the scientific literature to identify substances of potential interest.

Contact Information: Office of Nomination and Selection, Dr. Scott Masten, *masten@niehs.nih.gov*.

Nomination website: *http://ntp.niehs.nih.gov/go/nom*

Review and Selection Process

Reviewing and selecting substances and issues nominated for study is a multi-step process (see figure 5 and http://ntp.niehs.nih.gov/go/156) that addresses a broad range of concerns from participating representatives from the NIEHS, other Federal agencies, NTP BSC (see page 8), NTP Executive Committees' POCs (see page 12), and the public. This multi-step evaluative process provides the NTP with direction and guidance to ensure that its testing program addresses toxicological concerns in all areas of public health and that there is balance among the types of substances selected for study (e.g., industrial chemicals, consumer products, therapeutic agents). Figure 5 summarizes the study nomination review process, and Table 12 lists the nominations reviewed in FY 2011 by the NTP BSC.

Table 12. Research Concepts Reviewed by the BSC in FY2011

Substance [CASRN] Nominator	Nomination Rationale	Study Recommendations
N-Butylbenzene-sulfonamide [3622-84-2] NIEHS	– High production and use as a plasticizer in industrial and consumer product – Lack of adequate toxicological data – Suspicion of toxicity based on limited toxicity studies in rodents and the presence of structural features which suggestive of potential hazard	– *In vitro* toxicity studies to assess potential for endocrine activity and neurotoxicity – ADME and toxicokinetics studies – Subchronic toxicity studies including assessments of reproductive, developmental, immune and neurologic toxicity – Chronic toxicity and carcinogenicity studies
Drinking water disinfection by-products: HMG-CoA reductase inhibition and developmental toxicity; Interactive effects of antilipidemic agents and drinking water contaminants in producing developmental toxicity Private Individual	– Co-occurrence in drinking water of therapeutic drugs, environmental contaminants and disinfection by-products with known developmental and/or reproductive toxicities – Inadequate data to understand potential hazard of mixed exposures	– Mechanistic studies to explore individual and interactive effects of prenatal exposure to agents that modulate cholesterol and lipid pathways – A tiered program of mixture studies to include other drinking water contaminants that affect lipid pathways and produce developmental toxicities by similar but different modes of action
Hydroxyurea [127-07-1] Private Individual	– Long term safety concern when used as therapy for sickle cell anemia – NTP CERHR Expert Panel identified a critical data need for multi-generation experimental animal studies to assess the long-term effects of prenatal and postnatal exposures on postnatal development including developmental neurotoxicity, reproductive function, and carcinogenicity	– Multigenerational developmental and reproductive toxicity studies including neurotoxicity and immunotoxicity assessments – Carcinogenicity studies
Isoflavones in soy infant formula NIEHS	– Widespread exposure and concern for potential adverse effects on human development – Address certain critical data gaps and research needs identified in the NTP CERHR Expert Panel Report on Soy Infant Formula	– Studies to determine the feasibility of direct oral administration of soy infant formula to rodents (rats and/or mice) during the period of lactation – Reproductive development and fertility study in rodents with soy infant formula and a mixture of isoflavones at the ratio found in soy infant formula (oral administration to pups during period of lactation) – Uterotrophic assay to assess interactions among the individual isoflavones in soy infant formula – PK studies to assess metabolism of daidzin to equol during the period of lactation

Evaluation

In carrying out its mission, the NTP provides toxicological evaluations on substances of public health concern. The NTP can initiate bioassays to characterize potential carcinogenicity of only a small fraction of the thousands of substances for which there is little or no information. Many more substances are also studied to assess a variety of health effects not related to cancer, for example, reproductive and developmental toxicities, immunotoxicity, neurotoxicity, and genotoxicity. Other biological parameters are often assessed to understand susceptibility to toxic substances, such as the absorption, distribution, metabolism, and excretion (ADME) of substances biochemical markers that indicate exposures, and genetic changes in enzymes that metabolize drugs.

An NTP project review committee evaluates a study's project plan (e.g., design, methods, hypothesis, etc.). The toxicological evaluation for carcinogenicity generally involves repeated administration of a substance to groups of laboratory animals for up to two years. Many short-term, subchronic studies are designed to provide dose-setting information for longer, chronic exposure studies and to address specific gaps in the toxicology database. The adverse health effects from short- or long-term exposures to different dose levels of a substance are examined by observation, histopathology, and several toxicology endpoints, comparing them with control groups of animals not exposed to the substance. Many substances are also studied using protocols specifically designed to address how the substance causes particular toxic effects. The NTP has specific requirements that testing laboratories comply with the Animal Welfare Act of 1966 and adhere to the principles in the *Guide for the Care and Use of Laboratory Animals* (NRC, 2011). General information about the objectives and procedures of NTP study protocols is available on the NTP website (*http://ntp.niehs.nih.gov/go/type*). Current testing status can be found at *http://ntp.niehs.nih.gov:8080/index.html?col=010stat*.

The NTP carries out toxicology and carcinogenesis testing through two primary mechanisms: laboratory studies conducted in contract laboratories (Table 13) and studies conducted via IAGs at agencies (see page 68). In addition to toxicology research on compounds and exposures, the NTP supports developing new techniques and methods to improve the ability to identify and assess potential environmental toxicants and to develop and validate novel and alternative testing methods that will reduce, replace, or refine animal use. The NTP also supports developing improved statistical methods for designing and evaluating the results of toxicology studies.

Table 13. NTP Contracts That Supported NTP Testing Activities in FY 2011

Description	Contractor
ADME Chemical Disposition	Lovelace Biomedical
Archives and Specimen Repository	Experimental Pathology Labs
Bioinformatics Methylation Project	Murdock Research Institute
Cell Phone Radiation	IIT Research Institute
Chemistry Support	Midwest Research Institute
Chemistry Support	Research Triangle Institute
Chemistry Support	Battelle Memorial
Collaboration Between BPA Grantees and NTP	Professional and Scientific
Collaborative Work	Ramazzini Institute
Environmental and Therapeutic Agents	Virginia Commonwealth University
Evaluation of Test Agents in Laboratory Animals	Battelle Memorial
Evaluation of Test Agents via Inhalation Exposure	Battelle Memorial
Evaluate Toxicological Potential of Test Agents	Battelle Memorial
Evaluate Toxicological Potential of Test Agents	Southern Research

Description	Contractor
Genetic Toxicity in Bacteria and Rodents	Integrated Laboratory Systems
Investigative Research Support Contract	Integrated Laboratory Systems
NTP Computing and CEBS Support	Vistronix, Inc.
NTP Information Systems Support	SciMetrika
NTP Statistical and Computer Support	SRA International
NTP Technical Reports Preparation Service	Biotechnical Services
Pathology Support	Charles River
Pathology Support	Integrated Laboratory Systems
Provantis Software for NTP	INSTEM LSS
Quality Assessment/Pathology Support	Experimental Pathology Labs
Quality Assessment Reports for Audits and Inspections	Dynamac
Reproductive Assessments by Continuous Breeding	Research Triangle Institute
Sperm Count Vaginal Cytology Evaluation	Research Triangle Institute
Support/Consultation for Provantis Software	Labscience, Inc.
Production of B6C3F$_1$ Mice	Taconic Farms (2)

Review and Dissemination

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

- Technical Reports (TR). This series presents the results of long-term, generally 2-year, toxicology and carcinogenicity studies, typically conducted in rats and mice. Results of genetic toxicology, ADME, and toxicokinetic studies are often included in the reports. The draft reports are reviewed by *ad hoc* expert panels (*http://ntp.niehs.nih.gov/go/36144*).
- NTP Toxicity (TOX) Reports. TOX reports are prepared for studies where the substance exposure period is short term, generally up to 13 weeks. Draft reports are typically peer reviewed by letter review.
- Genetically Modified Models (GMM) Reports. NTP began the GMM report series in May 2003. This report series presents the results of substances evaluated by NTP in transgenic mouse strains (e.g., p53+/- heterozygous and Tg.AC mice).

Abstracts of the TR, TOX, and GMM series are posted on the NTP website, and PDF files of completed reports are available at the NTP website (*http://ntp.niehs.nih.gov/go/reports*) and are also catalogued in PubMed. Pathology data from the NTP rodent studies included in these reports undergo several reviews. The final review is by a pathology working group (PWG), a panel of experts convened by the NTP to review the microscopic evaluations. After the NTP PWG review, pathology tables and body weight and survival graphs for the completed studies are made publicly available (*http://ntp.niehs.nih.gov/go/peerreview*) until draft study reports are completed for peer review. When the draft reports are completed for peer-review, the abstracts are put on the NTP website with the list of reports. The pathology tables and the body weight and survival graphs are accessible at the end of the abstract text. Following peer review, the NTP finalizes the report, posts it on its website (*http://ntp.niehs.nih.gov/go/reports*) and provides electronic links to the final pathology tables and the curves for body weight and survival. Study summaries for other types of studies, such as immunotoxicity, developmental toxicity, and reproductive toxicity studies, are also available on the "NTP Study Reports" page on the website. New criteria for immunotoxicity, developmental, and reproductive studies were finalized in 2009 and NTP will publish these studies as technical reports following peer review. All types of NTP studies may also be published in peer-reviewed scientific journals.

Chronic Toxicity/Carcinogenicity Studies

In the area of general toxicology assessments, the scope and types of studies performed are dictated mainly by the data needs for the specific substance being studied. General toxicology studies usually fall into two categories: subchronic or pre-chronic studies, and 2-year chronic toxicology and carcinogenicity studies. Two-year studies in rodents are a method by which chemicals or physical agents are identified as having the potential to be hazardous to humans.

The chronic toxicology and carcinogenicity studies in conventional rodent models generally use both male and female rats (Fischer 344/N, Harlan Sprague Dawley, or Wistar Han) and mice (B6C3F1 hybrid), with three exposure levels plus untreated controls, in groups of 50 animals, for two years; other rodent models (e.g., genetically modified mice) are used as needed. If adequate data exist in the literature for one rodent species (rats or mice), then typically only the remaining species is studied. The NTP interfaces its testing with regulatory agencies and the private sector to minimize duplication of effort. Studies ongoing, initiated, completed, and published in FY 2011 are listed in Tables 14, 15, 16, and 17, respectively.

The NTP describes the results of individual experiments on a chemical agent and notes the strength of evidence for conclusions of each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than do control animals, do not necessarily mean that a chemical is not a carcinogen, because the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential to be hazardous to humans.

Table 14. Chronic Toxicity/Carcinogenicity Studies Ongoing During FY 2011

Study	CASRN	Species/Strain	Study Route	Length	Project Leader
Aging cohort study - 129/SvlmJ mouse		Mice: 129S1/SvlmJ	N/A	2 years	French
Aging cohort study - B6C3F1J mouse		Mice: B6C3F1 (Jackson)	N/A	2 years	French
Aging cohort study - C3H/HeJ mouse		Mice: C3H/HeJ	N/A	2 years	French
Aging cohort study - C57/BL/6J mouse		Mice: C57BL/6J (Jackson)	N/A	2 years	French
Aging cohort study - CAST/EiJ mouse		Mice: CAST/EiJ (M. m. castaneus)	N/A	2 years	French
Aging cohort study - NZO/HiLtJ mouse		Mice: NZO/HiLtJ	N/A	2 years	French
Aging Cohort Study - PWK/PhJ mouse		Mice: PWK/PhJ	N/A	2 years	French
Aging cohort study - WSB/EIJ mouse		Mice:WSB/EiJ (M. m. domesticus)	N/A	2 years	French
Aging cohort study - A/J mouse		Mice: A/J	N/A	2 years	French
Aging cohort study - NOD. B10Sn-H2(b)/J		Mice: NOD. B10Sn-H2(b)/J	N/A	2 years	French
Antimony trioxide	1309-64-4	Rats: Wistar Han Mice: B6C3F1/N	Inhalation	2 years	Stout
3′-Azido-3′-deoxythymidine (AZT)*	30516-87-1	Mice: C3B6F1-+/ TRP53<TM1BRD> (NCTR)	Gavage	9 months	Leakey
AZT/Drug Combinations Transplacental/Neonatal Study		Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Gavage	2 years	Beland
AZT/Drug Combinations Transplacental Carcinogenesis Study		Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	*In Utero*	2 years	Beland
2,3-Butanedione (diacetyl)	431-03-8	Rats: Wistar Han Mice: B6C3F1/N	Inhalation	2 years	Morgan

Study	CASRN	Species/Strain	Study Route	Length	Project Leader
Cobalt	7440-48-4	Rats: F344/NTac Mice: B6C3F1/N	Inhalation	2 years	Hooth
Dibutyl phthalate	84-74-2	Rats: Harlan SD Mice: B6C3F1/N	Feed	2 years	Blystone
N,N-Dimethyl-*p*-toluidine	99-97-8	Rats: F344/N Mice: B6C3F1/N	Gavage	2 years	Dunnick
Furan	110-00-9	Rats: F344 (NCTR)	Gavage	2 years	Beland
Ginkgo biloba extract	90045-36-6	Rats: F344/N Mice: B6C3F1/N	Gavage	2 years	Chan
Glycidamide	5694-00-8	Rats: F344 (NCTR) Mice:B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Water	2 years	Beland
Green tea extract		Rats: Wistar Han Mice: B6C3F1/N	Gavage	2 years	Chan
Indole-3-carbinol	700-06-1	Rats: Harlan SD Mice: B6C3F1/N	Gavage	2 years	Wyde
Metal working fluids (CIMSTAR 3800)		Rats: Wistar Han Mice: B6C3F1/N	Inhalation	2 years	Morgan
Metal working fluids (Trim VX)		Rats: Wistar Han Mice: B6C3F1/N	Inhalation	2 years	Morgan
Pentabromodiphenyl oxide (technical) (DE 71)	32534-81-9	Rats: Wistar Han Mice: B6C3F1/N	Gavage	2 years	Dunnick
Perfluorooctanoic acid (PFOA)	335-67-1	Rats: Harlan SD	Feed	2 years	Blystone
beta-Picoline	108-99-6	Rats: F344/N Mice: B6C3F1/N	Water	2 years	Wyde
Pyrogallol	87-66-1	Rats: F344/N Mice: B6C3F1/N	Topical Application	2 years	Mercado-Feliciano
Tetrabromobisphenol A	79-94-7	Rats: Wistar Han Mice B6C3F1/N	Gavage	2 years	Dunnick
Trimethylolpropane triacrylate	15625-89-5	Rats: F344/N Mice: B6C3F1/N	Topical Application	2 years	Surh / Chhabra
Tripelennamine hydrochloride	154-69-8	Rats: F344/N Mice: B6C3F1/N	Feed	11 months	Jackson
Vinylidene chloride	75-35-4	Rats: F344/N Mice: B6C3F1/N	Inhalation	2 years	Wyde
Water disinfection byproducts (bromodichloroacetic acid)	71133-14-7	Rats: F344/NTac Mice: B6C3F1/N	Water	2 years	Hooth
Zinc carbonate, basic	5263-02-5	Rats: Harlan SD	Feed	2 years	Wyde

** Indicates study conducted using genetically-modified model*

Table 15. Chronic Toxicity/Carcinogenicity Studies initiated during FY 2011

Study	CASRN	Species/Strain	Study Route	Length	Project Leader
p-Chloro-a,a,a-trifluorotoluene	98-56-6	Rats: Harlan SD Mice: B6C3F1/N	Inhalation	2 years	Stout
Di(2-ethylhexyl) phthalate	117-81-7	Rats: Harlan SD	Feed	2 years	Foster
2-Hydroxy-4-methoxybenzophenone	131-57-7	Rats: Harlan SD Mice: B6C3F1/N	Feed	2 years	Auerbach
Insertional mutagenesis – definitive vector study		Mice: C57BL/6	Intravenous	14 months	Germolec

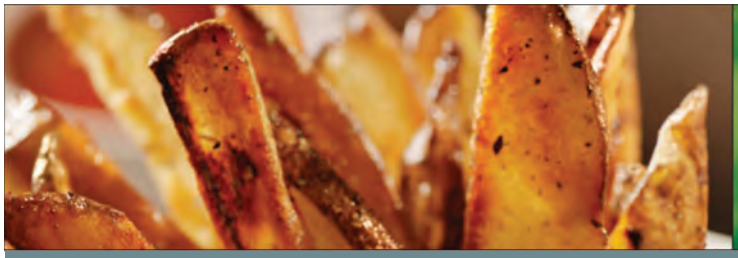
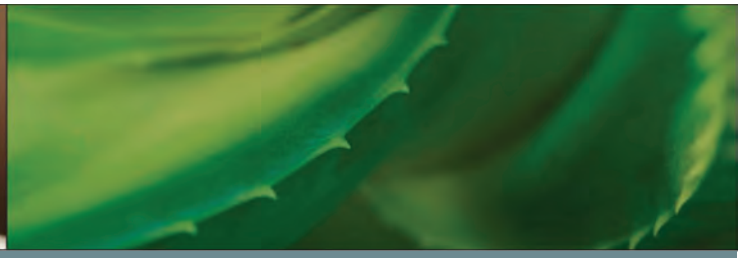
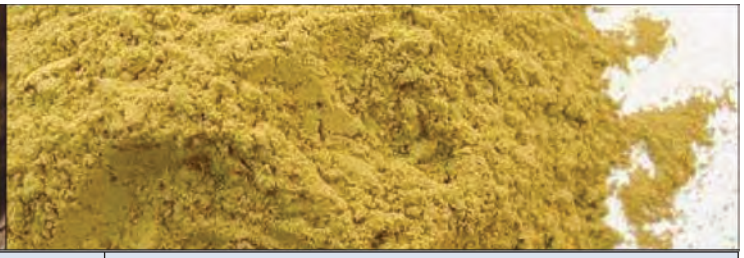



Table 16. Technical Reports Completed in FY 2011

Chemical/Exposure – Study Type	Technical Report Number/ [CASRN]	Use	Levels of Evidence of Carcinogenic Activity			
			Male Rats	Female Rats	Male Mice	Female Mice
Acrylamide Drinking water– toxicology and carcinogenesis	TR-575 [79-06-1]	Polyacrylamides and dye intermediate; flocculants; waste and water treatment; paper and pulp industry. Associated with tobacco: reported either as a natural component of tobacco, pyrolysis product (in tobacco smoke), or additive for one or more types of tobacco products.	Clear Evidence	Clear Evidence	Clear Evidence	Clear Evidence
Aloe vera whole leaf extract (native) Drinking water- toxicology and carcinogenesis	TR-577	Recognized as a therapeutic dermatologic agent; extracts incorporated in a variety of topical health care products and cosmetics.	Clear Evidence	Clear Evidence	No Evidence	No Evidence
AIDS Therapeutics: 3'-Azido-3'-Deoxythymidine (AZT), Lamivudine (3T3), Nevirapine (NVP), and Nelfinavir Mesylate (NFV) Transplacental – toxicology and carcinogenesis	TR-569 [30516-87-1] [134678-17-4] [129618-40-2] [159989-65-8]	Used in the treatment of AIDS.	N/A	N/A	No evidence of carcinogenic activity of AZT in male B6C3F1 mice and equivocal evidence of carcinogenic activity in female B6C3F1 mice No evidence of carcinogenic activity of mixtures of AZT and 3TC in male B6C3F1 mice and equivocal evidence of carcinogenic activity in female B6C3F1 mice Some evidence of carcinogenic activity of mixtures of AZT, 3TC, and NVP in male B6C3F1 mice and equivocal evidence of carcinogenic activity in female B6C3F1 mice No evidence of carcinogenic activity of mixtures of AZT, 3TC, and NFV in male or female B6C3F1 mice	
Kava kava extract Gavage – toxicology and carcinogenesis	TR-571 [9000-38-8]	Herbal supplement alternative to anti-anxiety drugs, used to help children with hyperactivity and as a skin-conditioning agent in cosmetics.	Equivocal Evidence	No Evidence	Clear Evidence	Some Evidence



Chemical/Exposure – Study Type	Technical Report Number/ [CASRN]	Use	Levels of Evidence of Carcinogenic Activity			
			Male Rats	Female Rats	Male Mice	Female Mice
Methyl *trans*-styryl ketone Feed and dermal – toxicology and carcinogenesis	TR-572 [1896-62-4]	Reactive carbonyl compound used in organic synthetic reactions such as intermediate in organic synthesis, electroplating chemical; pharmaceutical intermediate, biochemical reagent, agricultural chemical intermediate, proposed sunscreen intermediate. Used as flavoring and fragrance additive. Associated with tobacco: reported either as a natural component of tobacco, pyrolysis product (in tobacco smoke), or additive for one or more types of tobacco products.	No Evidence	No Evidence	No Evidence	No Evidence
All-*trans*-retinyl palmitate Simulated solar light and topical application study – photocarcinogenesis	TR-568 [79-81-2]	Retinol compound (Vitamin A) used in skin products.	Topical treatment of SKH-1 mice with the control cream resulted in earlier onsets of in-life skin lesions and higher incidences and multiplicities of in-life skin lesions, when compared to untreated controls, in the absence and presence of simulated solar light (SSL). The topical treatment of SKH-1 mice with control cream resulted in higher incidences and multiplicities of squamous cell neoplasms of the skin when compared to untreated controls in the absence and presence of SSL. Compared to the control cream, retinoic acid further enhanced the effects of SSL in SKH-1 mice based upon earlier onsets and increased multiplicities of in-life skin lesions. Compared to the control cream, retinyl palmitate further enhanced the effects of SSL in SKH-1 mice based upon earlier onsets and increased multiplicities of in-life skin lesions. Compared to the control cream, retinyl palmitate further enhanced the photocarcinogenic activity of SSL in SKH-1 mice based upon increased incidences and multiplicities of squamous cell neoplasms of the skin.			
*Senna (powdered) Feed – toxicology and carcinogenesis	GMM-15 [8013-11-4]	Herbal product, extract of senna fruit, used in laxative preparations.	N/A	N/A	No Evidence	No Evidence
alpha/beta Thujone mixture Gavage – toxicology and carcinogenesis	TR-570 [76231-76-0]	The essential oils derived from natural oil of cedar leaves in which thujone occurs are used in herbal medicine and as flavorings, fragrances, and rodent and mite repellents. Thujone is banned as a direct food additive in the U.S. Thujone-containing plant oils are used as flavoring substances in the alcoholic drink industry.	Some Evidence	No Evidence	No Evidence	No Evidence

**Indicates study conducted using genetically-modified model*

CLEAR Evidence | SOME Evidence | EQUIVOCAL Evidence | NO Evidence

Table 17. Technical Reports Published in FY 2011

Chemical /Exposure Study Type	Technical Report Number/ [CASRN]	Use	Levels of Evidence of Carcinogenic Activity			
			Male Rats	Female Rats	Male Mice	Female Mice
1-Bromopropane Inhalation – toxicology and carcinogenesis	TR-564 [106-94-5]	Laboratory reagent; replacement chemical for chlorinated solvents; metal cleaning and degreasing; and adhesives.	Some Evidence	Clear Evidence	No Evidence	Clear Evidence
bis(2-Chloroethoxy)methane Topical – toxicology and carcinogenesis	TR-536 [111-91-1]	Used as a starting compound to produce polysulfide elastomers and as a solvent.	No Evidence	No Evidence	No Evidence	No Evidence
Ginseng Gavage – toxicology and carcinogenesis	TR-567 [50647-08-0]	Used as herbal remedy, dietary supplement, food additive, and in cosmetics.	No Evidence	No Evidence	No Evidence	No Evidence
Milk thistle extract Feed – toxicology and carcinogenesis	TR-565 [84604-20-6]	Used as an herbal supplement and medicinally as a hepatoprotectant. Used for treatment of chronic inflammatory liver disorders.	No Evidence	No Evidence	No Evidence	No Evidence
β-Myrcene Gavage – toxicology and carcinogenesis	TR-557 [123-35-3]	Intermediate in the commercial production of terpene alcohols that serve as intermediates for the production of large-volume aroma and flavor chemicals. Used as scenting agents in cosmetics, soaps, and detergents; as a peripheral analgesic substance; and as the active ingredient in lemongrass tea. Identified in over 200 plants and detected in emissions of plywood veneer dryers.	Clear Evidence	Equivocal Evidence	Clear Evidence	Equivocal Evidence
2,3',4,4',5-Pentachlorobiphenyl (PCB 118) Gavage – toxicology and carcinogenesis	TR-559 [31508-00-6]	PCBs and their mixtures including PCB 118 were produced commercially before 1977 for the electric industry as dielectric insulating fluids for transformers and capacitors. One of 2 dioxin-like chemicals being tested to determine if the toxic equivalency factors (TEFs) for these chemicals would be predictive of rodent carcinogenicity.	N/A	Clear Evidence	N/A	N/A

CLEAR Evidence SOME Evidence EQUIVOCAL Evidence NO Evidence

Chemical /Exposure Study Type	Technical Report Number/ [CASRN]	Use	Levels of Evidence of Carcinogenic Activity			
			Male Rats	Female Rats	Male Mice	Female Mice
Pulegone Gavage – toxicology and carcinogenesis	TR-563 [89-82-7]	Major constituent of oil of pennyroyal. Used for flavoring foods and drinks, as a fragrance agent, and as an herbal medicine.	No Evidence	Clear Evidence	Clear Evidence	Clear Evidence
3,3′,4,4′-Tetrachloroazobenzene (TCAB) Gavage – toxicology and carcinogenesis	TR-558 [14047-09-7]	Impurity in dichloroaniline (DCA) and herbicides derived from DCA. Formed as an unwanted byproduct in the manufacture of 3,4-DCA and its herbicidal derivatives Propanil®, Linuron®, and Diuron®. Environmental contamination by 3,3′,4,4′-TCAB occurs from the degradation of chloranilide herbicides and the photolysis and biolysis of 3,4-DCA.	Clear Evidence	Clear Evidence	Clear Evidence	Clear Evidence
Tetralin Inhalation – toxicology and carcinogenesis	TR-561 [119-64-2]	Solvents in paints, waxes, and polishes derived from naphthalene. Insecticide.	Some Evidence	Some Evidence	No Evidence	Equivocal Evidence

Only summaries of carcinogenic activity conclusions are included in the tables. Complete information is available in the full study reports found at http://ntp.niehs.nih.gov/. The NTP anticipates that seven Technical Reports will undergo peer review in FY 2012, as shown in Table 18.

Table 18. Technical Reports Expected to Undergo Peer Review in FY 2012

Chemical	Technical Report Number/ [CASRN]	Use
Ginkgo biloba extract	TR-578 [90045-36-6]	Herbal supplement.
β-Picolene	TR-580 [108-99-6]	Used as a solvent in the synthesis of pharmaceuticals, resins, dyes, and rubber accelerators and as a lab reagent. Also used as an intermediate in the manufacture of insecticides, waterproofing agents, niacin and niacinamide.
Pyrogallol	TR-574 [87-66-1]	Naturally occurring in food. Used as a modifier in oxidation dyes including hair dyes and colors; as developer in photography; as a mordant for dying wool; as a reagent for antimony and bismuth; as a reducer for gold, silver and mercury salts; for process engraving; for making colloidal solutions of metals; and in the manufacture of pharmaceuticals and pesticides.
N,N-Dimethyl-*p*-toluidine	TR-579 [99-97-8]	Used as a polymerization accelerator for the manufacture of bone cements and dental materials. Found in industrial glues and artificial fingernail preparations. Intermediate in dye and pesticide synthesis.
AZT*	GMM-14 [30516-87-1]	Pyrimidine nucleoside analog with antiviral activity used in the treatment of AIDS.
Mixtures AZT, 3TC, and NVP*	GMM-14 [30516-87-1] [134678-17-4] [129618-40-2]	Special combination to study AIDS therapeutics.
Trimethylolpropane triacrylate	[15625-89-5]	Used in the production of ultraviolet-curable inks, electron beam irradiation-curable coatings, and polymers and resins; as a component of photopolymer and flexographic printing plates and photoresists; and as an ingredient in acrylic glues and anaerobic sealants. Also used in paper and wood impregnates, wire and cable extrusion, polymer-impregnated concrete, and polymer concrete structural composites.

**Indicates study conducted using genetically-modified model*

General Toxicology Studies

The NTP performs prechronic toxicity studies to address specific deficiencies in toxicology databases for chemicals, such as an understanding of toxicity with repeated exposures; to identify target organs for more in depth systems toxicology evaluations and mechanistic studies; and to provide dose-setting information for possible chronic studies.

Although designs are flexible, prechronic studies usually involve exposures of rats and mice of both sexes to substances for periods of 14-90 days. Assessments almost always include tissue histopathology, clinical pathology, and sperm motility or measurements of estrous cycle length. The frequency of malformed red blood cells (micronucleated erythrocytes, a measure of chromosomal damage) is determined as an *in vivo* measure of genotoxic potential.

The study protocol may include more detailed or focused studies when findings published in the existing scientific literature or identified in initial NTP studies suggest a target organ or system. The study protocol may include separate studies of reproductive, genetic, or immunological toxicity based on the outcome of the toxicity screens and may use additional endpoints to improve our understanding of the mechanisms and modes of action of a chemical.

In some cases, the NTP uses alternative models, including genetically modified mouse models and non-mammalian models, for prechronic studies. Such studies are presented in the section "Genetic and Alternative Test Systems" (page 62). Tables 19-22 list the toxicity studies that were ongoing, initiated, completed, and published respectively, during FY 2011. Information is available at *http://ntp.niehs.nih.gov/go/reports*. Table 23 lists toxicity studies planned for FY 2012.

Table 19. Ongoing Toxicity Studies during FY 2011

Study	CASRN	Species/Strain	Study Route	Length	Project Leader
3'-Azido-3'-deoxythymidine (AZT)*	30516-87-1	Mice: P53 +/- (FVB/N)	Gavage	9 months	Leakey
BPA	80-05-7	Rats: SD (NCTR)	Gavage	13 weeks	Delclos
Cell phone radiation (CDMA)		Rats: Harlan SD Mice: B6C3F1	Whole-body exposure	5 days 49 days 28 day	Wyde
Cell phone radiation (GSM)		Rats: Harlan SD Mice: B6C3F1	Whole-body exposure	5 days 49 days 28 day	Wyde
bis(2-Chloroethoxy)methane	111-91-1	Mice: C57BL/6J (Jackson) Mice: C3H/HeJ Mice: B6C3F1 (Jackson)	Gavage	3 days, 10 days	Dunnick
Diet evaluation study		Mice: CD-1 Reg.[Crl:CD1(ICR)],	Feed	13 weeks	Delclos
Ephedrine + caffeine combination	299-42-3 58-08-2	Mice: C57BL/6J (Jackson) Mice: C3H/HeJ Mice: B6C3F1 (Jackson)	Gavage	3 days, 10 days	Dunnick
Glucosamine hydrochloride + chondroitin sulfate	66-84-2 9007-28-7	Rats: Zucker - Obese (HsdHlr: ZUCKER-Leprfa) Rats: Zucker - Lean (HsdHlr: ZUCKER-Lepr+)	Gavage	13 weeks	Leakey
1020 Long multiwalled CNTs		Rats: Harlan SD Mice: B6C3F1/N	Inhalation	30 days	Walker
Melamine + cyanuric acid combination	108-78-1 108-80-5	Rats: F344	Gavage	13 weeks	Gamboa de Costa
Nanoscale Ag	7440-22-4	Rats: SD	Gavage	13 weeks	Walker

Study	CASRN	Species/Strain	Study Route	Length	Project Leader
Serotype 2 Adeno-associated Viral Vector hAQP1 (rAAV2hAQP1)		Mice: BALB/c	Intraductal cannulation	13 weeks	Germolec
Triclosan	3380-34-5	Mice: B6C3F1/N	Dermal	13 weeks	Fang
Usnea lichen		Rats: F344 Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Feed	2 weeks 13 weeks	Leakey
(+)-Usnic Acid	7562-61-0	Rats: F344 Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Feed	2 weeks 13 weeks	Leakey
Vincamine	1617-90-9	Rats: Harlan SD Mice: B6C3F1/N	Gavage	2 weeks	Chan

** Indicates study conducted using genetically-modified model*

Table 20. Toxicity Studies Initiated during FY 2011

Study	CASRN	Species/Strain	Study Route	Length	Project Leader
2-Aminopyridine	504-29-0	Rats: F344/NTac Mice: B6C3F1	Gavage	14 days	Dunnick
3-Aminopyridine	462-08-8	Rats: F344/NTac Mice: B6C3F1	Gavage	14 days	Dunnick
4-Aminopyridine	504-24-5	Rats: F344/NTac Mice: B6C3F1	Gavage	14 days	Dunnick
Comparison study of aminopyridines/troponin levels	504-29-0 462-08-8 504-24-5	Rats: F344/NTac Mice: B6C3F1	Gavage	1 and 4 hours	Dunnick
Cell phone radiation (CDMA)		Rats: Harlan SD Mice: B6C3F1	Whole-body exposure	5 days 49 days 28 day	Wyde
Cell phone radiation (GSM)		Rats: Harlan SD Mice: B6C3F1	Whole-body exposure	5 days 49 days 28 day	Wyde
Diet evaluation study		Mice: CD-1 Reg.[Crl:CD1(ICR)]	Feed	13 weeks	Delclos
1020 Long multiwalled CNTs		Rats: Harlan SD Mice: B6C3F1/N	Inhalation	30 days	Walker
Melamine + cyanuric acid combination	108-78-1 108-80-5	Rats: F344	Gavage	13 weeks	Gamboa de Costa
Microcystin-LA (TGMX)	96180-79-9	Rats: Wistar Han	Intravenous	1/2/6/24 hours	Walker
Microcystin mixture (TGMX)	96180-79-9 101043-37-2	Rats: Wistar Han	Intravenous	1/2/6/24 hours	Walker
Nanoscale Ag	7440-22-4	Rats: SD	Gavage	13 weeks	Walker
Pyridine	110-86-1	Mice: B6C3F1	Gavage	14 days	Dunnick
Serotype 2 adeno-associated viral vector hAQP1 (rAAV2hAQP1)		Mice: BALB/c	Intraductal cannulation	13 weeks	Germolec
Triclosan	3380-34-5	Mice: B6C3F1/N	Dermal	13 weeks	Fang
Vincamine	1617-90-9	Rats: Harlan SD Mice: B6C3F1	Gavage	2 weeks	Chan

Table 21. Toxicity Studies Completed during FY 2011					
Study	**CASRN**	**Species/Strain**	**Study Route**	**Length**	**Project Leader**
3-Aminopyridine	462-08-8	Rats: F344/NTac Mice: B6C3F1	Gavage	14 days	Dunnick
2-Aminopyridine	504-29-0	Rats: F344/NTac Mice: B6C3F1	Gavage	14 days	Dunnick
4-Aminopyridine	504-24-5	Rats: F344/NTac Mice: B6C3F1	Gavage	14 days	Dunnick
Comparison study of aminopyridines/troponin levels	462-08-8 504-29-0 504-24-5	Rats: F344/NTac Mice: B6C3F1	Gavage	1 and 4 hours	Dunnick
Black cohosh	84776-26-1	Mice: B6C3F1	Gavage	13 weeks	Mercado-Feliciano
Insertional mutagenesis (radiation levels)		Mice: B6.SJL-Ptprc[a] Pepc[b]/BoyJ	Whole-body Exposure	8 weeks	Germolec
Microcystin-LA (TGMX)	96180-79-9	Rats: Wistar Han	Intravenous	1/2/6/24 hours	Walker
Microcystin-LR (TGMX)	101043-37-2	Rats: Wistar Han	Intravenous	1/2/6/24 hours	Walker
Microcystin mixture (TGMX)	96180-79-9 101043-37-2	Rats: Wistar Han	Intravenous	1/2/6/24 hours	Walker
2,3-Pentanedione	600-14-6	Rats: Wistar Han Mice: B6C3F1/N	Inhalation	13 weeks	Morgan
Pregnancy rate comparison study		Rats: Harlan SD (Indianapolis Facility) Rats: Harlan SD (Dublin Facility)	N/A	16 weeks	Vallant
Pyridine	110-86-1	Mice: B6C3F1	Gavage	14 days	Dunnick
QT drugs (bepridil hydrochloride)	74764-40-2	Dog: Beagles	Oral (capsule)	1 day	Hooth
QT drugs (diltiazem hydrochloride)	33286-22-5	Dog: Beagles	Oral (capsule)	1 day	Hooth
QT drugs (Loratadine)	79794-75-5	Dog: Beagles	Oral (capsule)	1 day	Hooth
QT drugs (Lovastatin)	75330-75-5	Dog: Beagles	Oral (capsule)	1 day	Hooth
QT drugs (sotalol hydrochloride)	959-24-0	Dog: Beagles	Oral (capsule)	1 day	Hooth
QT drugs (terfenadine)	50679-08-8	Dog: Beagles	Oral (capsule)	1 day	Hooth
Sodium tungstate, dihydrate	10213-10-2	Rats: Harlan SD Mice: B6C3F1/N	Water	13 weeks	Hooth
Tris(2-chloroisopropyl)phosphate	13674-84-5	Rats: Harlan SD Mice: B6C3F1/N	Feed	13 weeks	Stout

Table 22. Toxicity Studies Published during FY 2011

Chemical/Exposure – Study Type	Toxicity Report Number/ CASRN	Use	Evidence of Carcinogenic Activity
Estragole Gavage – Toxicity Studies	TOX-82 140-67-0	Used in perfumes and as flavor in foods and liquors; as an antimicrobial agent against acid-tolerant food microflora. Found naturally in tarragon, basil, and fennel.	Under the conditions of these 3-month studies, estragole showed carcinogenic activity based on the occurrence of two cholangiocarcinomas and one hepatocellular adenoma in the liver of three of 10 male F344/N rats in the high dose group. Because rats and mice were exposed for only 3 months, these studies do not access the full carcinogenic potential of estragole. Nonneoplastic effects were observed in the liver, glandular stomach, nose, kidney, and salivary gland of male and female rats and in the testes, epididymides, and pituitary gland of male rats. Nonneoplastic effects were also observed in the liver and nose of male and female mice and in the stomach of female mice.
2,4-Decadienal Gavage – Toxicity Studies	TOX-76 25152-84-5	Synthetic flavoring and fragrance material; also evaluated as a corrosion inhibitor for steel in oil field operations.	2,4-decadienal administration caused decreased body weights and increased incidences of forestomach lesions in the 3-month studies in rats and mice. In addition, treatment-related lesions of the olfactory epithelium were observed in male rats and male and female mice. The no-observed-adverse-effect level was determined to be 100 mg/kg in rats and mice. 2,4-Decadienal was not mutagenic *in vitro* or *in vivo*.

Table 23. Toxicity Studies Planned for FY 2012*

Study	CASRN	Species/Strain	Study Route	Length	Project Leader
(4-Chloro-6-(2,3-xylidino)-2-pyrimidinylthio) acetic acid (WY-14643)	50892-23-4	Rats: Harlan SD	Gavage	28 days	Blystone
Diet evaluation study		Mice: CD-1 Reg.[Crl:CD1(ICR)]	Feed	13 weeks	Delclos
Perfluorohexane-1-sulphonic acid - potassium salt	3871-99-6	Rats: Harlan SD	Gavage	28 days	Blystone
1-Perfluorobutanesulfonic acid	375-73-5	Rats: Harlan SD	Gavage	28 days	Blystone
Perfluorodecanoic acid (PFDA)	335-76-2	Rats: Harlan SD	Gavage	28 days	Blystone
Perfluorohexanoic acid (PFHXA)	307-24-4	Rats: Harlan SD	Gavage	28 days	Blystone
Perfluorononanoic acid (PFNA)	375-95-1	Rats: Harlan SD	Gavage	28 days	Blystone
Perfluorooctane Sulfonate, (PFOS)	1763-23-1	Rats: Harlan SD	Gavage	28 days	Blystone
Perfluorooctanoic acid (PFOA)	335-67-1	Rats: Harlan SD	Gavage	28 days	Blystone

** Known test articles as of 10/1/2011. Others may be scheduled as protocols are finalized.*

Mutagenesis and Genetic Toxicity

Genetic toxicity test results are used to help interpret toxicity, carcinogenicity, or other *in vivo* test results and to provide a database for use in structure-activity analyses. Analysis of the early, multi-test database showed that positive results for a chemical in the *Salmonella* gene mutation assay were sometimes correlated with carcinogenicity in several species/sexes of rodents and at several tissue sites. Subsequently, studies of the correlation between mutagenicity test data and rodent carcinogenicity showed a strong association between clearly positive results in long-term mouse peripheral blood micronucleus tests and rodent carcinogenicity. The importance of genetic toxicity test data in assessing exposure hazard for NTP chemicals is underscored by the fact that most organic chemicals (other than hormones) identified as human carcinogens by the International Agency for Research on Cancer (IARC) are genotoxic, and the vast majority of them are detected by both the *Salmonella* assay and rodent micronucleus tests. Additional assays may be conducted with certain chemicals to gain further insight into the types of DNA and chromosomal damage induced by a chemical. Gene mutations and DNA damage are examined in tumors from NTP studies on a case-by-case basis; cytogenetic effects, measured as the induction of micronuclei, are generally examined in bone marrow cells or in peripheral erythrocytes. Substances tested for genetic toxicity during FY 2011 are listed in Table 24. Information is available at *http://ntp.niehs.nih.gov/go/reports*.

Table 24. Ongoing and Completed Genetic Toxicity Studies during FY 2011

Chemical	[CASRN]	Testing Battery
3'-Azido-3'-deoxythymidine (AZT)	30516-87-1	*Salmonella*
Black cohosh	84776-26-1	Micronucleus
Chlorhexidine	55-56-1	*Salmonella*
N-Butylbenzenesulfonamide	3622-84-2	*Salmonella*
2,6-Diethylaniline (2,6-DEA)	579-66-8	*Salmonella*
N,N-Dimethyl-*p*-toluidine	99-97-8	Micronucleus
2',2'''-Dithiobisbenzanilide	135-57-9	*Salmonella*
2-Ethylaniline	578-54-1	*Salmonella*
3-Ethylaniline	587-02-0	*Salmonella*
4-Ethylaniline	589-16-2	*Salmonella*
2-metyl-6-ethylanline (2M6EA)	24549-06-2	*Salmonella*
Nelfinavir	159989-64-7	*Salmonella*
Nevirapine	129618-40-2	*Salmonella*
2-nitro-1-propanol	2902-96-7	*Salmonella*
2-Nitro-2-ethyl-1,3-propanediol	597-09-1	*Salmonella*
2-Nitro-2-methyl-1,3-propanediol	77-49-6	*Salmonella*
Styrene-acrylonitrile trimer		Micronucleus
m-Toluidine	108-44-1	*Salmonella*
p-Toluidine	106-49-0	*Salmonella*
2,3-Pentanedione	600-14-6	Micronucleus
3TC (AIDS initiative)	134678-17-4	*Salmonella*
Valerian (various)		*Salmonella*
Zinc carbonate, basic	5263-02-5	Micronucleus

Organ System Toxicity

Nervous System, Developmental, and Reproductive Toxicity

Behavioral and neurological alterations in response to deleterious environmental agents often represent the earliest evidence of toxicity. These testing batteries examine the sensory, motor, autonomic, and peripheral nervous systems. The Functional Observational Battery employs observational screening, while the NIEHS test battery uses automated test systems to evaluate the various nervous system components.

As part of its charge to test chemicals of concern for potential toxicity, the NTP evaluates developmental and reproductive toxicity primarily by using teratology and Reproductive Assessment by Continuous Breeding (RACB) study designs (see *http://ntp.niehs.nih.gov/go/33668*). The RACB study design was developed by the NTP to identify potential hazards from toxic effects on male and/or female reproduction, to characterize that toxicity, and to define the dose-response relationships for each compound. The study design has evolved over the years: initially the studies mainly used mice as the test species; now, they use rats almost exclusively. As our knowledge has improved and use of sensitive endpoints has increased, these advances have been incorporated into revisions of the study design. Table 25 lists completed and ongoing nervous system, developmental, and reproductive studies during FY 2011.

Table 25. Ongoing and Completed Organ Systems Toxicity Studies During FY 2011

Chemical	CASRN	Species/Strain	Route	Project Leader	Testing Battery
Acrylamide	79-06-1	Rats: F344	Gavage	Beland	Neurotox assessment
Bitter orange		Rats: SD	Gavage	Hansen	Developmental
Bitter orange with caffeine		Rats: SD	Gavage	Hansen	Developmental
Black cohosh	84776-26-1	Rats: Harlan SD	Gavage	Mercado-Feliciano	RACB – range-finding
Black cohosh	84776-26-1	Rats: Harlan SD	Gavage	Mercado-Feliciano	Continuous breeding
tris(2-Chloroisopropyl)phosphate	13674-84-5	Rats: Harlan SD	Gavage	Stout	Prenatal developmental toxicity
Endocrine disruptor (Nonylphenol)	84852-15-3	Rats: SD	Feed	Newbold, Delclos	Multigeneration
2-Hydroxy-4-methoxybenzophenone	131-57-7	Rats: Harlan SD	Feed	Hansen	Total reproductive capacity
4-Methylimidazole	822-36-6	Rats: Harlan SD	Feed	Bishop	RACB – range-finding
p-Synephrine	94-07-5	Rats: SD	Gavage	Hansen	Developmental
p-Synephrine and caffeine	58-08-2 94-07-5	Rats: SD	Gavage	Hansen	Developmental
3,3',4,4'-Tetrachloroazobenzene	14047-09-7	Rats: Crl:CD SD	Gavage	Hooth	Developmental – pre-implantation
3,3',4,4'-Tetrachloroazobenzene	14047-09-7	Rats: Crl:CD SD	Gavage	Hooth	Postnatal developmental toxicity

The NTP's Modified One-generation Reproduction Study (see http://ntp.niehs.nih.gov/go/MG) design evolved from (1) the NTP changing its default exposure paradigm in rat cancer bioassays to include treatment exposure during pregnancy and early life, (2) the increased knowledge of critical windows of exposure, which indicates the need for a larger focus on evaluating the potential for postnatal adverse effects, and (3) the updates to standard study designs with more functional endpoints to assess how agents affect the reproductive and endocrine status of animals. The classical study used to evaluate reproductive toxicity is the multigenerational reproduction experimental design. The NTP has modified this classical study design to better utilize the animals produced and to reduce animal use by improved experimental design and statistical power. Table 26 lists planned or ongoing Modified One-generation studies. Table 27 lists RACB studies planned for FY 2012.

Table 26. Planned or Ongoing Modified One-generation Studies

Chemical	CASRN	Species/Strain	Study Route	Planned Cohorts	Project Leader
Bisphenol AF	1478-61-1	Rats: Harlan SD	Feed	Dose range-finding Maternal transfer Developmental toxicity Fertility assessment Neurotoxicity assessment	Mercado-Felliciano
N-Butylbenznensulfonamide	3622-84-2	Rats: Harlan SD	Feed	Dose range-finding Fertility assessment Developmental toxicity Maternal transfer Neurotoxicity assessment Subchronic toxicity	Rider
Dong quai *(Angelica sinesis)* root extract	299184-76-2	Rats: Harlan SD	Gavage	Dose range-finding Fertility assessment Developmental toxicity Neurotoxicity assessment	McIntyre
2-Ethylhexyl *p*-methoxycinnamate	5466-77-3	Rats: Harlan SD	Feed	Dose range-finding	McIntyre
Hydroquinone	123-31-9	Rats: Harlan SD	Gavage	Dose range-finding Fertility assessment Developmental toxicity Neurotoxicity assessment	DeVito
2-Hydroxy-4-methoxybenzophenone	131-57-7	Rats: Harlan SD	Feed	Dose range-finding Fertility assessment Developmental toxicity Neurotoxicity assessment	McIntyre
Hydroxyurea	127-07-1	Rats: Harlan SD	Gavage	Dose range-finding Fertility assessment Subchronic toxicity Neurotoxicity assessment Developmental toxicity	McIntyre
Isopropylphenyl phosphate	68937-41-7	Rats: Harlan SD	Feed	Dose range-finding Neurotoxicity assessment	Behl
Triphenyl phosphate	115-86-6	Rats: Harlan SD	Feed	Dose range-finding Neurotoxicity assessment	Behl

Table 27. RACB Studies Planned for FY 2012 *

Chemical	CASRN	Species/Strain	Route	Testing Battery
n-Butyl glycidyl ether	2426-08-6	Rats: Harlan SD	TBD	RACB – range-finding
n-Butyl glycidyl ether	2426-08-6	Rats: Harlan SD	TBD	RACB
p-Chloro-α,α,α-trifluorotoluene	98-56-6	Rats: Harlan SD	Inhalation	RACB
Sodium tungstate, dihydrate	10213-10-2	Rats: Harlan SD	TBD	RACB

** Known test articles as of 10/1/2011. Others may be scheduled as protocols are finalized.*

Immunotoxicity

NTP immunotoxicity studies address adverse effects on the immune system that may result from exposure to environmental chemicals, biological materials, or therapeutic agents. The identification of substances that have potential to cause injury to the immune system is of considerable public health significance as alterations in immune function can lead to increased incidence of hypersensitivity disorders, autoimmune or infectious disease, or neoplasia. Immunotoxicity caused by exposure to chemicals can be divided into two broad research areas: (1) studies of altered hematopoietic (blood cell development) or other immunologic events associated with exposure of humans and animals to chemicals and (2) studies of immune-mediated hypersensitivity (allergy and autoimmunity) resulting from exposure to environmental chemicals or therapeutics. In the former case, the immune system acts as a passive target (nonspecific) for the foreign substance, and the result may be an increased incidence or severity of infectious disease or neoplasia because of the inability to respond adequately to the invading agent. In hypersensitivity (i.e., allergy), the immune system responds to small molecular weight compounds that bind to host tissue, recognizing the complex as foreign antigen. This immune response to the chemical-host tissue complex may lead to diseases, such as respiratory tract allergies (e.g., asthma, rhinitis) or allergic contact (skin) dermatitis. Autoimmunity, another form of immune-mediated disease, is characterized by an immune response against constituents of the body's own tissues (autoantigens). Table 28 lists ongoing and completed immunotoxicity studies during FY 2011.

Table 28. Ongoing and Complete Immunotoxicity Studies During FY 2011

Chemical	CASRN	Species/Strain	Route	Project Leader	Testing Battery
Abrasive blasting agents (blasting sand)		Rats: Harlan SD	Inhalation	Roycroft	Immunosuppression
Abrasive, blasting agents (specular hematite)		Rats: Harlan SD	Inhalation	Roycroft	Immunosuppression
Autumn sunset true color concentrate		Mice: CBA/ Ca Jackson	Subcutaneous injection	Howard	Hypersensitivity
3'-Azido-3'-deoxythymidine (AZT)	30516-87-1	Mice: B6C3F1	Gavage	Germolec	Immunosuppression – range-finding Developmental
Black cohosh	84776-26-1	Mice: B6C3F1	Gavage	Mercado-Feliciano	Immunosuppression
2,3-Butanedione (diacetyl)	431-03-8	Mice: BALB/c	Topical application	Morgan	Hypersensitivity
2,3-Butanedione (diacetyl)	431-03-8	Mice: BALB/c	Inhalation	Morgan	Immunosuppression-range-finding
o-Cresol	95-48-7	Mice: BALB/c	Topical application	Chhabra	Hypersensitivity
Dibenz(a,h)anthracene	53-70-3	Mice: B6C3F1	Gavage	Germolec	Immunosuppression-range-finding - full protocol Developmental
2,3-Dibromo-7,8-dichlorodibenzo-*p*-dioxin	50585-40-5	Mice: B6C3F1	Gavage	DeVito	Immunosuppression
1,3-Dichloropropene (Telone II)	542-75-6	Mice: B6C3F1	Water	Germolec	Immunosuppression-full protocol
Dimethylamine borane	74-94-2	Mice: BALB/c	Topical application	Germolec	Hypersensitivity
Double dark fudge true color concentrate		Mice: CBA/ Ca Jackson	Subcutaneous injection	Howard	Hypersensitivity
Double fudge concentrate		Mice: CBA/ Ca Jackson	Subcutaneous injection	Howard	Hypersensitivity

Chemical	CASRN	Species/Strain	Route	Project Leader	Testing Battery
Echinacea purpurea, extract	90028-20-9	Mice: B6C3F1	Gavage	Germolec	Immunosuppression – full protocol
Elmiron (sodium pentosanpolysulfate)	37319-17-8	Mice: B6C3F1	Gavage	Germolec	Immunosuppression-range-finding – full protocol
Endocrine disruptor (Nonylphenol)	84852-15-3	Rats: SD	Feed	Newbold, Delclos	Multigeneration
2-Ethylhexyl *p*-methoxycinnamate	5466-77-3	Mice: BALB/c	Topical application	McIntyre	Hypersensitivity
Genistein	446-72-0	Mice: NOD/MrKTac	Gavage	Germolec	Autoimmunity
Gum guggul extract		Mice: B6C3F1	Gavage	Thakur	Immunosuppression – range-finding
Ionic liquid (1-butyl-1-methylpyrrolidinium chloride)	479500-35-1	Mice: BALB/c	Topical application	Hooth	Hypersensitivity
Ionic liquid (*n*-butylpyridinium chloride)	1124-64-7	Mice: BALB/c	Topical application	Hooth	Hypersensitivity
Lovastatin	75330-75-5	Mice: B6C3F1	Gavage	Germolec	Immunosuppression – range-finding
2-Methoxy-4-nitroaniline	97-52-9	Mice: BALB/c	Dermal	Surh	Hypersensitivity
4-Methylimidazole	822-36-6	Rats: Harlan SD	Feed	Bishop	Range-finding
Monoclonal antibody protein therapeutics (CD-4)		Mice: B6C3F1	Intraperitoneal injection	Germolec	Immunosuppression – full protocol
Monoclonal antibody protein therapeutics (CD-8)		Mice: B6C3F1	Intraperitoneal injection	Germolec	Immunosuppression – full protocol
Nanoscale material (Fullerene-C60 1 micron)	99685-96-8	Rats: Wistar Han	Inhalation	Walker	Immunosuppression – range-finding
Nanoscale material (Fullerene-C60 1 micron)	99685-96-8	Mice: B6C3F1	Inhalation	Walker	Immunosuppression – rang- finding
Nanoscale material (Fullerene-C60 50 nanometers)	99685-96-8	Rats: Wistar Han	Inhalation	Walker	Immunosuppression – range-finding
Nanoscale material (Fullerene-C60 50 nanometers)	99685-96-8	Mice: B6C3F1	Inhalation	Walker	Immunosuppression – range-finding
1,5-Naphthalene diisocyanate	3173-72-6	Mice: BALB/c	Topical application	Germolec	Hypersensitivity
Nelfinavir mesylate	159989-65-8	Mice: B6C3F1	Gavage	Germolec	Immunosuppression – full protocol Developmental
Nevirapine	129618-40-2	Mice: B6C3F1	Gavage	Germolec	Immunosuppression – full protocol – developmental
1,2,3,7,8-Pentabromodibenzofuran	107555-93-1	Mice: B6C3F1	Gavage	DeVito	Immunosuppression
2,3,4,7,8-Pentabromodibenzofuran	13116-92-2	Mice: B6C3F1	Gavage	DeVito	Immunosuppression
1,2,3,7,8-Pentachlorodibenzofuran (PCDF)	57117-41-6	Mice: B6C3F1	Gavage	DeVito	Immunosuppression
2,3,4,7,8-Pentachlorodibenzofuran	57117-31-4	Mice: B6C3F1	Gavage	DeVito	Immunosuppression
2,3-Pentanedione	600-14-6	Mice: BALB/c	Topical application	Germolec	Hypersensitivity
Perfluorodecanoic acid (PFDA)	335-76-2	Rats: Harlan SD	Gavage	Blystone	Immunosuppression

Chemical	CASRN	Species/Strain	Route	Project Leader	Testing Battery
Phenol	108-95-2	Mice: B6C3F1	Water	Germolec	Immunosuppression – full protocol
Resveratrol	501-36-0	Mice: B6C3F1	Gavage	Germolec	Immunosuppression – range finding
Rosewood true color concentrate		Mice: CBA/ Ca Jackson	Subcutaneous injection	Howard	Hypersensitivity
Sodium tungstate, dihydrate	10213-10-2	Mice: B6C3F1	Water	Hooth	Immunosuppression – full protocol
2,3,7,8-Tetrabromodibenzofuran	67733-57-7	Mice: B6C3F1	Gavage	DeVito	Immunosuppression
3,3',4,4'-Tetrachloroazobenzene	14047-09-7	Rats: SD	Gavage	Behl	Immunosuppression – range finding – developmental
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	1746-01-6	Mice: B6C3F1	Gavage	DeVito	Immunosuppression
2,3,7,8-Tetrachlorodibenzofuran	51207-31-9	Mice: B6C3F1	Gavage	DeVito	Immunosuppression
2,3,7-Tribromodibenzo-*p*-dioxin	51974-40-4	Mice: B6C3F1	Gavage	DeVito	Immunosuppression

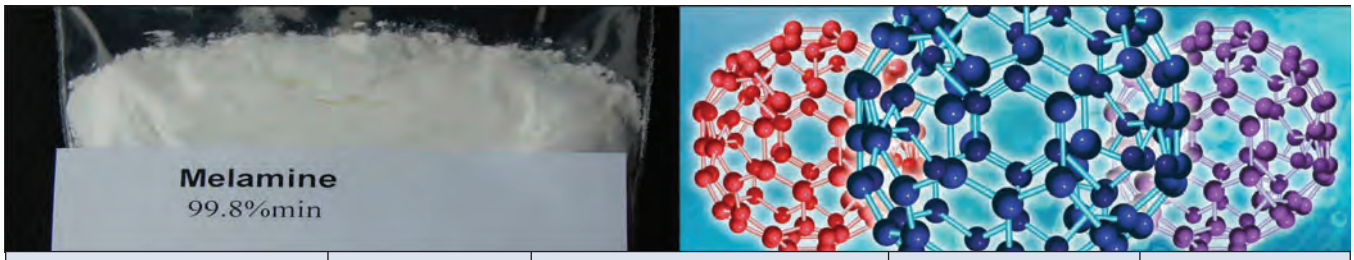
Disposition, Metabolism, and Toxicokinetic Studies

Complete dosimetry of a chemical or physical agent describes its absorption, distribution, metabolism, and excretion (ADME) in the body at differing levels of exposure, over all ages, via several routes of exposure, and under varying genetic backgrounds in humans and test animals. Data from NTP chemical disposition and toxicokinetic studies are used in these studies. Substances evaluated during FY 2011 are listed in Table 29, and studies planned for FY 2012 are listed in Table 30. Most studies are conducted in intact laboratory animals; some require incubating human and rodent tissues (liver slices) with the chemical. This information provides dosimetric data that can be combined with other anatomical, biochemical, and physiological information to develop models based on biochemistry and physiologically based pharmacokinetics. Such models are used increasingly in risk assessment to extrapolate between species, across dose ranges, and across different routes of exposure.

Table 29. Ongoing and Complete Disposition, Metabolism, and Toxicokinetic Studies During FY 2011

Chemical	CASRN	Species/Strain	Route	Project Leader
Anatase (TiO_2)	1317-70-0	Mice: Tg.AC (FVB/N) Mice: FVB/N	Topical application	NCTR
Benzene	71-43-2	Mice: BALB/cByJ Mice: WSB/EiJ *(M. m. domesticus)* Mice: CAST/EiJ *(M. m. castaneus)* Mice: C3H/HeJ Mice: DBA/2 Jackson Mice: BTBR T+ tf/J 2 Mice:C57BL/6 Mice: FVB/NJ Mice: KK/HlJ Mice: AKR/J Mice: NZW/LacJ Mice: A/J Mice: NOD/LtJ Mice: B6C3F1 Mice: PWD/PhJ *(M. m. musculus)* Mice: MOLF/EiJ *(M. m. molossinus)* Mice: 129S1/SvImJ	Gavage	Cunningham

Chemical	CASRN	Species/Strain	Route	Project Leader
Bisphenol A	80-05-7	Rats: SD	*In-vitro*	NCTR
Bisphenol AF	1478-61-1	Mice: B6C3F1 Rats: Harlan SD	*In-vitro*	Waidyanatha
2,3-Butanedione (diacetyl)	431-03-8	Mice: B6C3F1 Rats: Harlan SD	Oropharyngeal	Waidyanatha
2,3-Butanedione (diacetyl)	431-03-8		*In-vitro*	Waidyanatha
2-Butene-1,4-diol	110-64-5		*In-vitro*	NCTR
n-Butyl-*p*-hydroxybenzoate	94-26-8	Rats: Harlan SD	Intravenous	Blystone
Cumene	98-82-8	Rats: Fischer 344 Mice: B6C3F1	Gavage	Chan
1,3-Dichloro-2-propanol	96-23-1	Rats: Harlan SD Mice: B6C3F1	Gavage	Chan
Di(2-ethylhexyl) phthalate	117-81-7	Monkey: Rhesus	Gavage	Delclos
N,N-Dimethylacetoacetamide	2044-64-6	Rats: Fischer 344/N Charles River	Gavage	Waidyanatha
Dimethylamine borane	74-94-2	Human skin cells Rats: Harlan SD	*In-vitro*	Germolec
Dimethylethanolamine	108-01-0	Rats: Wistar Mice: B6C3F1	Gavage	Waidyanatha
2,2′-Dimorpholinodiethyl ether	6425-39-4	Rats: Harlan SD Mice: B6C3F1/N	Dermal	Waidyanatha
2',2'''-Dithiobisbenzanilide	135-57-9	Rats; Harlan SD Mice: B6C3F1	Gavage	Waidyanatha
Ephedrine + caffeine combination	58-08-2 299-42-3	Rats: Fischer 344	Gavage	Dunnick
2-Ethylhexyl *p*-methoxycinnamate	5466-77-3	Rats: Harlan SD Mice: B6C3F1	Dermal	McIntyre
2-Ethylhexyl *p*-methoxycinnamate	5466-77-3	Rats: SD	Gavage	Mercado-Feliciano
Furan	110-00-9	Rats: Fischer 344	Gavage	Waidyanatha
Furan	110-00-9	Rats: Tg.Lac1/C57BL/6 (Big Blue)	Gavage	Waidyanatha
Gum guggul extract		Human liver microsomes	*In-vitro*	Thakur
Isocyanuric acid	108-80-5	Rats: Fischer 344	Gavage	NCTR
Isocyanuric acid	108-80-5	Rats: Fischer 344	Intravenous	NCTR
2-Hydroxy-4-methoxybenzophenone	131-57-7	Rats: Harlan SD Mice: B6C3F1	Dermal	Auerbach
Melamine	108-78-1	Rats: Fischer 344	Gavage	NCTR
Melamine	108-78-1	Rats: Fischer 344	Intravenous	NCTR



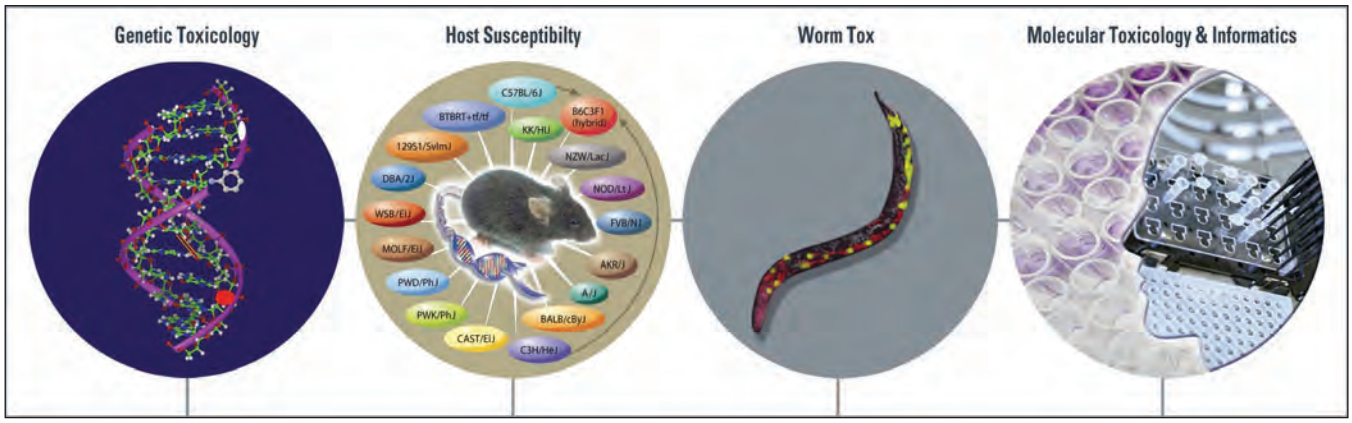
Chemical	CASRN	Species/Strain	Route	Project Leader
Melamine cyanurate	37640-57-6	Rats: Fischer 344	Gavage	NCTR
Melamine + cyanuric acid combination	108-78-1 108-80-5	Rats: Fischer 344	Feed	NCTR
Melamine + cyanuric acid combination	108-78-1 108-80-5	Rats: Fischer 344	Intravenous	NCTR
2-Methoxy-4-nitroaniline	97-52-9	Rats: Harlan SD Mice: B6C3F1	Gavage	Auerbach
L-beta-Methylaminoalanine	15920-93-1	Rats: Harlan SD Mice: B6C3F1	Gavage	Waidyanatha
Nanoscale material (Fullerene C60)	99685-96-8	Rats: Fischer 344/N	Intratracheal	Waidyanatha
Nanoscale material (rutile titanium dioxide)	1317-80-2	Mice: SKH-1 Hairless	Topical application	NCTR
Nanoscale Ag	7440-22-4	Rats: SD	Gavage	Walker
Nanoscale Ag	7440-22-4	Rats: SD	Intravenous	Walker
Ag acetate	563-63-3	Rats: SD	Intravenous	NCTR
Ag acetate	563-63-3	Rats: SD	Gavage	NCTR
Triclosan	3380-34-5	Mice: B6C3F1 Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-) Rats: Harlan SD	Topical	NCTR
Tris(4-chlorophenyl)methane	27575-78-6	Rats: Harlan SD Mice: B6C3F1	Gavage	Surh
Tris(4-chlorophenyl)methanol	3010-80-8	Rats: Harlan SD	Gavage	Surh

Table 30: Disposition on, Metabolism and Toxicokinetic Studies Planned for FY 2012*

Chemical	CASRN	Species/Strain	Route
Bisphenol AF	1478-61-1	Rats: Harlan SD Mice: B6C3F1	Intravenous
Tris(2-chlorisopropyl) phosphate	13674-84-5	Mice: B6C3F1 Rats: Harlan SD	Feed

** Known test articles as of 10/1/2011. Others may be scheduled as protocols are finalized.*

Genetic and Alternative Test Systems



Biomolecular Screening

In FY 2008, the NTP established a high throughput screening (HTS) initiative, representing a new paradigm in toxicological testing. During FY 2011, the NTP continued using this HTS approach to screen for mechanistic targets active within cellular pathways critical to carcinogenicity, reproductive and developmental toxicity, genotoxicity, neurotoxicity, and immunotoxicity. The NTP's HTS program is administered through the Biomolecular Screening Branch (BSB). The goals of the HTS Program are to:

- prioritize substances for further in-depth toxicological evaluation (to judiciously allocate efforts and resources to maximize public health impact)
- identify mechanisms of action for further investigation (e.g., disease-associated pathways)
- develop predictive models for biological responses in humans and animals (predictive toxicology)

Much of the research conducted in support of the HTS program is coordinated with the EPA, the National Human Genome Research Institute (NHGRI), and the FDA through a Memorandum of Understanding (see page 73).

Contact Information: Dr. Raymond Tice, Chief, BSB, *tice@niehs.nih.gov*. HTS website *http://ntp.niehs.nih.gov/go/28213*.

Cellular and Molecular Pathology

Comparative Pathology

At NTP emphasis is increasingly being placed upon the toxicologic pathology produced by acute, subchronic, and chronic chemical exposures in rodent bioassays for potential translation to human hazard identification. Many of these studies produce data that can be utilized by regulatory agencies in setting exposure limits in the workplace (for example, the ongoing studies of chemical-induced bronchial fibrosis). Numerous animal models of human disease, such as asthma, pneumonitis, nonalcoholic fatty liver disease, and bleomycin induced pulmonary fibrosis are regularly interpreted by the Cellular and Molecular Pathology Branch (CMPB) in collaboration with NIEHS colleagues. Comparative pathology, both morphologic and molecular, is also of paramount importance in assessing chemical-induced neoplasia, as demonstrated by the recent NIEHS and NCTR collaborative studies of chemical-induced intestinal tumors. Recent efforts by the CMPB have also focused upon the development of necropsy techniques for the rapid collection of rodent tissues for gene expression studies; these innovative techniques, combined with the use of laser capture microdissection, have resulted in the successful collection of high quality RNA from the pulmonary airways and from the epithelium of the nasal cavity. Ongoing CMPB cellular and molecular approaches are thus providing greater opportunities for comparing responses between animal models and humans and for determining human relevance.

Molecular Mechanisms of Chemically Induced Neoplasia

NTP studies have identified several genetic alterations in chemically induced rodent neoplasms that have potential mechanistic implications for human cancer. These studies provide convincing molecular data that serve to complement standard histopathology data. Taken together, these data aid the NTP in assessment of several compounds that are potentially hazardous. Epigenetic as well as genetic mechanisms play an important role in the pathogenesis of cancer. Several independent and collaborative studies have been initiated to investigate the epigenetic changes occurring in chemically induced and spontaneous neoplasms, including global methylation profiling and pyrosequencing to better understand how these changes influence the process of tumorigenesis. These studies further complement our investigations of genetic alterations in liver, lung, breast, mesothelioma, and colon tumors induced by compounds in NTP studies. Protocols to standardize frozen tissue collection from NTP chronic studies for molecular biology analysis including gene expression and protein analysis have been initiated. Using the high quality samples obtained from the NTP chronic studies in conjunction with high-throughput global gene expression profiling, important similarities were discovered between mouse and human tumors at the molecular level. Additionally, this technology provided important information on chemical-specific events leading to tumorigenesis. It is becoming increasingly important in NTP studies to identify pre-disease early genetic and epigenetic events in the process of toxicity and carcinogenicity in order to establish predictive as well as preventive measures to minimize human health hazards. In order to achieve that objective, study design of new NTP studies have included early timepoints for molecular evaluation. Investigation of gene and protein expression alterations in tissues during the pre-neoplastic stages will provide important data about the initiating events that will provide critical information on predictive events in the pathogenesis of chemically induced neoplasms in NTP studies. NTP contributors were Drs. Mark Hoenerhoff, Sachin Bhusari, and Robert Sills, Ms. Janice Harvey, Ms. Hue Hua Hong and Mr. Tai-Vu Ton.

NTP Nonneoplastic Lesion Atlas

Given the increased attention to nonneoplastic diseases in humans, and the potential to contribute to the body of knowledge on nonneoplastic diseases, the NTP has been working to investigate the relevance of nonneoplastic lesions seen in its toxicity and carcinogenicity studies to humans. A great deal of variation occurs among

pathologists regarding the terminology and recording for nonneoplastic lesions, creating inconsistency in the NTP's nonneoplastic lesion database. To resolve these issues, the NTP plans to implement a set of guidelines for the diagnosis of nonneoplastic lesions, similar to the system currently used for neoplastic lesions. These guidelines will be presented in the NTP Nonneoplastic Lesion Atlas (NNLA), which will improve the organization and diagnostic consistency of the NTP's nonneoplastic lesion database. This will facilitate database searches and allow the generation of historical control data for nonneoplastic lesions.

The NNLA will be divided into 22 sections, each covering a particular organ or organ system. The sections will consist of a series of documents and will include high-quality images of the lesions, a comments section, a recommendations section that presents the diagnostic guidelines, and a list of references. Each section will be prepared by a group of 2 or 3 pathologists familiar with NTP studies, and will be reviewed by a non-NTP pathologist (generally, a recognized expert on the particular organ or organ system) and by a group of NTP pathologists. Currently, two of the 22 sections have been completed, and an additional 10 sections are in review. The remaining sections will be in review by mid-2012 and the atlas is scheduled to be completed by late 2013. The NNLA will be published as a downloadable web document, will be updated periodically, and will be available as an app for use on smart phones and tablets eventually.

Additionally, NTP pathologists are in working groups for the Society of Toxicologic Pathology (STP) and International Harmonization of Nomenclature and Diagnostic Criteria (INHAND) committee, which has a goal of a worldwide nomenclature standardization of rodent neoplastic and non-neoplastic lesions. The international efforts are relying heavily on NTP expertise and opinion as well as using the NTP's digital database of >60,000 pathology images for examples for the atlases. Some organ systems are complete. The NTP Pathology Group also provided assistance and attended meetings to address pathology issues for the pending conversion of the NTP's toxicology data management system to the new Provantis system.

NTP Satellite Meeting

The 2011 annual NTP Satellite Symposium, titled *Pathology Potpourri*, was held in Denver, Colorado in advance of the STP 30th Annual Meeting in June 2011. Some of the topics covered during the symposium include: proliferative lesions from various fish species including ameloblastoma, gas gland hyperplasia, nodular regenerative hepatocellular hyperplasia, and malignant granulosa cell tumor; spontaneous cystic hyperplasia in the stomach of CD1 mice and histiocytic aggregates in the duodenal villous tips of treated mice; an olfactory

neuroblastoma in a cynomolgus monkey; various rodent skin lesions including follicular parakeratotic hyperkeratosis, adnexal degeneration, and epithelial intracytoplasmic accumulations; oligodendroglioma and microgliomas in rats; a diagnostically challenging microcytic, hypochromic, responsive anemia in rats; a review of microcytes and microcytosis; nasal lesions associated with green tea extract and *Ginkgo biloba* in rats; corneal dystrophy in Dutch belted rabbits; valvulopathy in rats; and lymphoproliferative disease in a cynomolgus monkey. Dr. Susan Elmore organized and chaired the Satellite Symposium.

Digital Imaging

The NTP Pathology Group has continued to foster the exploration and utilization of digital photo microscopy and slide scanning technologies for NTP and NIEHS studies. Such efforts have contributed towards abilities for publishing and presenting stellar microscopic images, providing web-based telepathology to conduct pathology peer reviews, and obtaining instantaneous opinions from pathologists at remote locations around the world. The NTP has completed the last of 12 studies designed to compare digital and light microscopy for diagnostic accuracy in pathology peer review.

Pathology Support Core Activities

Photo courtesy of EHP

Based on the recommendations of an onsite External Scientific Review of the CMPB Core Laboratories conducted in 2010, CMPB has undertaken several steps to modify the Core Labs Infrastructure: (1) the Immunohistochemistry and Electron Microscopy (EM) Cores have retained the services of onsite pathologists, (2) the Immunohistochemistry Core Laboratory has procured a new fully automated, robotic immunohistochemistry stainer, (3) the Immunohistochemistry Core Laboratory has added polymer-based technology for protein detection to the IHC staining protocols, (4) a weeklong workshop in immunohistochemistry was conducted at NIEHS to refresh and enhance the knowledge base of the Immunohistochemistry lab staff and to provide them an opportunity to be familiar with the state of the art techniques in immunohistochemistry, (5) the Immunohistochemistry Core Laboratory has worked to standardize the protocols for immunofluorescence microscopy and is now able to provide more immunofluorescence service to the researchers in the coming year, (6) the EM Core has purchased a new state-of-the-art, 11-megapixel, fiber-optic coupled camera to replace an out dated camera that is no longer being manufactured, (7) Core staff have worked with computer IT support to refine, improve, and update the computerized Immunhistochemistry/Necropsy/Histology Core Laboratory Tracking Applications, and (8) key Necropsy/Histology Core staff attended a five-day off-site retraining to reinforce and refine their skills in histotechnology and to keep them up to date on new procedures and methods.

As part of the Pathology Services Core, the Special Techniques Laboratory (STL) provides services to DIR and DNTP in the areas of laser capture microdissection (LCM), imaging and mouse phenotyping with an emphasis on embryonic lethality. In FY 2011, new services were offered to support investigators, which include extraction of DNA and RNA from tissue, as well as, the amplification of these end products for final analysis by the investigators. The imaging core acquired a microscopic slide scanner capable of digitizing fluorescence-stained slides. The other support service in STL, mouse phenotyping, places a focus on assisting investigators to identify embryonic lethality in genetically engineered mice. In 2011, multiple investigators were assisted with projects such as, evaluating CRE toxicity and development of special stains to detect bone anomalies. In addition, studies were designed and conducted to troubleshoot fixation and paraffin embedding problems with embryo samples.

Contact Information: Cellular and Molecular Pathology Branch, Dr. Robert Sills, Chief, *sills@niehs.nih.gov*.

NTP Archives

Established in 1984, the NTP Archives is a state-of-the-art facility, providing the primary public resource for toxicology research. The Archives houses an unmatched collection of research specimens and supporting data from over 2,000 NTP studies. The facility consists of repositories for storage of histologic slides, paraffin blocks, formalin-fixed "wet" tissue, frozen tissues, and printed, microfiched, and electronic study records. Frozen samples include normal tissue, neoplastic lesions, tumor specimens, DNA, RNA, blood serum, BAL supernatant, urine, and sperm suspensions from treated and control rats and mice.

Contact Information: Dr. Ron Herbert, *herbert1@niehs.nih.gov*

NTP Laboratory

Reorganization of NTP into a separate division yielded the new NTP Laboratory. The NTP Laboratory provides high quality laboratory capabilities and support for the performance of agent-specific, targeted research directly related to developing and applying tools of modern toxicology and molecular biology to the evaluation of specific substances of concern to NTP, issues of central importance to NTP programs, or methods development to advance the NTP mission. Another key focus of the laboratory is to develop better methods to study the developmental origins of adult diseases.

Dr. Michael Waalkes is Laboratory Chief and Drs. Sue Fenton, Darlene Dixon, Jean Harry, and Daniel Morgan are group leaders within the Laboratory, while other NTP scientists join projects on an as need basis. Several studies are being initiated or formulated as the Laboratory further develops its project repertoire. Mechanistic studies on formaldehyde and hematopoietic cancers, genomics of early life exposures and adulthood cancers in arsenic exposed humans, metal particle dissolution by macrophage, and effects of environmental estrogens are just some of the first studies in design or process.

Contact Information: Dr. Michael Waalkes, *waalkes@niehs.nih.gov* and at *http://www.niehs.nih.gov/research/atniehs/labs/ntp/index.cfm*

NTP Postdoctoral Training Programs

Laboratory Animal Medicine Training Program

This four-year training program, under the direction of Dr. Angela King-Herbert, includes clinical and surgical responsibilities, management of animal care facilities, participation in research projects, and laboratory animal pathology. The training program is a collaborative effort between NIEHS and the University of North Carolina at Chapel Hill. Fellows interact with laboratory animal veterinarians at NIEHS and at local area academic, industrial, and government facilities to receive didactic and hands-on training in laboratory animal medicine. Two postdoctoral fellows, Drs. Jacquelyn Tubbs and Dr. Coralie Zegre-Cannon, completed the program and passed the American College of Laboratory Animal Medicine certifying examination in June 2011.

Contact Information: Dr. Angela King-Herbert, *kingher1@niehs.nih.gov*

Toxicological Pathology Training Program

Since formalizing a training program in toxicological pathology in 2003, Dr. David Malarkey, training coordinator, and other CMPB staff have mentored 11 post-doctoral fellows and over 30 veterinary student externs. In 2011, the training program included the training of IRTA fellows, multiple externs who come to CMPB for a few weeks, and other local pathology trainees. Three postdoctoral fellows and six veterinary students participated in the program during 2011. The program is designed to introduce students to the field and career opportunities in veterinary and toxicological pathology while also providing hands-on projects often leading to abstracts and publications. Postdoctoral fellows learn rodent and toxicological pathology, participate in NTP and other DIR research projects, work to achieve accuracy of NTP pathology data by assisting the NTP pathologist on NTP studies, and continue education towards achievement of board certification by the American College of Veterinary Pathologists. CMPB staff also served as committee members for three PhD graduate school students at North Carolina State University.

Contact Information: Dr. David Malarkey, *malarkey@niehs.nih.gov*

Toxicology and Carcinogenesis Training Program

Trainees in this program learn to perform all aspects of contracted toxicology studies for carcinogenic or non-carcinogenic endpoints (e.g., reproductive and developmental effects, immune system function). They learn about NTP efforts in molecular toxicology and HTS and receive training applicable to regulatory or industrial toxicology. By serving as study scientists in non-laboratory positions, they evaluate the toxicity of substances of interest to the NTP. Trainees actively participate in designing, conducting, and evaluating studies and interact extensively with chemistry, pathology, toxicokinetics, toxicogenomics, genetics, epidemiology, statistics, and molecular biology staff. The program currently has three postdoctoral fellows: Drs. Minerva Mercado-Feliciano, In Ok Surh, and Sheetal Thakur. Two NTP trainees, Drs. Mamta Behl and Sang-Hyun Kim, successfully transitioned to other full time appointments on completion of their training program.

Contact Information: Dr. Paul Foster, *foster2@niehs.nih.gov*

Interagency Agreements

NIEHS/NCTR Interagency Agreement

In 1992, FDA entered into an IAG with NIEHS. The IAG is an instrument that allows chemicals nominated to the NTP to be studied for toxicity using the unique resources and facilities at NCTR. The research conducted under the IAG allows the FDA to better assess study design input and initial data on the safety of FDA-regulated products. It has allowed continued collaborative toxicity testing on compounds of interest to the FDA and NTP and led to investigations of mechanisms of action and assessments of toxicity for many classes of chemicals including cosmetics, endocrine-disrupting compounds, food contaminants, food cooking by-products, dietary supplements, drugs, and anesthetics. The IAG supports the Phototoxicity Research and Testing Laboratory at the NTP Center for Phototoxicology and the Nanotechnology Core Facility at the NCTR/Office of Regulatory Affairs. All toxicology studies conducted under the IAG are designed with input from FDA regulatory scientists, NCTR and NIEHS scientists, scientists from other agencies, and invited subject matter experts. The IAG uses resources from public funds and exceptional scientific expertise to provide the best possible assessment of product safety through toxicological studies. Table 31 lists projects completed or ongoing in FY 2011.

Table 31. NIEHS/NCTR Interagency Agreement Projects in FY 2011

Study [CASRN] *Principal Investigator*	Objective and/or Rationale
Assessment of Molecular Changes in Male and Female SD Rats Orally Exposed to BPA from GD 6 through PND 90 [80-05-7] *Camacho*	To determine BPA-induced molecular changes in gene expression, protein levels, and epigenetic modifications in tissues collected from SD rats orally exposed to BPA from GD 6 through PND 90.
Evaluation of Toxicity of BPA in Male and Female SD/NCTR Rats Exposed Orally from GD 6 through PND 90 [80-05-7] *Delclos*	(1) To assess the toxicity of BPA in rats dosed perinatally via gavage, and (2) to evaluate estrogenic endpoints from the F1 generation.
Evaluation of Various Diets on Endpoints Critical to the Evaluation of BPA and other Endocrine Active Agents *Delclos*	To evaluate reproductive and developmental endpoints in F_0-F_2 generation in CD-1 mice with various chows (e.g., Purina Mills 5K96, NIH-41, Purina Mills 5001), some of which have low isoflavone levels, in preparation of studies on BPA in CD-1 mice
The Role of Perinatal Development on Pharmacokinetics of BPA [80-05-7] *Doerge*	To develop additional data from rat and monkey exposures that will provide data to be used in the creation and validation of a PBPK model to predict internal exposures to free BPA in the appropriate target tissues of fetuses and babies that are derived from food contact and medical-device exposures.
13-week Studies to Determine the Pathogenesis of the Whole Leaf Extract of the *Aloe vera* Plant in the Cecum and Large Intestine of the F344 Rat [85507-69-3] *Boudreau*	To investigate the pathogenesis of *Aloe vera* extracts and gel, with and without added Aloin A, in the cecum and large intestine of the F344 rat. Senna, having similar components to those in *Aloe vera*, will also be studied to determine if it exerts comparable effects when administered in the drinking water of F344 rats.
Bioassays in the F344 Rat and the B6C3F1 Mouse Administered *Aloe vera* Plant Constituents in Drinking Water *Boudreau*	(1) To determine dose ranges for future toxicology studies, (2) to determine the toxic effects and highest tolerated doses of the different *Aloe vera* components, including the gel and whole leaf extracts [filtered and non-filtered], and (3) to determine the chronic toxicity and carcinogenic potential of *Aloe vera* whole leaf extract in the rat and mouse by drinking water exposure.
Assessment of the Nephrotoxic Effect of a Combined Exposure to Melamine and Cyanuric Acid [108-78-1, 108-90-5] *Gamboa*	To investigate the toxic effects noted in cats and small children who were exposed to melamine and cyanuric acid via adulterated food supplies.
Assessment of the Nephrotoxicity from the 90-day Combined Exposure to Melamine and Cyanuric Acid in F344 Rats [108-78-1, 108-90-5] *Gamboa*	To investigate the nephrotoxic effects noted in F344 rats exposed in NTP Study #C10119 to melamine, cyanuric acid and melamine cyanurate. The initial toxicity was reported in the kidneys of the pets and children exposed to adulterated foods.
13-week Study to Evaluate the Toxicology of Ag Nanoparticles in SD Rats [744-22-4] *Boudreau*	To determine if exposure over a 13-week period to nanoscale (10, 70, and 107 nm) Ag particles induces toxicity.
Toxicological Evaluation of Nanoscale Ag Particles in Rodents [744-22-4] *Boudreau*	(1) To determine if reducing the size of Ag particles to nanoscale changes the absorption, biodistribution, excretion, and toxicity, and (2) to determine the effects of reducing the particle size to nanoscale of a compound that has been regarded as nontoxic in micro and above sizes.
13-Week Dermal Toxicity of Triclosan in B6C3F1 Mice [3380-34-5] *Fang*	(1) To determine the toxicity of dermally applied triclosan with ethanol as the vehicle, and (2) to determine the possible toxicity and phototoxicity of triclosan under normal use conditions.

Study [CASRN] *Principal Investigator*	Objective and/or Rationale
Vehicle Selection for Triclosan Dermal Toxicity Studies in B6C3F1 Mice [3380-34-5] *Fang*	To determine ADME, toxicokinetics, and penetration of triclosan after an appropriate solvent is determined for dermal application.
Dose-finding Study of Reproductive and Developmental Toxicity Study of Oxybenzone [2-Hydroxy-4-methoxybenzophenone] [131-57-7] *Hansen*	(1) To determine doses for a full reproductive developmental toxicity study with oxybenzone, a component of sunscreens, and (2) to assess the possible biological activity of oxybenzone due to its high volume of use in individuals.
Neurotoxicity Assessment of Cell Phone Radio Frequency Radiation (RFR) using Rat and Bovine Brain Microvascular Endothelial Cells as Model Blood Brain Barrier Systems, PC-12 Cultured Cells, and Whole Animal Models *Ali*	(1) To determine whether power levels of RFR that are emitted from mobile phones produces any changes in the CNS of mice and rats, and (2) to determine if there are disruptions in the blood brain barrier after being subjected to RFR radiation.
Mechanisms of Nevirapine Carcinogenicity [129618-40-2] *Beland*	To determine the mechanism by which nevirapine induces tumors in rats.
The Two-year Carcinogenicity Bioassay of Furan in Fischer 344 Rats [110-00-9] *Beland*	To determine the dose-response relationship for the carcinogenicity of furan in F344/N/Nctr male rats in a 2-year bioassay.
Determination of Carcinogenic Mechanism for Furan in Male Fischer 344 Rats [110-00-9] *Doerge*	To determine the pharmacokinetic mechanisms, mutagenesis, and hepatotoxicity of low doses of furan, similar to those ingested by humans from heat processed food.
Range-finding, Mechanistic and Toxicokinetic Studies of Usnic Acid and *Usnea barbata* Herb in Fischer 344 Rats and B6C3F1 Mice. [125-46-2, 84696-53-7] *Leakey*	To complete the standard NTP 14-day range-finding study with both usnic acid and *Usnea barbata* administered in feed.
Subchronic Toxicity of *Usnea* Lichen in Male and Female Fischer 344 Rats and B6C3F1 Mice [84696-53-7] *Leakey*	To evaluate the subchronic toxicity of *Usnea* lichen in 90-day toxicology study with dose administered in chow. Acute toxicity in humans has been reported from the consumption of the active agent (usnic acid) in the herbal product.
Subchronic Studies of Usnic Acid in Fischer 344 Rats and B6C3F1 Mice [125-56-2] *Leakey*	To evaluate the subchronic toxicity of usnic acid in male and female Fischer 344 rats and B6C3F1 mice using a 90-day toxicology studies. Usnic acid had been shown to be hepatotoxic when consumed by humans in large doses for weight loss.
Toxicity Studies of Glucosamine and Glucosamine/ Chondroitin Sulfate Combination in Obese and Lean Zucker Rats [3416-24-8, 9007-28-7] *Leakey*	To investigate the potential toxicity of glucosamine and glucosamine/chondroitin sulfate combinations, administered by oral gavage in male rats.
Perinatal Carcinogenicity of Drug Combinations Used to Prevent Mother-to-Child Transmission of HIV [30616-87-1, 134678-17-4] Beland	To determine the carcinogenicity, genotoxicity and metabolism of antiretroviral drug combinations administered to mice transplacentally and perinatally. The studies include 14-day range-finding and 2-year chronic in pregnant C57BL6N females and in B6C3F1 hybrid offspring.
Toxicity Studies of Combination of AIDS Drugs in p53(+/-) Transgenic Mice [30616-87-1, 134678-17-4] *Leakey*	(1) To evaluate the potential toxicity and carcinogenicity of perinatal and chronic exposures to AIDS drugs, AZT and 3TC in C3B6F1trp53(+/-) haplodeficient F1 transgenic mice in a range-finding and a 6-9 month chronic phase, and (2) to evaluate the potential toxicity and carcinogenicity of AZT/3TC/NVP combinations in C3B6F1trp53(+/-) in a 9 month exposure in mice.
Developmental Neurotoxicity Assessment of Acrylamide in Rats: Long-term [79-06-01] *Paule*	To determine the consequences of long-term exposure to acrylamide on a variety of developmental milestones and measures of nervous system integrity throughout life.
Genotoxicity and Carcinogenicity of Acrylamide and its Metabolite Gycidamide in Rodents [79-06-1, 5694-00-8] *Beland*	To determine the genotoxicity and carcinogenicity of acrylamide and its metabolite gycidamide in male and female Fischer 344 rats and B6C3F1 mice using range-finding, subchronic, and 2-year chronic carcinogenicity studies.
Physiological Effects of Bitter Orange in Rats [94-07-5] *Hansen*	To determine potential physiological effects of synthetic synephrine as well as an extract from the botanical *Citrus aurantium* alone and in combination with caffeine in rats, with and without exercise.
Potential Developmental Toxicity of Synthetic Synephrine and *Citrus aurantium* Extract in Rats [94-07-5] *Hansen*	To determine the potential developmental toxicity of synthetic synephrine, *Citrus aurantium* and possible potentiation of the toxicity by caffeine.
Effect of Topically Applied Skin Creams Containing retinyl palmitate (RP) on the Photocarcinogenicity of Simulated Solar Light (SSL) in SKH-1 Mice [79-81-2] *Boudreau*	(1) To determine if RP applied to the skin of SKH-1 hairless mice alters the incidence of tumors produced by SSL and/or UV light, and (2) to determine the mechanisms of tumor promotion by RP.
An Evaluation of the Effect of Vehicle Cream on the Photocarcinogenicity of RP in SKH-1 Mice [79-81-2, 6938-94-9] *Boudreau*	(1) To determine the stability and homogeneity of RP in the control cream used in the dermal *Aloe vera* study conducted at the NCTR, (2) to evaluate the Photocarcinogenicity of RP, incorporated in the *Aloe vera* control cream when applied to the skins of SKH-1 mice in the absence and presence of SSL, and (3) to determine the Photocarcinogenicity of diisopropyl adipate which was used as the filler in the previous NTP RP dermal SKH-1 study.

Contact Information: Dr. Paul Howard, paul.howard@fda.hhs.gov and Dr. Nigel Walker, walker3@niehs.nih.gov.

NIEHS/NIOSH Interagency Agreement — Comprehensive Assessment of Occupationally-Relevant Exposures

The NTP is coordinating an effort with NIOSH to better understand worker exposures, identify occupational health research gaps, and educate workers. Current efforts listed in Table 32 address worker exposures to welding fumes, nano-sized materials, food flavorings, bisphenol A, indium compounds, and other industrial chemicals.

Table 32 . NIEHS/NIOSH Interagency Aggrement on Occupationally Relevant Exposures, FY 2011

Study *Principal Investigator*	Objective and/or Rationale
Administrative Support *DeBord*	To enable NIOSH scientists to (1) participate in review and oversight of NTP activities, and (2) attend NTP-related meetings in Research Triangle Park, NC and Washington, DC.
Assess the Feasibility of an Occupational Exposure Assessment of Welding Fume with Emphasis on Mn Compounds *Hanley*	(1) To identify industries (e.g., construction, shipbuilding, railroad, and manufacturing), companies, and/or unions involved in welding operations where the potential for substantial manganese exposure exists, for exposure assessments; (2) to develop methods to identify specific manganese compounds, different valence states, and potential solubility contained within various welding fumes matrices; and (3) to characterize welding fume exposures based on welding-associated jobs, tasks, and processes.
Exposure Assessment of Diacetyl and Other Flavorings in Food Production Industries *Curwin*	(1) To characterize workplace inhalation exposures to diacetyl in food production industries that use food flavorings, (2) to document high-exposure activities and processes in the flavored food production industries, (3) to identify work practices and procedures that affect exposure, (4) to document engineering controls, and (5) to field test novel techniques for both gravimetric and volatile sampling.
Exposure Assessment of Dithiobisbenzanilide (DTBBA) in a Manufacturing Setting *Wurzelbacher*	(1) To identify worker populations at increased risk of inhalation and surface exposure to DTBBA during a manufacturing process; (2) to develop a NIOSH analytical method for quantitatively assessing DTBBA airborne particulate and surface exposures; and (3) to characterize industry-wide occupational exposures, including total number of workers, and evaluate patterns of exposure to DTBBA.
A Pilot Exposure Assessment for 2-methoxy-4-nitroaniline (2M4N) in a Manufacturing Setting *Wurzelbacher*	(1) To identify worker populations at increased risk of inhalation and surface exposure to 2M4N during a manufacturing process; (2) to develop a NIOSH analytical method for quantitatively assessing 2M4N airborne particulate and surface exposures; and (3) to characterize industry-wide occupational exposures, including total number of workers, and evaluate patterns of exposure to 2M4N.
Assessment of Use of Indium and Indium Compounds in the Workplace *Hines*	(1) To contact and visit companies to determine indium materials being used, jobs and processes with potential indium exposure, exposure controls, and indium use trends, and (2) to conduct preliminary sampling for indium, if possible.
Exposure Assessment of Engineered Nanoparticles *Geraci*	(1) To identify workplaces engaged in the synthesis, manufacture, and use of engineered nanomaterials, and (2) to characterize workplace exposure to selected engineered nanoparticles.
Exposure Assessment of 1-Chloro-4-(trifluoromethyl) benzene (PCBTF) *Harper*	(1) To identify worker populations at elevated risk of inhalation and surface exposure to PCBTF during manufacturing processes; (2) to update a previously published analytical method for quantitatively assessing PCBTF airborne vapors and surface exposures to allow the use of capillary column chromatography; and (3) to characterize industry-wide occupational exposures, including total number of workers, and evaluate patterns of exposure to PCBTF.
A Pilot Exposure Assessment for Ethylene Glycol 2-Ethylhexyl Ether (EGEHE) in a Manufacturing Setting *Harper*	(1) To identify worker populations at elevated risk of inhalation and surface exposure to EGEHE during manufacturing processes; (2) to develop an analytical method for quantitatively assessing EGEHE airborne aerosols, vapors, and surface contamination; and (3) to characterize industry-wide occupational exposures, including total number of workers, and evaluate patterns of exposure to EGEHE.
Durability of Nanoscale Cellulose Fibers in Artificial Human Lung Fluids *Stefaniak*	To investigate the *in vitro* durability of nanocellulose materials in artificial lung fluids. Data generated from this study will be used to inform larger and more costly *in vivo* inhalation studies.

Study *Principal Investigator*	Objective and/or Rationale
Exposure Characterization and Reproductive Health of Men Working with BPA in the United States *Hines*	(1) To determine BPA usage in industry, e.g., which industries and jobs use BPA and which tasks are associated with exposure; (2) to develop air and wipe sampling methods for BPA using LC-MS (liquid chromatography mass spectrometry) and LC-UV (liquid chromatography with UV detection); (3) to assess exposure to BPA among workers in these industries through air, wipe, and urine sample collection. If worker exposures are confirmed; (4) to assess the reproductive health of men exposed to BPA in the workplace; and (5) to determine if there is a relationship between occupational exposure to BPA and reproductive health.

Contact Information: Dr. Dori Germolec, *germolec@niehs.nih.gov* and Dr. Elizabeth Whelan, *eaw0@cdc.gov*

NIEHS/NIOSH Interagency Agreement–Immunotoxicology

The goal of this IAG is to provide support of NTP hazard identification activities aimed at preventing diseases or adverse effects caused by environmental exposure to chemical or physical agents. These cooperative studies continue to improve risk assessment by measuring what constitutes an adverse health effect on the immune system in humans. The studies, listed in Table 33, evaluate unique cohorts of individuals from professions associated with immune-mediated occupational diseases, including asthma, contact dermatitis, allergy to mold spores, chronic beryllium disease, and allergic rhinitis. These cohorts are being studied for a number of endpoints including impact of genetic polymorphisms on development of inflammatory disease and clinical outcomes, and identification of unique immunological biomarkers for disease. The NIOSH Laboratory for Occupational Genomics serves as a resource for obtaining samples from individuals with occupational and occupationally related diseases.

Table 33. NIEHS/NIOSH Interagency Agreement on Immunotoxicology Studies, FY 2011

Study *Principal Investigator*	Objective and/or Rationale
Chronic Sinusitis and Mold Exposure *Beezhold*	(1) To investigate the role of fungi in chronic sinusitis, and (2) to determine if the prevalence of fungal sensitization is different to other seasonal allergens in chronic rhinosinusitis patients. To date, the chronic rhinosinusitis and control patients have been recruited and tested. The dataset has been collected and statistically analyzed.
Heading off Environmental Asthma in Louisiana *Beezhold*	(1) To evaluate the effectiveness of a novel asthma case management intervention among children with asthma after Hurricane Katrina in New Orleans, and (2) to assess total immunoglobulin E (IgE) and mold specific IgE in asthmatic children before and after intervention. This project is completed. All sera have been screened and the dataset has been statistically analyzed.
NIEHS Agricultural Pesticide Study *Beezhold*	To evaluate allergic sensitization in a cohort of 677 farmers with or without pesticide exposures. To date, 677 farmers have been recruited and the serum total IgE and specific IgE quantified using Phadia ImmunoCap. Serum concentrations of the fungal mycotoxin, deoxynivalenol, have been additionally quantified. The second phase of the study has begun and includes the evaluation of a cohort of >1,500 farmers located in Iowa and North Carolina for allergic sensitization. Currently, all farmer sera have been screened for total IgE and specific IgE measurements will be in 2012.
A Marker for *Aspergillus terreus* Exposure *Beezhold*	To develop new and improved methods for detecting fungal exposure. In this project the emerging opportunistic fungal pathogen, *A. terreus*, has been used as a model fungal species. Terrelysin, a cytolysin and potential biomarker of fungal infection, was characterized and a recombinant protein produced. The recombinant terrelysin was then used to immunize mice to produce terrelysin-specific mAbs. Seven specific mAbs were produced and used to characterize the production of terrelysin. mAb binding sites are currently being determined in epitope mapping experiments. The development of a sensitive immunoassay that can be used in the serological detection of this biomarker is anticipated.

Study *Principal Investigator*	Objective and/or Rationale
Animal Model for Airway Exposure to Dry Fungal Aerosols *Beezhold*	To develop a murine model of dry fungal exposure to better mimic natural human exposures to fungi. An acoustical generation system has been developed. In preliminary experiments, histopathology and BALF analysis demonstrated pulmonary deposition of conidia following dry fungal bioaerosol exposure. Currently, the system is being optimized for the generation of fungal and hyphal fragments. Once the system has been fully characterized, experiments are planned to further characterize the immune responses associated with various fungal species that frequently colonize water-damaged buildings or are occupationally relevant.
Characterization of Fungal Diversity in the Indoor Built Environment *Beezhold*	To investigate and characterize the diversity of fungal bioaerosols in the indoor built environment using large-scale ribosomal RNA (rRNA) sequencing in collaboration with the Kansas City Safe and Healthy Home Partnership Project. In preliminary studies, various methods of extraction were compared and tested on occupational dust samples. Currently, bulk dust samples derived from the project are being sequenced. Air samples collected with NIOSH two stage samplers will also be processed in 2012.
The Role of Genetic Variation in Environmental and Occupational Diseases – Irritant Contact Dermatitis (ICD) *Yucesoy*	(1) To investigate whether the 24-hour irritant patch test is predictive of occupational hand dermatitis caused by high exposure to hand washing in health care workers, and (2) to investigate an association between genetic variations in specific candidate genes (with emphasis on variants of cytokines, MHC region, antioxidant enzyme genes and genes related to skin barrier integrity) and irritation threshold levels of the subjects with development of ICD. This study is in collaboration with Case Western Reserve and West Virginia Universities. Subject recruitment and genotyping have been completed. Data analyses have been initiated.
The Role of Genetic Variation in Environmental and Occupational Diseases – Allergic Contact Dermatitis (ACD) *Yucesoy*	(1) To investigate genetic factors in individuals predisposed to develop ACD, specifically induced by nickel, and (2) to investigate genetic factors involved in the development of ACD in individuals sensitized to weak allergens, individuals sensitized to allergens that require metabolism in the skin, and individuals who react to more than 3 allergens of the standard screening series. This study is in collaboration with Case Western Reserve University and Dartmouth-Hitchcock Medical Center. Subject enrollment and sample processing are currently underway.
The Role of Genetic Variation in Environmental and Occupational Diseases – Occupational Asthma (OA)*Yucesoy*	(1) To investigate whether genetic variations in specific candidate genes (e.g., cytokine, MHC region, antioxidant enzyme genes) are associated with asthma induced by diisocyanates, and (2) to investigate potential associations between genetic variations in candidate genes and occupational asthma caused by low molecular weight agents. This project is in collaboration with the Universities of Montreal and Cincinnati. Genotyping of antioxidant enzyme and MHC region variations have been completed and the dataset has been analyzed.
The Role of Genetic Variation in Environmental and Occupational Diseases – Chronic Beryllium Disease *Yucesoy*	To investigate the contribution of genetic variations in the MHC region to the development of beryllium sensitization and chronic beryllium disease. This study is in collaboration with National Jewish Medical and Research Center. Genotyping efforts are currently underway.
Investigations into Health Effects Caused by Exposure to Indoor Air Reaction Products *(supportive animal studies)* *Wells, Anderson*	(1) To identify and measure the reaction products of gas-phase compounds present in the indoor environment, especially oxygenated organics; (2) to further develop and validate a novel *in vitro* exposure method utilizing realistic indoor chemistry scenarios to expose cells and tissues to these indoor air reaction products; (3) to complete both *in vitro* and *in vivo* assays to assess adverse health effects caused by indoor air reaction products; and (4) to further investigate the role of structurally similar indoor air chemicals present in mixtures in the indoor environment.
Immunological Mechanisms of Occupational Rhinitis Induced by Diisocyanate Exposure *(supportive animal studies and field studies)* *Johnson*	(1) To use specific inhalation challenge with suspected diisocyanates to diagnose allergic rhinitis in workers from Canada and Spain who are exposed to diisocyanates and clinically phenotyped for upper and lower airway disease; (2) to collect nasal mucosal samples from worker with diisocyanate rhinitis and use whole genome approaches to study mechanisms of disease; (3) to identify molecular targets in the human nasal mucosa for biomarker development and validation using the NIOSH toluene diisocyanate rhinitis mouse model; and (4) to develop the mucosal sampling technique and identified biomarker(s) into a simple and non-invasive tool for worker health surveillance and early diagnosis of sensitization/disease.

Study *Principal Investigator*	Objective and/or Rationale
Diisocyanate Monoclonal Antibody Production and Characterization *(improved methods)* *Siegel*	(1) To develop mAbs that recognize methylene diphenyldiisocyanate conjugated protein as a potential biomonitoring and research tool; (2) to test the specificity of the mAbs; and (3) to evaluate the mAbs for potential use in immunoassay-based biomonitoring.
Alternative Methods for Chemical Allergen Identification and Assessment *Siegel*	(1) To develop an amine-based probe for kinetic assessment of chemical binding (haptenation) that will complement the thiol-based probe previously reported by NIOSH; (2) to assess potential for inclusion of a metabolic activation step in our kinetic-based assays for identification of prohaptens; and (3) to expand the compilation of chemical allergens assessed by kinetic electrophilic reactivity analyses for comparison to reported allergenic potencies (murine local lymph node assay EC3 values).
Analysis of Mycotoxins in Dust Samples from a Water-damaged Building *Park*	To develop the in-house laboratory protocol for analysis of macrocyclic trichothecene mycotoxins using GC tandem MS and to analyze existing dust samples from a water-damaged building. By modifying an existing method, a protocol that substantially improved extraction efficiency of mycotoxins in samples was developed. With the developed protocol, samples harvested from culture media with 7 different strains of *Stachybotrys chartarum*, building material samples inoculated with these fungi, and floor dust samples from water-damaged buildings for the mycotoxins were analyzed. In the course of the study, a potential matrix effect in the GC/MSMS analysis was detected which can substantially affect accurate quantification of the mycotoxins in samples. Current efforts involve further investigation of the potential matrix effect and development of a ^{13}C isotopically-labeled satratoxin internal standard to further improve the protocol.

Contact Information: Dr. Dori Germolec, *germolec@niehs.nih.gov* and Dr. Don Beezhold, *zec1@cdc.gov*

NIEHS/EPA Interagency Agreement – The Phthalate Initiative

Di(2-ethyl)hexyl phthalate (DEHP) and other phthalates have been nominated to the NTP for testing. To address these nominations, the NIEHS and EPA signed *The Phthalate Initiative* IAG in June 2008, which was renewed in July 2009 and 2010, and is now in the last year of funding. Many aspects of this IAG would fall under nominations previously approved by the BSC for the study of peroxisome proliferators (begun in the 1990s), the nomination of DEHP by the FDA in 2004, and the critical data need highlighted in the NTP Monograph on DEHP issued in 2006.

These studies will clarify how the peroxisome proliferator-activated receptor alpha (PPARα) develops in the rat and its relationship to DEHP-related cancer and other developmental toxicities. The studies will also provide critical data for future mixture studies using various models to inform on potential risks for toxicity over time and during development. Recent data have indicated that because phthalate esters have similar modes of action *in utero*, they show dose-addition when administered in combination. Therefore, it would be appropriate to consider cumulative risk for the class, since human subjects (including fetuses) are typically exposed to multiple phthalates.

The initiative has two major specific aims:

(1) Undertake an ontogeny study of PPARα in the rat to determine when the receptor is first expressed in target tissues. This study will test the hypothesis that PPARα is developmentally regulated in the rat and unlikely to contribute to toxicity initiated *in utero* after exposure to DEHP.

(2) Undertake perinatal phthalate mixture studies. These studies will test the hypothesis that exposures to mixtures of phthalates, based on their individual potencies, would result in dose-addition for cancer (and potentially other) outcomes.

Based on data generated in 2010 and 2011, using a specific short-term *in utero* screen developed in the initiative to evaluate individual phthalates and mixtures in the Harlan SD rat to alter fetal testicular testosterone production, phthalates induce changes in specific fetal testicular genes (especially related to steroidogenesis and testicular descent), and the induction of specific male reproductive tract malformations that have been termed the "Phthalate Syndrome."

Thus far, data indicating a positive response have been obtained from butylbenzyl, di-n-butyl, di-iso-butyl, di-ethylhexyl, di-n-propyl, di-pentyl, di-n-hexyl, di-iso-heptyl, di-n-heptyl, di-heptylpropyl, dimethoxyethyl, di-cyclohexyl, and 3 different preparations of di-iso-nonyl phthalate (a complex mixture). Brominated DEHP, dimethyl, diethyl, and di-isodecyl phthalate, and di-octyl terephthalate were negative in this fetal phthalate screen. Specific potency factors have been developed based on this screening information. Thus a five-day screen using minimal numbers of rats has been developed to discriminate positives from negatives. The concordance with long-term multigenerational and pubertal effects is 100%. In the mixture studies the IAG also examined the potential effect of a negative phthalate ester (diethyl phthalate) on the activity of a positive ester, since they use the same esteras activity to produce monoesters for excretion. Diethyl phthalate had no effect either on its own or in the mixture.

These data would guide selection of individual studies to investigate potential short-term biomarkers for toxicity, which in turn would support future perinatal bioassays and phthalate mixture work. The NTP has now designed both perinatal and standard bioassays to evaluate developmental and cancer potential from different exposure paradigms for DEHP, which commenced in-life evaluation in early 2011. This information will be valuable in assessing potential cumulative risk of phthalates, as has been advocated by a recent National Academy of Sciences committee report and efforts by EPA's IRIS program.

Work has also progressed on the ontogeny study and the development of a genomic signature for phthalates that induce reproductive toxicity *in utero*, where the IAG is evaluating the potential role of activation of PPAR pathways in the disruption of male sexual differentiation and testis development using custom-designed RT-PCR plates. These plates allow determination of relative mRNA expression of PPARα, PPARδ, PPARγ, and several genes activated by PPARα including CYP4a1 on a single sample simultaneously. For six positive phthalates examined so far, none of the PPAR genes, CYP4a1, or any other genes "downstream" of PPARα are activated by any of the phthalates studied to date at a single high dosage level (750 mg/kg/d GD 14-18) or at any dose in the dose response studies. PPARs α and δ mRNA were expressed in GD18 fetal testes whereas PPARγ was not detected. These results do not support the hypothesis that PPARα is involved in induction of the Phthalate Syndrome in rats. These results also are supported by the observation that administration of a potent PPARα agonist (Wyeth 14643) did not reduce anogenital distance or testicular testosterone levels in GD21 male rats, whereas the positive control di-iso-butyl phthalate did reduce the measures. Furthermore, maternal liver PPARα genes were induced in the Wyeth treated animals indicating a lifestage specific effect. These studies will be further extended looking at potential PPAR induction in the fetal liver.

The IAG has identified approximately 10 genes that are part of the genomic signature for phthalates that are consistently altered on the PCR array. The lack of response in the detection of PPARγ is of note since this is in direct contrast with the claim that PPARγ is part of the HTS "signature" for reproductive toxicity described by ToxCast, which included phthalate esters. In addition, the IAG has initiated a project in which they are interrogating the effects of phthalates on additional pathways using standard RT-PCR arrays to expand the genomic signature upstream. The IAG has had about 1000 additional genes identified so far from about 10 different pathways using seven different phthalate esters. During 2011, the IAG has produced four peer reviewed publications and four abstracts.

Contact Information: Dr. Paul Foster, *foster2@niehs.nih.gov*

NTP/NHGRI/EPA/FDA Interagency Memorandum of Understanding on High Throughput Screening, Toxicity Pathway Profiling, and Biological Interpretation of Findings

Much of the research conducted in support of the NTP's high throughput screening (HTS) program is coordinated through a Memorandum of Understanding (MOU), *High Throughput Screening, Toxicity Pathway Profiling and Biological Interpretation of Findings*, first signed on February 14, 2008. Information about the MOU is available at http://ntp.niehs.nih.gov/go/28213. Through this MOU, NTP formally entered into a partnership with the National Human Genome Research Institute's (NHGRI) NCGC and the U.S. EPA's National Center for Computational Toxicology located within the Office of Research and Development. This interagency partnership is the basis for the U.S. Tox21 Program, developed in response to the National Research Council's 2007 report *Toxicity Testing in the 21st Century: A Vision and a Strategy*. A central component of this MOU is exploration of quantitative high throughput screens (qHTS) and tests using phylogenetically lower animal species (e.g., fish, worms), as well as high throughput whole-genome analytical methods to evaluate mechanisms of toxicity. The ultimate goal of Tox21 is to provide the data generated by these new tools to risk assessors for use in their mission to protect human health and the environment. The MOU was amended in 2010, adding the FDA, which brings to the Tox21 partnership its experience in human diseases, animal models of human disease, and expertise in toxicity pathway analysis and computational toxicology. FDA's active participation is in recognition of its commitment to developing new methods to evaluate the toxicity of the substances it regulates.

The goals of Tox21 and the HTS program are the same (i.e., prioritization for further in-depth toxicological evaluation, identify mechanisms of action, predictive toxicology). The results of this collaborative effort should yield test methods for toxicity determination that are more scientifically and economically efficient, and models for risk assessment that are more biologically and mechanistically based. This approach should ultimately reduce or replace animals in regulatory testing and is anticipated to occur in parallel with an enhancement of the ability to evaluate the large numbers of chemicals that currently lack adequate toxicological evaluation. This interagency partnership makes it possible to pool resources to overcome the resource limitations of a single agency, build on existing expertise, and avoid the need to create a new administrative and support structure.

In Tox21 Phase I (FY 2006 through FY 2010), a library of approximately 2,800 compounds provided by the NTP and EPA to the NCGC was tested in approximately 100 qHTSs. These assays broadly evaluated the ability of compounds (1) to induce cytotoxicity, apoptosis, DNA damage, changes in methylation status, mitochondrial toxicity, and up-regulation of various stress response pathways (e.g., antioxidant, hypoxia, heat shock) in a variety of cell types or (2) to act as an agonist or antagonist for 12 different nuclear receptors including the estrogen and androgen receptors. Also evaluated in qHTS was the extent of differential sensitivity exhibited in terms of induction of cytotoxicity and/or apoptosis by 87 densely sequenced human lymphoblastoid cell lines (the HapMap project CEPH panel, which refers to the collection of cell lines established from Utah residents with ancestry from northern and western Europe) exposed to 240 toxic chemicals.

Results from Phase I were carefully evaluated during FY 2011 and used to determine the approach for Tox21 Phase II at the NCGC. Major emphasis was placed on acquiring the most robust assays (both full length and partial nuclear receptor assays) for evaluating the ability of environmental chemicals to interact with the estrogen and/or androgen receptors. In addition, other nuclear receptor assays, assays measuring the ability of chemicals to induce various stress response pathways (e.g., antioxidant, DNA damage, heat shock, hypoxia), and assays measuring specific toxicity endpoints such as mitochondrial membrane changes, caspase activation, and NFkB upregulation were included in the queue for Phase II screening during FY 2012. This screening is to be conducted in a new, high-speed robotics screening facility dedicated at the NCGC in March 2011 and built with funds provided by the NIEHS/NTP. This robot facility was designed to screen a 10,000 compound library in qHTS.

Phase II screening is scheduled to begin early in FY 2012, after the completion of the Tox21 10,000 compound library. EPA, NTP, and NCGC will each supply approximately one-third of the compounds for this library. The compounds cover a wide variety of classifications and include consumer products, food additives, chemicals found in industrial processes, and human and veterinary drugs. A complete list of the compounds is publicly available at *http://www.epa.gov/ncct/dsstox/*. Chemical analyses by the Program Operations Branch within DNTP to determine the identity, purity, and stability of all compounds in this library were initiated in FY 2011 and will continue through FY 2012. Testing was started on a subset of these compounds (~700) in Phase II of EPA's ToxCast™ Program (*http://www.epa.gov/ncct/toxcast/*). The data from all these assays, along with full chemical characterization and assay protocol details, are being deposited into publicly accessible, relational databases such as the National Library of Medicine's PubChem (*http://pubchem.ncbi.nlm.nih.gov/*), EPA's ACToR (*http://www.epa.gov/ACToR/*) and NTP's CEBS (*http://www.niehs.nih.gov/research/resources/databases/cebs/*).

In FY 2011, the differential cytotoxicity response of cells from humans was evaluated by screening ~1100 densely sequenced lymphoblastoid cell lines against 180 toxic chemicals. This study was designed to measure inter-individual differences in sensitivity to environmental toxicants, based on genotype. The data generated by this study will be evaluated during FY 2012.

Non-mammalian models – *Caenorhabditis elegans*

The NTP WormTox Facility develops toxicological assays using the nematode *C. elegans* and evaluates their utility as medium throughput screening tools. The use of *C. elegans* is consistent with NTP's strategy to reduce the number of mammals used in testing. Several toxicology assays and statistical analysis tools have been developed to monitor *C. elegans* feeding, growth, reproduction, and movement after chemical exposures. In FY 2011, screening began of the U.S. EPA's ToxCast Phase II chemical library, which consists of 700 compounds, using the *C. elegans* growth assay. The studies will continue through FY 2012. Also during FY 2011, development of a new assay to monitor *in vivo* gene expression changes in transgenic *C. elegans* after exposure to various classes of environmental toxicants was initiated. Table 34 lists ongoing and completed *C. elegans* studies.

Table 34. Completed and Ongoing C. *elegans* Studies During FY2011

Chemical	CASRN
Hexafluorosilicic acid	16961-83-4
Sodium fluoride	7681-49-4
Sodium hexafluorosilicate	16893-85-9
EPA ToxCast™ Phase 1 320 compounds	List of chemicals available at *http://www.epa.gov/ncct/toxcast/chemicals.html*
EPA ToxCast™ Phase II 700 compounds	

The NCGC BioPlanet

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

Toxicogenomics Studies

The NTP is working to bring the latest toxicogenomics technology into its testing program to help revolutionize the way NTP conducts its studies. Toxicogenomics examines how the entire genetic structure, or genome, is involved in an organism's response to environmental toxicants. It applies gene and protein technologies to environmental medicine by studying the effect of toxicants on gene activity and specific proteins produced by genes. This information could be useful to identify biomarkers of disease and exposure to toxic substances and for understanding individual genetic susceptibilities.

Preliminary toxicogenomic studies suggest that gene expression often is predictive for phenotypic alterations. The NTP is interested in determining if differential gene expression (DGE) analysis can provide indicators of toxicity at earlier time points and at lower doses than possible with traditional toxicology parameters. DGE may provide more than a genotypic link to a morphology, because it is expected to provide insights into the pathogenesis of the disease and how different rodent models respond to toxicants.

Perhaps the most exciting potential of toxicogenomics is the possibility to identify biomarkers of exposure or biomarkers of effect. Changes that can be found in easily obtainable samples (blood and urine) could then be monitored in clinical studies. When the technology is validated, it will allow repeated sampling during long-term NTP studies to determine whether chemical exposures can be detected or whether developing cancers will provide a genetic signature.

The NTP is currently evaluating study conditions that may contribute to gene expression (e.g., animal and tissue variability), best methods of tissue sampling, and establishing standards for conducting toxicogenomic studies under laboratory conditions. A long-term goal of the NTP is to identify more accurate methods of predicting carcinogenicity, because current NTP carcinogenicity studies take four to five years to complete and are costly. Planned or ongoing NTP toxicogenomic studies are listed in Table 35.

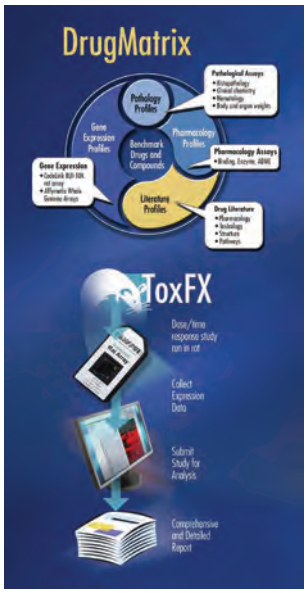
Table 35. Toxicogenomics studies (Ongoing, Completed, Initiated)

Chemical	CASRN	Species/Strain	Study Route	Study Length	Platform
1,2,3,7,8-Pentabromodibenzofuran 1,2,3,7,8-Pentachlorodibenzofuran 2,3-Dibromo-7,8-dichlorodibenzo-*p*-dioxin 2,3,4,7,8-Pentabromodibenzofuran 2,3,4,7,8-Pentachlorodibenzofuran 2,3,7,8-Tetrabromodibenzofuran	107555-93-1 57117-41-6 50585-40-5 13116-92-2 57117-31-4 67733-57-7	Mice: B6C3F1	Gavage	3/11 days	Microarray qPCR
Acetochlor Bisphenol A Carbaryl *N,N*-Dimethyl-*p*-toluidine Flusilazole Perfluorooctane sulfonic acid 2,5-Pyridinedicarboxylic acid, dipropyl ester Simazine Triclosan	34256-82-1 80-05-7 63-25-2 99-97-8 85509-19-9 335-67-1 136-45-8 122-34-9 3380-34-5	Rats: Harlan Sprague–Dawley	Gavage	4 days	Microarray
Aflatoxin B1	1162-65-8	Rats: F344/N	Feed	90 days	NextGen Sequence, qPCR
Aloe vera extract	NA	Rats: F344/N	Oral	2 years	qPCR
Antimony trioxide	1309-64-4	Mice: B6C3F1	Oral	2 years	Microarray
Bromodichloroacetic acid (BDCA)	71133-14-7	Rats: F344	Oral	2 years	qPCR
Effect on loss of ROR-α and TAK1 in knockout mice on metabolomics profile – no chemical	NA	Mouse: C57/BL6	NA	NA	NMR, LC-MS/MS

Chemical	CASRN	Species/Strain	Study Route	Study Length	Platform
Effect of diet on liver transcriptome – no chemical	NA	Rats: Wistar Han	NA	90 days	Microarray
Ginkgo biloba extract	NA	Mice: BC3F1	Oral	2 years	Microarray
Oxybenzone	131-57-7	Rats: Harlan SD	Gavage	90 days	Microarray
BDE 47 BDE 71 BDE 99 DE 153 BDE Mixture	5436-43-1 32534-81-9 60348-60-9 68631-49-2 Mixtures	Rats: Wistar Han Mice: B6C3F1/N	Gavage	14/90 days	Microarray
Pentabromodiphenyl oxide (technical) (DE 71)	32534-81-9	Rats: Wistar Han	Gavage	GD 6 – PD 21	Microarray
2,3,-Pentanedione	600-14-6	Rats: F344	Inhalation	3 weeks	Microarray
Sodium arsenite	7784-46-5	Human/RWPE-1 prostate cells	*In vitro*	30 weeks	NextGen Sequence
Spontaneous Liver and Lung tumors	NA	Mice: B6C3F1	NA	NA	Microarray
Trimethyltin hydroxide	56-24-6	Mice: CD-1	Intra-peritoneal injection	2 days	qNPA
Vinylidene chloride	75-35-4	Rats: F344/N Mice: B6C3F1	Oral	2 years	Microarray

Mining the NTP Tissue Archives for Gene Signatures

The NTP archives contain stained histopathology slides, paraffin tissue blocks, formalin-fixed tissues and organs, and selected frozen tissue from over 2,000 studies including toxicity, carcinogenicity, immunotoxicity, reproductive, and developmental studies. In FY 2010, NTP initiated pilot studies to evaluate the extent to which gene expression signatures can be reliably derived from the molecular analysis of tissue samples collected from the laboratory animals used in NTP's toxicological studies and stored as formalin-fixed, paraffin-embedded (FFPE) tissues in the NTP archives. Signature expression profiles are critical sets of altered transcripts or proteins that distinguish toxicity and disease from a comparable normal state. Two sets of studies were conducted during FY 2011. In one study, RNA was extracted from a limited number of four-year old paraffin blocks of liver and a selected set of genes evaluated for expression using RT-PCR. The results compared favorably with those obtained for the same genes using RNA from fresh samples, indicating that this technology could be applied to FFPE samples. In a second study, a different transcript profiling technique–qNPA–was used to compare transcripts from fresh or FFPE brain and liver. Results again demonstrated the usefulness of archival tissue blocks for gene profiling. Future studies will make a wider and more systematic query of NTP archival materials of different organs and storage times for their value in transcript profiling.



DrugMatrix®

Related to the goal of developing analysis tools and approaches to allow an integrated assessment of HTS endpoints and associations with findings from traditional toxicology and cancer models, the NTP acquired DrugMatrix,® a toxicogenomics reference database, the accompanying extensive frozen tissue archives, and the informatics system. This resource will expand NTP's ability to develop predictive models for toxicological effects based on gene signatures, provide additional tools for linking *in vitro* data to *in vivo* gene signatures and disease outcomes, and provide additional tissue samples for NextGen-based investigations. In late FY 2011, DrugMatrix® and its companion, automated analysis tool, ToxFX®, were made accessible to the international scientific community in beta release format at https://ntp.niehs.nih.gov/drugmatrix and https://ntp.niehs.nih.gov/toxfx/, respectively. To date, over 100 researchers have registered to use the DrugMatrix® database. In addition, the data and biological samples from DrugMatrix® are a focal point in a number of collaborations between DNTP scientists and research groups from the FDA's National Center for Toxicological Research, the City of Hope, Stanford University, Boston University, U.S. EPA, Health Canada, Abbott Laboratories, Eli Lilly and Company, SAS, Maastrich University, GeneData, University of Massachusetts, and University of North Dakota. The goal of these collaborations is to use the DrugMatrix® data to better understand the molecular underpinnings of disease and toxicological pathology.

Host Susceptibility Program

Host Susceptibility Aging Cohort

Genetic and epigenetic differences between individuals within the human population are believed to be the basis for individual susceptibility to environmental stressors, including idiosyncratic drug toxicities. However, at present, environmental and drug safety assessments are conducted with a small number of commonly used animal models with limited genetic diversity that is insufficient to evaluate the influence of individual genetic differences on chemical and drug toxicity and is of limited value in extrapolating to human toxicity and disease. To improve the extrapolation of results from rodent models to human hazard identification and risk assessment, an aging study to produce a benchmark reference data set was started in FY 2009 using 10 inbred strains of mice (including the 8 used in the Collaborative Cross; see Diversity Outbred mice below) to provide data on survival rates, spontaneous disease incidence, histopathology, hematology, clinical chemistry, quantitative trait loci, and behavioral observations, as well as for collecting tissue/fluids for future genetic/genomic/metabolomic analysis. The strains selected include classical and wild-derived inbred strains that represent the greatest degree of genetic diversity in the mouse genome that is known at the present (based upon the analysis of the NTP-Perlegen genotyping initiative data). This study is expected be completed in FY 2012 and study results will continue to be analyzed during FY 2013; the results will aid scientists in selecting the most appropriate mouse strains for study and aid in the extrapolation of response to toxicant exposure and prediction between species.

Diversity Outbred (DO) Mice and Population Based Models for Toxicology and Disease

Population-based models are required in order to quantify the impact of genetic and epigenetic diversity (based upon sequence variation) on toxicity and associated disease. From ADME studies initiated in FY2009 using a panel of 18 inbred strains (including the 8 used in the Collaborative Cross), we had identified significant inbred strain variation (10-36X kinetic differences) in both area under the curve (AUC) and clearance from blood and bone marrow using [14C]-benzene following a single oral dose. In particular, the difference in clearance of [14C]-benzene, including metabolites, from the bone marrow suggests that significant population based

differences might be observed for benzene-induced genotoxicity and hematotoxicity. Using the data from the NTP-Perlegen sequencing effort, researchers at The Jackson Laboratory and UNC-Chapel Hill have performed a "collaborative cross" using an 8-way parental outcross that incorporated 90% of all the known genetic diversity observed in all inbred laboratory and wild-derived strains. From this complex outcross, more than 300 advanced intercross lines are being produced. From a large sample of male and female mice from the 4th and 5th generation, a large randomized breeding program was created to produce the diversity outbred mouse population with low inbreeding coefficient. Due to the large number of meiotic recombination events, the genomes of the 8 parental lines (included in the aforementioned ADME studies panel) were segregated into small segments resulting in minor allele variants of no less than 10% across the genomes. This feature significantly improves the power to detect genotype-phenotype differences in this genetically diverse random breeding population. Research was initiated on this outbred stock for utility in the NTP research and testing program in late FY2011 using 28-day old DO male mice exposed to inhaled benzene (0, 1, 10, or 100 ppm; 75 mice/group) for 5 days/week for 4 weeks in two independent studies. Benzene is a known mouse and human toxicant and carcinogen with a significant published literature that aids data correlation between mouse and human toxicity. Pre-exposure differences in blood cell and red blood cell micronuclei values in samples from 300 male DO male mice were significant. A repeat study will occur in FY 2012. The data from two independent studies of DO mice will be evaluated using computation toxicology and quantitative genotype-phenotype analysis.

Host Susceptibility to Ionizing Radiation

Genetically engineered mouse models (GEMM) have been effectively used as surrogates for studying human cancers and for determining the mode/mechanistic basis of action for carcinogens. In FY 2009, six different p53 haploinsufficient F1 mouse strains were created by outcross of females from selected strains (A/J, BALB/C, BTBR.T/J, C3H/HeJ, DBA2/J, or 129S1.SvlmJ), based upon their genetic diversity in DNA double strand break repair, to B6.129-Trp53^{tm1Brd} N12 homozygous null males. At 8 weeks of age, the F1 progeny were exposed to 0, 3, or 6 Gy of ionizing radiation. A dominant feature of carcinogen-induced tumors in this mouse model is the loss of the *Trp53* wildtype allele and genome wide loss of heterozygosity (LOH) often associated with loss of tumor suppressor gene function in human cancer. The pattern of LOH suggests significant changes in gene copy number variation (gene deletions and gene duplications). This project is focused on the further development of GEMM of tumor suppressor gene deficient mice for predicting carcinogenicity, determining the mode of action, and the presumptive risk of environmental exposures to humans. An additional aim is the identification of causally related genes and the specific functional allelic and copy number variants within inbred strains of mice that modify carcinogen potency. Preliminary results indicate significant differences across the six different p53 haploinsufficient F1 strains employed in terms of survival, median time to tumor, tumor phenotype spectrum, and tumor prevalence. The results implicate dysregulation of DNA strand break repair. In FY 2012, a tiered approach will be used to define system level differences in toxicogenomics associated with differences in strain susceptibilities and to better define a short-term cancer bioassay for research and testing. Determination of the allelic variants of genes causally related to DNA damage and repair with altered function may be critical to understand the differences in risk due to exposure to environmental mutagens.

NIH Mouse Methylome Project

An individual's response to exposure-related toxicity and concomitant disease is influenced at the genomic level by genetic, epigenetic, gene-gene interactions (intrinsic factors), and interaction with the environment (extrinsic factors). Individual DNA sequence variation does not account for all of the heritability for susceptibility to toxicity or diseases such as asthma, cancer, and diabetes. An intrinsic factor that quantitative and molecular geneticists believe is the basis for the observed "missing heritability" is the methylome, an individual's genome-wide methylated CpG sequence pattern. The methylome (a component of the epigenome) may be the major epigenetic modifier of the susceptibility to cancer and other chemical exposure-related diseases. Presently, there is no mouse reference database for the methylome. The absence of a methylome reference database for the mouse significantly handicaps understanding of the mouse model in toxicology and environmentally related diseases and in designing and conducting hypothesis based genetic and epigenetic research studies to understand the associated mechanisms. To produce a methylome reference database based for 5-methylcytosine genome wide patterns in mice relevant to the NTP studies, we outcrossed C56BL/6N females to C3H/HeN males and vice versa to produce F1 siblings under NTP dietary and environmental specifications. Five tissues (brain, liver, cardiac and skeletal muscle, brown and white fat, epididymal sperm) were collected at the average age mice would start an NTP subchronic toxicity study and flash-frozen for DNA/RNA isolation and sequencing of liver (starting in FY 2011 and continuing through FY 2012) from each parental line and outcross and gender are being used to (1) determine genome wide methylated CpG sites by deep sequencing of bisulfite treated genomic DNA to determine sequence context and cytosine methylation variation (BIS-Seq) and RNA (RNA-Seq) and (2) fractionate DNA sequences using differential restriction and/or affinity capture (MMDE-seq) to enrich for methylated DNA sequences. Together, these tools allow targeted interrogation of CpG regions of interest using bioinformatic data mining tools and a determination of within and between strain variations as well as parent of origin differences. These data will allow creation of a definitive map of the mouse liver methylome from these parental strains (C57BL/6N and C3H/HeN) and their F1 hybrid offspring that exhibit dramatically different rates of interstrain and sex dependent spontaneous liver cancer that often confound NTP 2-year toxicology and carcinogenesis studies.

Appendix I

Agency Staff and Contact Information

NTP staff are listed alphabetically by agency

NCTR/NTP		
Babb, Amy	(870) 543-7697	amy .babb@fda.hhs.gov
Beland, Frederick	(870) 543-7205	frederick.beland@fda.hhs.gov
Boudreau, Mary	(870) 543-7526	mary .boudreau@fda.hhs.gov
Brakebill, Nancy	(870) 543-7785	nancy .brakebill@fda.hhs.gov
Chen, Xinping	(870) 543-7702	xinping.chen@fda.hhs.gov
Chidambaram, Mani	(870) 543-7368	mani.chidambaram@fda.hhs.gov
Churchwell, Mona	(870) 543-7698	mona.churchwell@fda.hhs.gov
Corlett, Angela	(870) 543-7403	angela.corlett@fda.hhs.gov
Couch, Letha	(870) 543-7137	letha.couch@fda.hhs.gov
Cozart, Christy	(870) 543-7602	christy.cozart@fda.hhs.gov
Cunningham, Candice	(870) 543-7886	candice.cunningham@fda.hhs
Delclos, Barry	(870) 543-7372	barry .delclos@fda.hhs.gov
Doerge, Daniel	(870) 543-7943	daniel.doerge@fda.hhs.gov
Duffy, Peter	(870) 543-7054	peter.duffy@fda.hhs.gov
Fang, Jia-Long	(870) 543-7612	jia-long.fang@fda.hhs.gov
Felton, Robert	(870) 543-7504	robert.felton@fda.hhs.gov
Ferguson, Sherry	(870) 543-7589	sherry .ferguson@fda.hhs.gov
Fisher, Jeffrey	(870) 543-7703	jeffrey.fisher@fda.hhs.gov
Gamboa, Goncalo	(870) 543-7400	goncalo.gamboa@fda.hhs.gov
Guo, Lei	(870) 543-7048	lei.guo@fda.hhs.gov
Hansen, Deborah	(870) 543-7480	deborah.hansen@fda.hhs.gov
Heflich, Robert	(870) 543-7493	robert.heflich@fda.hhs.gov
Heinze, Thomas	(870) 543-7468	thomas.henize@fda.hhs.gov
Howard, Paul C.	(870) 543-7672	paul.howard@fda.hhs.gov
Imam, Mohammed Sadiq	(870) 543-7127	mohammed.imam@fda.hhs.gov
Keasling, Adam	(870) 543-7441	adam.keasling@fda.hhs.gov
Koturbash, Igor	(870) 543-7724	igor.koturbash@fda.hhs.gov
Law, Charles	(870) 543-7013	charles.law@fda.hhs.gov
Leakey, Julian	(870) 543-7916	julian.leakey@fda.hhs.gov
Lewis, Sherry	(870) 543-7627	sherrym.lewis@fda.hhs.gov
Loukotkova, Lucie	(870) 543-7406	lucie.loukotkova@fda.hhs.gov
McDaniel, Lea	(870) 543-7213	lea.mcdaniel@fda.hhs.gov
Mendoza, Maria	(870) 543-7844	maria.mendoza@fda.hhs.gov
Mittelstaedt, Roberta	(870) 543-7190	roberta.mittelstaedt@fda.hhs.gov
Moon, Steven	(870) 543-7124	steven.moon@fda.hhs.gov
Nichols, Jasyl	(870) 543-7210	jasyl.nichols@fda.hhs.gov
Nysia, George	(870) 543-7047	nysia.george@fda.hhs.gov
Pack, Lindsay	(870) 543-7681	lindsay.pack@fda.hhs.gov
Paredes, Angel	(870) 543-7949	angel.paredes@fda.hhs.gov
Paule, Merle	(870) 543-7147	merle.paule@fda.hhs.gov
Pogribna, Marta	(870) 543-7681	marta.pogribna@fda.hhs.gov
Pogribny, Igor	(870) 543-7096	igor.pogribny@fda.hhs.gov
Sepehr, Estatira	(870) 543-7902	estatira.sepehr@fda.hhs.gov
Siitonen, Paul	(870) 543-7656	paul.siitonen@fda.hhs.gov
Shaddock, Joseph	(870) 543-7280	joseph.shaddock@fda.hhs.gov
Stingley, Robin	(870) 543-7350	robin.stingley@fda.hhs.gov
Surratt, Gordon	(870) 543-7608	gordon.surratt@fda.hhs.gov
Thorn, Brett	(870) 543-7338	brett.thorn@fda.hhs.gov
Trbojevich, Raul	(870) 543-7490	raul.trbojevich@fda.hhs.gov
Twaddle, Nathan	(870) 543-7178	nathan.twaddle@fda.hhs.gov
Vanlandingham, Michelle	(870) 543-7458	michelle.vanlandingham@fda.hhs.gov
VonTungeln, Linda	(870) 543-7620	linda.vontungeln@fda.hhs.gov
Wang, Cheng	(870) 543-7259	cheng.wang@fda.hhs.gov
Weis, Connie	(870) 543-7378	connie.weis@fda.hhs.gov
Willingham, Evelyn	(870) 543-7938	evelyn.willingham@fda.hhs.gov
Woodling, Kellie	(870) 543-7491	lkellie.woodling@fda.hhs.gov

NIEHS/NTP		
Alden, Charles	(919) 541-5722	alden@niehs.nih.gov
Allen, Bonnie	(919) 541-3449	allenb@niehs.nih.gov
Allen, David	(919) 316-4664	allen7@niehs.nih.gov
Alper, Scott	(919) 541-4377	alpers@niehs.nih.gov
Andrews, Danica	(919) 541-2595	andrewsda@niehs.nih.gov
Auerbach, Scott	(919) 541-4505	auerbachs@niehs.nih.gov
Bhusari, Sachin	(919) 541-3069	bhusaris@niehs.nih.gov
Birnbaum, Linda	(919) 541-3201	birnbaumls@niehs.nih.gov
Bishop, Jack	(919) 541-1876	bishop@niehs.nih.gov
Blystone, Chad	(919) 541-2741	blystonecr@niehs.nih.gov
Borde, Aditi	(919) 541-0461	(special volunteer to Dr. Fenton)
Borde, Pretish	(919) 541-4141	(special volunteer to Dr. Fenton)
Bowden, Beth	(919) 541-3355	bowden1@niehs.nih.gov
Boyd, Windy	(919) 541-9810	boydw@niehs.nih.gov
Boyle, Michael	(919) 541-1676	boylemc@niehs.nih.gov
Boyles, Abee	(919) 541-7886	boylesa@niehs.nih.gov
Brown, Quashana	(919) 541-4069	brownqd@niehs.nih.gov
Bucher, John	(919) 541-4532	bucher@niehs.nih.gov
Casey, Warren	(919) 316-4729	warren.casey@nih.gov

Caspary, William	(919) 541-2150	caspary@niehs.nih.gov
Castro, Lysandra	(919) 541-3373	castro@niehs.nih.gov
Cesta, Mark	(919) 541-3229	cesta@niehs.nih.gov
Chan, Po-Chuen	(919) 541-7561	chanp@niehs.nih.gov
Chan, Melissa	(919) 541-3857	chanp2@niehs.nih.gov
Chang, Xiaoging	(919) 541-2373	changx@niehs.nih.gov
Chen, Vivian	(919) 541-3474	(special volunteer w/S Elmore)
Chhabra, Rajendra	(919) 541-3386	chhabrar@niehs.nih.gov
Clayton, Natasha	(919) 541-7843	clayton2@niehs.nih.gov
Collins, Bradley	(919) 541-4666	collin10@niehs.nih.gov
Cora, Michelle	(1919) 316-4717	coramc@niehs.nih.gov
Corniffe, Glenda	(919) 541-4880	corniffe@niehs.nih.gov
Cunningham, Michael	(919) 541-3799	cunning1@niehs.nih.gov
Cunny, Helen	(919) 541-5717	cunnyh@niehs.nih.gov
de Serres, Frederick	(919) 541-0718	deserres@niehs.nih.gov
DeVito, Michael	(919) 541-4142	devitom@niehs.nih.gov
Di, Xudong	(919) 316-4611	dix3@niehs.nih.gokamel
Dixon, Darlene	(919) 541-3814	dixon@niehs.nih.gov
Dunlap, Paul	(919) 541-2679	dunlapp@niehs.nih.gov
Dunnick, June	(919) 541-4811	dunnickj@niehs.nih.gov
Elmore, Susan	(919) 541-3474	elmore@niehs.nih.gov
Faustman, Elaine	(919) 541-7539	faustman@niehs.nih.gov
Fenton, Suzanne	(919) 541-4141	fentonse@niehs.nih.gov
Fields, Sally	(919) 541-3971	fields3@niehs.nih.gov
Filgo, Adam	(919) 541-4672	adam.filgo@nih.gov
Flagler, Norris	(919) 541-2397	flagler@niehs.nih.gov
Flake, Gordon	(919) 541-0037	flake@niehs.nih.gov
Foley, Julie	(919) 541-3772	foley1@niehs.nih.gov
Fostel, Jennifer	(919) 541-5055	fostel@niehs.nih.gov
Foster, Paul	(919) 541-2513	foster2@niehs.nih.gov
Fraller, Deirdre	(919) 541-0927	frallerdb@niehs.nih.gov
Frawley, Rachel	(919) 541-2151	frawleyr@niehs.nih.gov
Freedman, Jonathan	(919) 541-7899	freedma1@niehs.nih.gov
French, Jef	(919) 541-2569	french@niehs.nih.gov
Fuhrman, Laura	(919) 541-3415	Laura.Fuhrman@nih.gov
Gao, Xiaohua	(919) 316-4611	gaox3@niehs.nih.gov
Germolec, Dori	(919) 541-3230	germolec@niehs.nih.gov
Goldsmith, Rachel	(919) 541-2522	Rachel.goldsmith@nih.gov
Guy, Robbin	(919) 541-4363	guyr2@niehs.nih.gov
Gwinn, William	(919) 541-0598	gwinnwm@niehs.nih.gov
Hall, Carolyn	(919) 541-4995	hall7@niehs.nih.gov
Hall, Julie	(919) 541-2679	Hall2@niehs.nih.gov
Hall, Laura	(919) 541-7931	hall@niehs.nih.gov
Harry, Jean	(919) 541-0927	harry@niehs.nih.gov
Harvey, Janice	(919) 541-1745	janice.harvey@nih.gov
Herbert, Ronald	(919) 541-4613	herbert1@niehs.nih.gov
Hoenerhoff, Mark	(919) 541-3440	hoenerhm@niehs.nih.gov
Hong, Hue-Hua	(919) 541-2141	hong5@niehs.nih.gov
Hooth, Michelle	(919) 316-4643	hooth@niehs.nih.gov
Howdeshell, Kembra	(919) 316-4708	howdeshellkl@niehs.nih.gov
Hsieh, Jui-Hua	(919) 316-4879	hsiehj2@niehs.nih.gov
Irwin, Richard	(919) 541-3340	irwin@niehs.nih.gov
Jahnke, Gloria	(919) 541-3376	jahnke@niehs.nih.gov
Jameson, CW (Bill)	(919) 541-4096	(special volunteer - Dr Bucher)
Jayaram, Beby	(919) 541-1480	jayaram1@niehs.nih.gov
Jensen, Heather	(919) 541-4075	jensen1@niehs.nih.gov
Jeter, Shawn	(919) 541-3476	jeter@niehs.nih.gov
Johnson, Frank	(919) 541-3503	johnso54@niehs.nih.gov
Jones, Tina	(919) 541-2836	jones30@niehs.nih.gov
Kim, Sang-Hyun	(919) 541-9468	sang-hyum.kim@nih.gov
King, Debra	(919) 541-0698	kingdh@niehs.nih.gov
King-Herbert, Angela	(919) 541-3464	kingher1@niehs.nih.gov
Kissling, Grace	(919) 541-1756	kissling@niehs.nih.gov
Koivisto, Christopher	(919) 541-3241	koivist@niehs.nih.gov
Lahousse, Stephanie	(919) 541-3069	lahousses@niehs.nih.gov
Lasko, Denise	(919) 541-0255	lasko@niehs.nih.gov
Liu, Ailin	(919) 541-2679	Liua2@niehs.nih.gov
Litton, Dan	(919) 541-2100	litton@niehs.nih.gov
Lunn, Ruth	(919) 316-4637	lunn@niehs.nih.gov
Macon, Madisa	(919) 541-4703	madisa.macon@nih.gov
Malarkey, David	(919) 541-1745	malarkey@niehs.nih.gov
Malling, Heinrich	(919) 541-3378	malling@niehs.nih.gov
Masinde, Tiwanda	(919) 541-4069	marsh2@niehs.nih.gov
Masten, Scott	(919) 541-5710	masten@niehs.nih.gov
Maull, Elizabeth	(919) 316-4668	maull@niehs.nih.gov
McCarley, Deborah	(919) 541-2384	mccarley@niehs.nih.gov
McIntyre, Barry	(919) 316-4747	mcintyrebs@niehs.nih.gov
McPherson, Chris	(919) 541-0167	Mcphers1@niehs.nih.gov
Melnick, Ronald	(919) 541-4142	melnickr@niehs.nih.gov
Mercado-Feliciano, Minerva	(919) 541-2756	mercadofelicim@niehs.nih.gov
Merrick, Alex	(919) 541-1531	merrick1@niehs.nih.gov
Moore, Alicia	(919) 541-7914	moore5@niehs.nih.gov
Morgan, Daniel	(919) 541-2264	morgan3@niehs.nih.gov
Newbold, Retha	(919) 541-0738	newbold1@niehs.nih.gov
Ney, Elizabeth	(919) 541-5182	ney@niehs.nih.gov
Ngalame, Ntube	(919) 541-5436	ngalamenn@niehs.nih.gov
Nichols, Sharon	(919) 541-7992	nicholss2@niehs.nih.gov
Orihuela Garcia, Ruben	(919) 541-0540	ruben.orihuela@nih.gov

Ovwigho, Pamela	(919) 541-3278	ovwighope@niehs.nih.gov
Parham, Frederick	(919) 541-0760	parham@niehs.nih.gov
Person, Rachel	919) 541-0685	rachel.person@nih.gov
Qu, Wei	(919) 541-0540	qu@niehs.nih.gov
Quist, Erin	(919) 541-3036	erin.quist@nih.gov
Rebolloso, Yvette	(919) 541-4209	rebollo1@niehs.nih.gov
Rice, Julie	(919) 541-2533	ricej2@niehs.nih.gov
Rider, Cynthia	(919) 541-7638	ridercv@niehs.nih.gov
Roach, Donna	(919) 541-3023	roachd@od.nih.gov
Robinson, Deidre	(919) 541-4141	deidre.robinson@nih.gov
Robinson, Veronica	(919) 541-2238	godfrey@niehs.nih.gov
Rooney, Andrew	(919) 316-4704	rooneyaa@niehs.nih.gov
Rowley, Michael	(919) 541-3436	rowley@niehs.nih.gov
Roycroft, Joseph	(919) 541-3627	roycroft@niehs.nih.gov
Sanders, Michael	(919) 541-1872	sander10@niehs.nih.gov
Shelby, Michael	(919) 541-3455	shelby@niehs.nih.gov
Shines, Cassandra	(919) 541-0959	shines1@niehs.nih.gov
Shockley, Keith	(919) 541-3033	shockleykr@niehs.nih.gov
Sills, Robert	(919) 541-0180	sills@niehs.nih.gov
Smith, Cynthia	(919) 541-3473	smith19@niehs.nih.gov
Soward, Sharon	(919) 541-5132	soward@niehs.nih.gov
Spencer, Diane	(919) 541-2759	spencer2@niehs.nih.gov
Stanko, Jason	(919) 541-0461	stankojp@niehs.nih.gov
Stockton, Patricia	(919) 541-4471	stockton@niehs.nih.gov
Stokes, William	(919) 541-7997	stokes@niehs.nih.gov
Stout, Matthew	(919) 541-3489	stoutm@niehs.nih.gov
Sun, Yang	(919) 541-9812	suny2@mail.nih.gov
Surh, In Ok	(919) 541-3862	surhi@niehs.nih.gov
Sutton, Deloris	(919) 541-5112	sutton2@niehs.nih.gov
Taylor, Kyla	(919) 316-4707	taylorkw@niehs.nih.gov
Teng, Christina	(919) 541-0344	teng1@niehs.nih.gov
Thakur, Sheetal	(919) 541-9468	thakursa@niehs.nih.gov
Thayer, Kristina	(919) 541-5021	thayer@niehs.nih.gov
Tice, Raymond	(919) 541-4482	tice@niehs.nih.gov
Tokar, Erik	(919) 541-3951	tokare@niehs.nih.gov
Ton, Thai-Vu	(919) 541-2118	ton@niehs.nih.gov
Travlos, Gregory	(919) 541-0653	travlos@niehs.nih.gov
Tubbs, Jacquelyn	(919) 541-2919	tubbsj@niehs.nih.gov
Vallant, Molly	(919) 541-5234	vallant@niehs.nih.gov
Waalkes, Michael	(919) 541-2328	waalkes@niehs.nih.gov
Waidyanatha, Suramya	(919) 541-2144	waidyanathas@niehs.nih.gov
Walker, Nigel	(919) 541-4893	walker3@niehs.nih.gov
Walker, Vickie	(919) 541-4514	ray3@niehs.nih.gov
White, Lori	(919) 541-9834	whiteld@niehs.nih.gov
Wilson, Ralph	(919) 541-4140	wilson23@niehs.nih.gov
Withers, Sheila	(919) 541-5066	withersg@niehs.nih.gov
Witt, Kristine	(919) 541-2761	witt@niehs.nih.gov
Wolfe, Mary	(919) 541-7539	wolfe@niehs.nih.gov
Wyde, Michael	(919) 316-4640	wyde@niehs.nih.gov
Xu, Yuanyuan	(919) 541-3024	Xuy5@mail.nih.gov
Yu, Xianhong	(919) 316-4599	yu1@niehs.nih.gov

NIOSH/NTP

Anderson, Stacy	(304) 285-6174-x2	dbx7@cdc.gov
Beezhold, Don	(304) 285-5963	zec1@cdc.gov
Brown, Kenneth	(513) 841-4364	krb1@cdc.gov
Chipinda, Itai	(304) 285-5721	clz0@cdc.gov
Curwin, Brian	(513) 841-4432	bic4@cdc.gov
DeBord, D. Gayle	(513) 533-8212	ded4@cdc.gov
Erdely, Aaron	(304) 285-5903	efi4@cdc.gov
Estill, Cherie	(513) 841-4476	clf4@cdc.gov
Franko, Jennifer	(304) 285-6174-x8	hfy0@cdc.gov
Geraci, Chuck	(513) 533-8339	ciu9@cdc.gov
Green, Brett	(304) 285-5884	dox6@cdc.gov
Hanley, Kevin	(513) 841-4113	kwh0@cdc.gov
Harper, Martin	(304) 285-6034	zzg7@cdc.gov
Hodson, Laura	(513) 533-8526	gey7@cdc.gov
Johnson, Victor	(304) 285-6249	vcj6@cdc.gov
Luster, Michael	(304) 285-5940	myl6@cdc.gov
Lynch, Dennis	(513) 533-8213	dwl1@cdc.gov
Methner, Mark	(513) 841-4325	mmm5@cdc.gov
Munson, Albert E.	(304) 285-6121	akm5@cdc.gov
Qian, Yong	(304) 285-6286	yaq2@cdc.gov
Reynolds, Steve	(304) 285-5806	sir6@cdc.gov
Schubauer-Berigan, Mary	(513) 841-4251	zcg3@cdc.gov
Siegel, Paul	(304) 285-5855	pds3@cdc.gov
Snawder, John	(513) 533-8496	jts5@cdc.gov
Stefaniak, Aleksandr	(304) 285-6302	boq9@cdc.gov
Streicher, Robert	(513) 841-4296	rps3@cdc.gov
Striley, Cynthia	(513) 533-8123	chs3@cdc.gov
Virji, Mohammed	(304) 285-5797	fnb8@cdc.gov
Wells, Ray	(304) 285-6341	ozw0@cdc.gov
Whelan, Elizabeth	(513) 841-4437	eaw0@cdc.gov
Wurzelbacher, Steve	(513) 841-4322	srw3@cdc.gov
Yucesoy, Berran	(304) 285-5993	yab7@cdc.gov

Appendix 2

NTP FY 2011 Bibliography

[7] Abdel-Rahman A, Anyangwe N, Carlacci L, Casper S, Danam RP, Enongene E, Erives G, Fabricant D, Gudi R, Hilmas CJ, Hines F, Howard P, Levy D, Lin Y, Moore RJ, Pfeiler E, Thurmond TS, Turujman S, Walker NJ. 2011. The safety and regulation of natural products used as foods and food ingredients. *Toxicol Sci* 123(2):333-48.

[7] Adams ET, Auerbach S, Blackshear PE, Bradley A, Gruebbel MM, Little PB, Malarkey D, Maronpot R, McKay JS, Miller RA, Moore RR, Morrison JP, Nyska A, Ramot Y, Rao D, Suttie A, Wells MY, Willson GA, Elmore SA. 2011. Proceedings of the 2010 National Toxicology Program Satellite Symposium. *Toxicol Pathol* 39, 240-266.

[7] Akgul Y, Derk RC, Meighan T, Rao KMK, Murono EP. 2011. The methoxychlor metabolite, HPTE, inhibits rat luteal cell progesterone production. *Rep Toxicol* 32(1):77-84.

[3] Ali AA, Lewis SM, Badgley HL, Allaben WT, Leakey JE. 2011. Oral glucosamine increases expression of transforming growth factor beta1 (TGFbeta1) and connective tissue growth factor (CTGF) mRNA in rat cartilage and kidney: Implications for human efficacy and toxicity. *Arch Biochem Biophys* 510(1):11-18.

[4] Ali R, Mittelstaedt RA, Shaddock JG, Ding W, Bhalli JA, Khan QM, Heflich RH. 2011. Comparative analysis of micronuclei and DNA damage induced by ochratoxin A in two mammalian cell lines. *Mut Res/Gen Toxoicol Envir Mut 723*(1):58-64.

[4] Ali S, Sharma HS. 2011. Substituted amphetamine-induces neurotoxicity and alterations in blood-brain-barrier function. *Tox Lett* 205:S26.

[4] Andrade JE, Twaddle NC, Helferich WG, Doerge DR. 2010. Absolute bioavailability of isoflavones from soy protein isolate-containing food in female Balb/c mice. *J Agric Food Chem* 58(7):4529-4536.

[1] Anderson SE, Siegel PD, Meade BJ. 2011. The LLNA: A brief review of recent advances and limitations. *J Allergy* (Cairo) Epub.

[2] Antonini JM, Roberts JR, Stone S, Chen BT, Schwegler-Berry D, Chapman R, Zeidler-Erdely PC, Andrews RN, Frazer DG. 2011. Persistence of deposited metals in the lungs after stainless steel and mild steel welding fume inhalation in rats. *ArchToxicol* 85(5):487-498.

[3] Antunes AMM, Godinho ALA, Martins IL, Oliveira MC, Gomes RA, Coelho AV, Beland FA, Marques MM. 2010. Protein adducts as prospective biomarkers of nevirapine toxicity. *Chem Res Toxicol* 23(11):1714-1725.

[2] Archer Hartmann SA, Sargent LM, Lowry DT, Holland LA. 2011. Microscale exoglycosidase processing and lectin capture of glycans with phospholipid assisted capillary electrophoresis separations. *Analyt Chem* 83(7):2740-2747.

[7] Asemu G, Fishbein K, Lao QZ, Ravindran A, Herbert R, Canuto HC, Spencer RG, Soldatov NM. 2011. Cardiac phenotype induced by a dysfunctional α1C transgene: A general problem for the transgenic approach. *Channels* 5(2):138-147.

[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 the NTP/NHGRI/EPA/FDA Interagency Memorandum of Understanding
[6] Funded by the NIEHS/EPA Interagency Agreement
[7] Funded by NIEHS voluntary allocations to the NTP

[7] Auerbach SS, Thomas R, Shah R, Xu H, Vallant MK, Nyska A, Dunnick JK. 2010. Comparative phenotypic assessment of cardiac pathology, physiology, and gene expression in C3H/HeJ, C57BL/6J, and B6C3F1/J mice. *Toxicol Path* 38(6):923-942.

[1] Beezhold DH. 2011. Monoclonal antibodies 3C3, 6D4, 7D11, 9G6, 24D11, 27C10, 27E2, and 29E5. *Hybridoma* 30(1):103-103.

[2] Beezhold K, Liu J, Kan H, Meighan T, Castranova V, Shi X, Chen F. 2011. miR-190-mediated downregulation of PHLPP contributes to arsenic-induced Akt activation and carcinogenesis. *Toxicol Sci* 123(2):411-420.

[1] Bernstein DI, Kissling GE, Hershey GK, Yucesoy B, Johnson VJ, Cartier A, Gautrin D, Sastre J, Boulet LP, Malo JL, Quirce S, Tarlo SM, Langmeyer S, Luster MI, Lummus ZL. 2011. Hexamethylene diisocyanate asthma is associated with genetic polymorphisms of CD14, IL-13, and IL-4 receptor alpha. *J Allergy Clin Immunol* 128(2):418-420.

[7] Bhave VS, Donthamsetty S, Latendresse JR, Cunningham ML, Mehendale HM. 2011. Secretory phospholipase A(2)-mediated progression of hepatotoxicity initiated by acetaminophen is exacerbated in the absence of hepatic COX-2. *Toxicol Appl Pharmacol* 251(3):173-180.

[2] B'Hymer C. 2011. Validation of an HPLC-MS-MS method for the determination of urinary S-benzylmercapturic acid and S-phenylmercapturic acid. *J Chrom Sci* 49(7):547-553.

[4] Binienda ZK, Beaudoin MA, Thorn BT, Ali SF. 2011. Analysis of electrical brain waves in neurotoxicology: Gamma-hydroxybutyrate. *Curr Neuropharm* 9(1):236-239.

[1] Blachere FM, Cao G, Lindsley WG, Noti JD, Beezhold DH. 2011. Enhanced detection of infectious airborne influenza virus. *J Virol Meth* 176(1-2):120-124.

[2] Blair A, Thomas K, Coble J, Sandler DP, Hines CJ, Lynch CF, Knott C, Purdue MP, Zahm SH, Alavanja MCR, Dosemeci M, Kamel F, Hoppin JA, Freeman LB, Lubin JH. 2011. Impact of pesticide exposure misclassification on estimates of relative risks in the Agricultural Health Study. *Occ Environ Med* 68(7):537-541.

[2] Bledsoe ML, Pinkerton LE, Silver S, Deddens JA, Biagini RE. 2011. Thyroxine and free thyroxine levels in workers occupationally exposed to inorganic lead. *Environ Health Insights* 5:55–61.

[7] Blystone CR, Elmore SA, Witt KL, Malarkey DE, Foster PM. 2011. Toxicity and carcinogenicity of androstenedione in F344/N rats and B6C3F1 mice. *Food Chem Toxicol* 49(9):2116-2124.

[4] Boctor SY, Ferguson SA. 2010. Altered adult locomotor activity in rats from phencyclidine treatment on postnatal days 7, 9 and 11, but not repeated ketamine treatment on postnatal day 7. *Neurotoxicol* 31(1):42-54.

[7] Boyles AL, Harris SF, Rooney AA, Thayer KA. 2011. Forest Plot Viewer: a fast, flexible graphing tool. *Epidemiol* 22(5):746-747.

[7] Bucher JR, Thayer K, Birnbaum LS. 2011. The Office of Health Assessment and Translation: A problem-solving resource for The National Toxicology Program. *Environ Health Perspec* 119(5):a196-a197.

[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 the NTP/NHGRI/EPA/FDA Interagency Memorandum of Understanding
[6] Funded by the NIEHS/EPA Interagency Agreement
[7] Funded by NIEHS voluntary allocations to the NTP

[2] Buck Louis GM, Schisterman EF, Sweeney AM, Wilcosky TC, Gore Langton RE, Lynch CD, Barr DB, Schrader SM, Kim S, Chen Z, Sundaram R. 2011. Designing prospective cohort studies for assessing reproductive and developmental toxicity during sensitive windows of human reproduction and development - the LIFE Study. *Paedi Perinatal Epidemiol* 25(5):413-424.

[1] Buskirk AD, Hettick JM, Chipinda I, Law BF, Siegel PD, Slaven JE, Green BJ, Beezhold DH. 2011. Fungal pigments inhibit the matrix-assisted laser desorption/ionization time-of-flight mass spectrometry analysis of darkly pigmented fungi. *Analyt Biochem* 411(1):122-128.

[2] Calvert GM, Ruder AM, Petersen MR. 2011. Mortality and end-stage renal disease incidence among dry cleaning workers. *Occ Environ Med* 68(10):709-716.

[7] Cannon CZ, Kissling GE, Hoenerhoff MJ, King-Herbert AP, Blankenship-Paris T. 2010. Evaluation of dosages and routes of administration of tramadol analgesia in rats using hot-plate and tail-flick tests. *Lab Animals* 39(11):342-351.

[7] Cannon CZ, Kissling GE, Goulding DR, King-Herbert AP and Blankenship-Paris T. 2011. Analgesic effects of tramadol, carprofen or multimodal analgesia in rats undergoing ventral laparotomy. *Lab Animals* 40(3):85-93.

[7] Carney EW, Ellis AL, Tyl RW, Foster PM, Scialli AR, Thompson K, Kim J. 2011. Critical evaluation of current developmental toxicity testing strategies: a case of babies and their bathwater. *Birth Defects Res B Dev Reprod Toxicol* 92:395-403.

[2] Carreon T, Hein MJ, Viet SM, Hanley KW, Ruder AM, Ward EM. 2010. Increased bladder cancer risk among workers exposed to o-toluidine and aniline: A reanalysis. *Occ Environ Med* 67(5):348-350.

[7] Casey W, Schmitt M, McFarland R, Isbrucker R, Levis R, Arciniega JL, Descamps J, Finn T, Hendriksen C, Horiuchi Y, Keller J, Kojima H, Sesardic D, Stickings P, Johnson NW, Lipscomb E, Allen D. 2011. Improving animal welfare and reducing animal use for human vaccine potency testing: state-of-the-science and future directions. In: International Workshop on Alternative Methods to Reduce, Refine, and Replace the Use of Animals in Vaccine Potency and Safety Testing: State of the Science and Future Directions (Kulpa-Eddy J, McFarland R, Stokes WS, eds). *Procedia Vaccinol* 5:33-46.

[2] Castranova V. 2011. Overview of current toxicological knowledge of engineered nanoparticles. *J Occ Environ Med* 53(6 Suppl):S14-S17.

[7] Chan PC, Ramot Y, Malarkey DE, Blackshear P, Kissling GE, Travlos G, Nyska A. 2010. Fourteen-week toxicity study of green tea extract in rats and mice. *Toxicol Path* 38(7):1070-1084.

[7] Chan PC, Peckham JC, Malarkey DE, Kissling GE, Travlos GS, Fu PP. 2011. Two-year toxicity and carcinogenicity studies of panax ginseng in Fischer 344 rats and B6C3F1 mice. *Amer J Chinese Med* 39(4):779-788.

[7] Chan PC. 2011. NTP technical report on the toxicity studies of 2,4-decadienal (CAS No. 25152-84-5) administered by gavage to F344/N rats and B6C3F1 mice. *Toxicity Report Series* 76:1-94.

[4] Chang CW, Beland FA, Hines WM, Fuscoe JC, Han T, Chen JJ. 2011. Identification and categorization of liver toxicity markers induced by a related pair of drugs. *Int J Mol Sci* 12(7):4609-4624.

[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 the NTP/NHGRI/EPA/FDA Interagency Memorandum of Understanding
[6] Funded by the NIEHS/EPA Interagency Agreement
[7] Funded by NIEHS voluntary allocations to the NTP

[4] Chang HC, Doerge DR, Hsieh CH, Lin YJ, Tsai FJ. 2011. The covalent binding of genistein to the non-prosthetic-heme-moiety of bovine lactoperoxidase leads to enzymatic inactivation. *Biomed Environ Sci* 24(3):284-290.

[4] Chelonis J, Kubacak B, Osborn S, Edwards M, Baldwin R, Paule M. 2011. The effects of stimulant medication on performance of an incremental repeated acquisition task in children with ADHD. *Neurotoxicol Teratol* 33(4):507-507.

[4] Chelonis JJ, Gravelin CR, Paule MG. 2011. Assessing motivation in children using a progressive ratio task. *Behav Proc* 87(2):203-209.

[4] Chelonis JJ, Johnson TA, Ferguson SA, Berry KJ, Kubacak B, Edwards MC, Paule MG. 2011. Effect of methylphenidate on motivation in children with Attention-Deficit/Hyperactivity Disorder. *Exp Clin Psychopharmacol* 19(2):145-153.

[2] Chen BT, Afshari A, Stone S, Jackson M, Schwegler-Berry D, Frazer DG, Castranova V, Thomas TA. 2010. Nanoparticles – containing spray can aerosol: characterization, exposure assessment, and generator design. *Inhal Toxicol* 22(13):1072-1082.

[7] Chen LJ, Wegerski CJ, Kramer DJ, Thomas LA, McDonald JD, Dix KJ, Sanders JM. 2011. Disposition and metabolism of cumene in F344 rats and B6C3F1 mice. *Drug Met Disp* 39(3):498-509.

[4] Chen T, Heflich RH, Moore MM, Mei N. 2010. Differential mutagenicity of aflatoxin B-1 in the liver of neonatal and adult mice. *Environ Mol Mut* 51(2):156-163.

[7] Cheng Y, Wright SH, Kuester RK, Hooth MJ, Sipes IG. 2011. Characterization of the inhibitory effects of N-butylpyridinium chloride and structurally related ionic liquids on kidney organic cation transporters. *Drug Metabolism and Disposition* 39(9): 1755-61.

[7] Chernoff N, Rogers EH, Zehr RD, Gage MI, Malarkey DE, Bradfield CA, Liu Y, Schmid JE, Jaskot RH, Richards JH, Wood CR, Rosen MB. 2011. Toxicity and recovery in the pregnant mouse after gestational exposure to the cyanobacterial toxin, cylindrospermopsin. *J Appl Toxicol* 31(3):242-254.

[1] Chipinda I, Blachere FM, Anderson SE, Siegel PD. 2011. Discrimination of haptens from prohaptens using the metabolically deficient Cpr(low/low) mouse. *Toxicol Appl Pharmacol* 252(3):268-272.

[1] Chipinda I, Hettick JM, Siegel PD. 2011. Haptenation: chemical reactivity and protein binding. *J Allergy* (Cairo) EPub.

[1] Chipinda I, Ruwona TB, Templeton SP, Siegel PD. 2011. Use of the human monocytic leukemia THP-1 cell line and co-incubation with microsomes to identify and differentiate hapten and prohapten sensitizers. *Toxicol* 280(3):135-143.

[2] Chirila MM, Lee T, Flemmer MM, Slaven JE, Harper M. 2011. Quantitative mid-infrared diffuse reflection of occupational wood dust exposures. *Appl Spectroscopy* 65(3):243-249.

[7] Chu IM, Michalowski AM, Hoenerhoff M, Szauter KM, Luger D, Sato M, Flanders K, Oshima A, Csiszar K, Green JE. 2011. GATA3 inhibits lysyl oxidase-mediated metastases of human basal triple-negative breast cancer cells. *Oncogene* doi: 10.1038/onc.2011.382.

[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 the NTP/NHGRI/EPA/FDA Interagency Memorandum of Understanding
[6] Funded by the NIEHS/EPA Interagency Agreement
[7] Funded by NIEHS voluntary allocations to the NTP

[7] Collins BJ, Stout MD, Levine KE, Kissling GE, Melnick RL, Fennell TR, Walden R, Abdo K, Pritchard JB, Fernando RA, Burka LT, Hooth MJ. 2010. Exposure to hexavalent chromium resulted in significantly higher tissue chromium burden compared with trivalent chromium following similar oral doses to male F344/N rats and female B6C3F1 mice. *Toxicol Sci* 118(2):368-379.

[7] Collins BJ, Stout MD, Levine KE, Kissling GE, Melnick RL, Fennell TR, Pritchard JB, Walden R, Abdo K, Fernando RA, Burka LT, Hooth MJ. 2011. Hexavalent chromium in drinking water, reply. *Toxicol Sci* 119(2):425-425.

[2] Connor TH, DeBord G, Pretty JR, Oliver MS, Roth TS, Lees PSJ, Krieg EF, Rogers B, Escalante CP, Toennis CA, Clark JC, Johnson BC, McDiarmid MA. 2010. Evaluation of antineoplastic drug exposure of health care workers at three university-based U.S. cancer centers. *J Occ Environ Med* 52(10):1019-1027.

[7] Corsini E, Avogadro A, Galbiati V, dell'Agli M, Marinovich M, Galli CL, Germolec DR. 2011. *In vitro* evaluation of the immunotoxic potential of perfluorinated compounds (PFCs). *Toxicol Appl Pharmacol* 250(2):108-116.

[2] Costa C, Silva S, Neves J, Coelho P, Costa S, Laffon B, Snawder J, Teixeira JP. 2011. Micronucleus frequencies in lymphocytes and reticulocytes in a pesticide-exposed population in Portugal. *J Toxicol Environ Health A* 74(15-16):960-970.

[7] Cowin PA, Gold E, Aleksova J, O'Bryan MK, Foster PMD, Scott HS, Risbridger GP. 2010. Vinclozolin exposure *in utero* induces postpubertal prostatitis and reduces sperm production via a reversible hormone-regulated mechanism. *Endocrinology* 151(2):783-792.

[7] Crawford LW, Foley JF, Elmore SA. 2010. Histology atlas of the developing mouse hepatobiliary system with emphasis on embryonic days 9.5-18.5. *Toxicol Path* 38(6):872-906.

[4] Cuevas E, Lantz SM, Tobon-Velasco JC, Newport GD, Wu Q, Virmani A, Ali SF, Santamaria A. 2011. On the *in vivo* early toxic properties of Abeta peptide in the rat hippocampus: Involvement of the receptor-for-advanced glycation-end-products and changes in gene expression. *Neurotoxicol Teratol* 33(2):288-296.

[1] Cummings KJ, Gaughan DM, Kullman GJ, Beezhold DH, Green BJ, Blachere FM, Bledsoe T, Kreiss K, Cox-Ganser J. 2010. Adverse respiratory outcomes associated with occupational exposures at a soy processing plant. *Eur Resp J* 36(5):1007-1015.

[7] Cunningham ML, Collins B, Hejtmancik M, Herbert R, Travlos G, Vallant M, Stout M. 2010. Effects of the PPAR alpha agonist and widely used antihyperlipidemic drug Gemfibrozil on hepatic toxicity and lipid metabolism. *PPAR Res* 681963.

[1] Dahm MM, Yencken MS, Schubauer-Berigan MK. 2011. Exposure control strategies in the carbonaceous nanomaterial industry. *J Occ Environ Med* 53 Suppl(6S):S68-S73.

[1] Day G, LeBouf R, Grote A, Pendergrass S, Cummings K, Kreiss K, Kullman G. 2011. Identification and measurement of diacetyl substitutes in dry bakery mix production. *J Occ Environ Hyg* 8(2):93-103.

[7] Dearfield KL, Thybaud V, Cimino MC, Custer L, Czich A, Harvey JS, Hester S, Kim JH, Kirkland D, Levy DD, Lorge E, Moore MM, Ouedraogo-Arras G, Schuler M, Suter W, Sweder K, Tarlo K, van Benthem J, van Goethem F, Witt KL. 2011. Follow-up actions from positive results of *in vitro* genetic toxicity testing. *Environ Mol Mut* 52(3):177-204.

[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 the NTP/NHGRI/EPA/FDA Interagency Memorandum of Understanding
[6] Funded by the NIEHS/EPA Interagency Agreement
[7] Funded by NIEHS voluntary allocations to the NTP

[7] Deng Y, Edin ML, Theken KN, Schuck RN, Flake GP, Kannon MA, DeGraff LM, Lih FB, Foley J, Bradbury JA, Graves JP, Tomer KB, Falck JR, Zeldin DC, Lee CR. 2011. Endothelial CYP epoxygenase overexpression and soluble epoxide hydrolase disruption attenuate acute vascular inflammatory responses in mice. *J Fed Amer Soc Exp Biol* 25(2):703-713.

[2] DiNapoli VA, Benkovic SA, Li X, Kelly KA, Miller DB, Rosen CL, Huber JD, O'Callaghan JP. 2010. Age exaggerates proinflammatory cytokine signaling and truncates signal transducers and activators of transcription 3 signaling following ischemic stroke in the rat. *Neurosci* 170(2):633-644.

[4] Dobrovolsky VN, Miura D, Heflich RH, Dertinger SD. 2010. The *in vivo* pig-a gene mutation assay, a potential tool for regulatory safety assessment. *Environ Mol Mut* 51(8-9):825-835.

[2] Dodrill MW, Fedan. 2010. Lipopolysaccharide hyperpolarizes guinea pig airway epithelium by increasing the activities of the epithelial Na+ channel and the Na+-K+ pump. *Amer J Physiol-Lung Cell Mol Physiol* 299(4):L550-L558.

[2] Dodrill MW, Beezhold DH, Meighan T, Kashon ML, Fedan JS. 2011. Lipopolysaccharide increases Na+,K+-pump, but not ENaC, expression in guinea-pig airway epithelium. *Eur J Pharmacol* 651(1-3):176-186.

[4] Doerge DR, Twaddle NC, Churchwell MI, Newbold RR, Delclos KB. 2010. Lactational transfer of the soy isoflavone, genistein, in Sprague-Dawley rats consuming dietary genistein. *Rep Toxicol* 30(3):493-493.

[3] Doerge DR, Twaddle NC, Woodling KA, Fisher JW. 2010. Pharmacokinetics of bisphenol A in neonatal and adult rhesus monkeys. *Toxicol Appl Pharmacol* 248(1):1-11.

[3] Doerge DR, Vanlandingham M, Twaddle NC, Delclos, KB. 2010. Lactational transfer of bisphenol A in Sprague-Dawley rats. *Toxicol Lett* 199(3):372-376.

[4] Doerge DR. 2011. Bioavailability of soy isoflavones through placental/lactational transfer and soy food. *Toxico Appl Pharmacol* 254(2):145-147.

[4] Dorne JL, Doerge D, Boobis A. 2011. Mechanistic basis for the harmonisation of ecological and human risk assessment. *Toxicol Lett* 205(S9).

[7] Dunnick JK, Singh B, Nyska A, Peckham J, Kissling GE, Sanders JM. 2011. Investigating the potential for toxicity from long-term use of the herbal products, goldenseal and milk thistle. *Toxicol Path* 39(2):398-409.

[7] Edin ML, Wang Z, Bradbury JA, Graves JP, Lih FB, Degraff LM, Foley JF, Torphy R, Ronnekleiv OK, Tomer KB, Lee CR, Zeldin DC. 2011. Endothelial expression of human cytochrome P450 epoxygenase CYP2C8 increases susceptibility to ischemia-reperfusion injury in isolated mouse heart. *J Fed Amer Soc Exp Biol* 25(10):3436-3447.

[4] Engel E, Vasold R, Santarelli F, Maisch T, Gopee NV, Howard PC, Landthaler M, Baumler W. 2010. Tattooing of skin results in transportation and light-induced decomposition of tattoo pigments – a first quantification *in vivo* using a mouse model. *Exp Dermatol* 19(1):54-60.

[2] Erdely A, Hulderman T, Salmen-Muniz R, Liston A, Zeidler-Erdely PC, Chen BT, Stone S, Frazer DG, Antonini JM, Simeonova PP. 2011. Inhalation exposure of gas-metal arc stainless steel welding fume increased atherosclerotic lesions in apolipoprotein E knockout mice. *Toxicol Lett* 204(1):12-16.

[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 the NTP/NHGRI/EPA/FDA Interagency Memorandum of Understanding
[6] Funded by the NIEHS/EPA Interagency Agreement
[7] Funded by NIEHS voluntary allocations to the NTP

[2] Erdely A, Liston A, Salmen-Muniz R, Hulderman T, Young SH, Zeidler-Erdely PC, Castranova V, Simeonova PP. 2011. Identification of systemic markers from a pulmonary carbon nanotube exposure. *J Occ Environ Med* 53(6 Suppl):S80-86.

[2] Erdely A, Salmen-Muniz R, Liston A, Hulderman T, Zeidler-Erdely PC, Antonini JM, Simeonova PP. 2011. Relationship between pulmonary and systemic markers of exposure to multiple types of welding particulate matter. *Toxicol* 287(1-3):153-159.

[2] Estill CF, Baron PA, Beard JK, Hein MJ, Larsen LD, Deye GJ, Rose L, Hodges L. 2011. Comparison of air sampling methods for aerosolized spores of B. anthracis Sterne. *J Occ Environ Hyg* 8(3):179-186.

[2] Fedan JS, Piedimonte G. 2010. Dr. R. Shiffmann's Asthmador: relevant to our times, or a snake oil remedy? *Curr Opin Pharmacol* 10(3):213-217.

[4] Ferguson S, Law C, Abshire J. 2011. Developmental bisphenol A (BPA) or ethinyl estradiol treatment at relatively low doses has no effects on early preweaning behaviors. *Neurotoxicol Teratol* 33(4):496-497.

[7] Fielden MR, Adai A, Dunn RT 2nd, Olaharski A, Searfoss G, Sina J, Aubrecht J, Boitier, E, Nioi P, Auerbach S, Jacobson-Kram D, Raghavan N, Yang Y, Kincaid A, Sherlock J, Chen SJ, Car B. 2011. Development and evaluation of a genomic signature for the prediction and mechanistic assessment of nongenotoxic hepatocarcinogens in the rat. *Toxicol Sci* 124:54-74.

[1] Franko J, Jackson LG, Meade BJ, Anderson SE. 2011. Allergic potential and immunotoxicity induced by topical application of 1-Chloro-4-(Trifluoromethyl) Benzene (PCBTF) in a murine model. *J Allergy* (Cairo) Epub.

[2] Frasch HF, Zang LY, Barbero AM, Anderson SE. 2010. *In vitro* dermal penetration of 4-Chloro-3-Methylphenol from commercial metal working fluid and aqueous vehicles. J Toxicol Environ Health-A 73(20):1394-1405.

[2] Frasch HF, Barbero AM, Hettick JM, Nitsche JM. 2011. Tissue binding affects the kinetics of theophylline diffusion through the stratum corneum barrier layer of skin. *J Pharm Sci* 100(7):2989-2995.

[7] Frawley R, White K, Jr., Brown R, Musgrove D, Walker N, Germolec D. 2011. Gene expression alterations in immune system pathways in the thymus after exposure to immunosuppressive chemicals. *Environ Health Perspect* 119(3):371-376.

[2] Freeman LEB, Rusiecki JA, Hoppin JA, Lubin JH, Koutros S, Andreotti G, Zahm SH, Hines CJ, Coble JB, Barone-Adesi F, Sloan J, Sandler DP, Blair A, Alavanja MCR. 2011. Atrazine and cancer incidence among pesticide applicators in the Agricultural Health Study (1994-2007). *Environ Health Perspect* 119(9):1253-1259.

[4] Fu PP, Chou MW, Churchwell M, Wang YP, Zhao YW, Xia QS, da Costa GG, Marques MM, Beland FA, Doerge DR. 2010. High-performance liquid chromatography electrospray ionization tandem mass spectrometry for the detection and quantitation of pyrrolizidine alkaloid-derived DNA adducts *in vitro* and *in vivo*. *Chem Res Toxicol* 23(3):637-652.

[7] Funk JA, Gohlke J, Kraft AD, McPherson CA, Collins JB, Jean Harry G. 2011. Voluntary exercise protects hippocampal neurons from trimethyltin injury: possible role of interleukin-6 to modulate tumor necrosis factor receptor-mediated neurotoxicity. *Brain Behav Immun* 25(6):1063-1077.

[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 the NTP/NHGRI/EPA/FDA Interagency Memorandum of Understanding
[6] Funded by the NIEHS/EPA Interagency Agreement
[7] Funded by NIEHS voluntary allocations to the NTP

[4] Galloway S, Lorge E, Aardema MJ, Eastmond D, Fellows M, Heflich R, Kirkland D, Levy DD, Lynch AM, Marzin D, Morita T, Schuler M, Speit G. 2011. Workshop summary: Top concentration for *in vitro* mammalian cell genotoxicity assays; and report from working group on toxicity measures and top concentration for *in vitro* cytogenetics assays (chromosome aberrations and micronucleus). *Mut Res-Gen Toxicol Environ Mut* 723(2):77-83.

[1] Geraci CL, Castranova V. 2010. Challenges in assessing nanomaterial toxicology: a personal perspective. *Wiley Interdisciplinary Rev - Nanomed Nanobiotechnol* 2(6):569-577.

[7] Goodman JI, Augustine KA, Cunningham ML, Dixon D, Dragan YP, Falls G, Rasoulpour RJ, Sills RC, Storer RD, Wolf DC, Pettit SD. 2010. What do we need to know prior to thinking about incorporating an epigenetic evaluation into safety assessments? *Toxicol Sci* 116:375-381.

[2] Grajewski B, Waters MA, Yong LC, Tseng CY, Zivkovich Z, Cassinelli RT 2nd. 2011. Airline pilot cosmic radiation and circadian disruption exposure assessment from logbooks and company records. *Ann Occ Hyg* 55(5):465-475.

[1] Green BJ, Beezhold DH. 2011. Industrial fungal enzymes: An occupational allergen perspective. *J Allergy* (Cairo) Epub.

[1] Green BJ, Cummings KJ, Rittenour WR, Hettick JM, Bledsoe TA, Blachere FM, Siegel PD, Gaughan DM, Kullman GJ, Kreiss K, Cox-Ganser J, Beezhold DH. 2011. Occupational sensitization to soy allergens in workers at a processing facility. *Clin Exp Allergy* 41(7):1022-1030.

[4] Guo L, Dial S, Shi L, Branham W, Liu J, Fang JL, Green B, Deng H, Kaput J, Ning B. 2011. Similarities and differences in the expression of drug-metabolizing enzymes between human hepatic cell lines and primary human hepatocytes. *Drug Met Disp* 39(3):528-538.

[4] Guo L, Shi Q, Dial S, Xia QS, Mei N, Li QZ, Chan PC, Fu P. 2010. Gene expression profiling in male B6C3F1 mouse livers exposed to kava identifies – changes in drug metabolizing genes and potential mechanisms linked to kava toxicity. *Food Chem Toxicol* 48(2):686-696.

[7] Guo TL, Germolec DR, Roesh DM, White KL. 2010. Immunomodulation in female B6C3F1 mice following treatment with the HIV protease inhibitor saquinavir for 28 days by gavage. *J Immunotoxicol* 7(4):289-297.

[7]Gwinn WM, Kapita MC, Wang PM, Cesta MF, Martin WJ, 2nd. 2011. Synthetic liposomes are protective from bleomycin-induced lung toxicity. *Amer J Physiol Lung Cell Mol Physiol* 301(2):L207-217.

[1] Ham JE, Wells JR. 2011. Surface chemistry of a pine-oil cleaner and other terpene mixtures with ozone on vinyl flooring tiles. *Chemosphere* 83(3):327-333.

[7] Hannas BR, Furr J, Lambright CS, Wilson VS, Foster PMD, Gray LE Jr. 2011. Di-pentyl phthalate dosing during sexual differentiation disrupts fetal testis function and postnatal development of the male Sprague-Dawley rat with greater relative potency than other phthalates. *Toxicol Sci* 120(1):184-193.

[6] Hannas BR, Lambright CS, Furr J, Howdeshell KL, Wilson VS, Gray LE Jr. 2011. Dose-response assessment of fetal testosterone production and gene expression levels in rat testes following *in utero* exposure to diethylhexyl phthalate, diisobutyl phthalate, diisoheptyl phthalate, and diisononyl phthalate. *Toxicol Sci* Sep;123(1):206-16.

[3] Hansen DK, Juliar BE, White GE, Pellicore LS. 2011. Developmental toxicity of *Citrus aurantium* in rats. *Birth Defects Res Part B-Devel Rep Toxicol* 92(3):216-223.

[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 the NTP/NHGRI/EPA/FDA Interagency Memorandum of Understanding
[6] Funded by the NIEHS/EPA Interagency Agreement
[7] Funded by NIEHS voluntary allocations to the NTP

[7] Haseman JK, Allen DG, Lipscomb EA, Truax JF, Stokes WS. 2011. Using fewer animals to identify chemical eye hazards: revised criteria necessary to maintain equivalent hazard classification. *Regul Toxicol Pharmacol* 61(1):98-104.

[7] Haseman JK, Strickland J, Allen D, Salicru E, Paris M, Tice RR, Stokes WS. 2011. Safety assessment of allergic contact dermatitis hazards: An analysis supporting reduced animal use for the murine local lymph node assay. *Reg Toxicol Pharmacol* 59(1):191-196.

[1] Hettick JM, Green BJ, Buskirk AD, Slaven JE, Kashon ML, Beezhold DH. 2011. Discrimination of fungi by MALDI-TOF mass spectrometry rapid characterization of microorganisms by mass spectrometry. Fenselau C, Demirev P, eds., Washington, DC; *Amer Chem Soc* 35-50.

[1] Hettick JM, Siegel PD. 2011. Determination of the toluene diisocyanate binding sites on human serum albumin by tandem mass spectrometry. *Anal Biochem* 414(2):232-238.

[7] Hill GD, Moore AB, Kissling GE, Flagler ND, Ney E, Cline JM, Dixon D. 2011. Effects of hormonally active agents on steroid hormone receptor expression and cell proliferation in the myometrium of ovariectomized macaques. *Toxicol Path* 39(3):508-515.

[2] Hines CJ, Hopf NB, Deddens JA, Silva MJ, Calafat AM. 2011. Estimated daily intake of phthalates in occupationally exposed groups. *J Exp Sci Environ Epidemiol* 21(2):133-141.

[7] Hnizdo V. 2011. Generalized second-order partial derivatives of 1/r. *Eur J Physics* 32(2):287-297.

[7] Hoenerhoff M, Chu IM, Green JE. 2011. BMI1 suffers a degrading experience. *Cell Cycle* 10(12):1895.

[7] Hoenerhoff MJ, Pandiri AR, Lahousse SA, Hong HH, Ton TV, Masinde T, Auerbach SS, Gerrish K, Bushel PR, Shockley KR, Peddada SD, Sills RC. 2011. Global gene profiling of spontaneous hepatocellular carcinoma in B6C3F1 mice: Similarities in the molecular landscape with human liver cancer. *Toxicol Path* 39(4):678-699.

[4] Holthoff JH, Woodling KA, Doerge DR, Burns ST, Hinson JA, Mayeux PR. 2010. Resveratrol, a dietary polyphenolic phytoalexin, is a functional scavenger of peroxynitrite. *Biochem Pharmacol* 80(8):1260-1265.

[5] Huang R, Cho M-H, Sakamuru S, Shinn P, Houck KA, Dix DJ, Judson RS, Witt KL, Kavlock RJ,Tice RR, Austin CP. 2011. Chemical genomics profiling of environmental chemical modulation of human nuclear receptors. *Environ Health Perspect* 119(8):1142-1148.

[2] Hubbs AF, Mercer RR, Benkovic SA, Harkema J, Sriram K, Schwegler-Berry D, Goravanahally MP, Nurkiewicz TR, Castranova V, Sargent LM. 2011. Nanotoxicology--a pathologist's perspective. *Toxicol Path* 39(2):301-324.

[7] Huff J, Chan P, Melnick R. 2010. Clarifying carcinogenicity of ethylbenzene. *Reg Toxicol Pharmacol* 58(2):167-169.

[3] Jacob CC, Gamboa da Costa G. 2011. Low-level quantification of melamine and cyanuric acid in limited samples of rat serum by UPLC-electrospray tandem mass spectrometry. *J Chrom B Anal Technol Biomed Life Sci* 879(9-10):652-656.

[3] Jacob CC, Reimschuessel R, Von Tungeln LS, Olson GR, Warbritton AR, Hattan DG, Beland FA, Gamboa da Costa G. 2011. Dose-response assessment of nephrotoxicity from a 7-day combined exposure to melamine and cyanuric acid in F344 rats. *Toxicol Sci* 119(2):391-397.

[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 the NTP/NHGRI/EPA/FDA Interagency Memorandum of Understanding
[6] Funded by the NIEHS/EPA Interagency Agreement
[7] Funded by NIEHS voluntary allocations to the NTP

[4] Jeannot E, Pogribny IP, Beland FA, Rusyn I. 2011. Chronic administration of ethanol leads to an increased incidence of hepatocellular adenoma by promoting H-ras-mutated cells. *Cancer Lett* 301(2):161-167.

[2] Jin CF, Sun YH, Islam A, Qian Y, Ducatman A. 2011. Perfluoroalkyl acids including perfluorooctane sulfonate and perfluorohexane sulfonate in firefighters. *J Occ Environ Med* 53(3):324-328.

[2] Jin Y, Hein MJ, Deddens JA, Hines CJ. 2011. Analysis of lognormally distributed exposure data with repeated measures and values below the limit of detection using SAS. *Ann Occ Hyg* 55(1):97-112.

[7] Jokinen MP, Lieuallen WG, Boyle MC, Johnson CL, Malarkey DE, Nyska A. 2011. Morphologic Aspects of Rodent Cardiotoxicity in a Retrospective Evaluation of National Toxicology Program Studies. *Toxicol Pathol* 39(5):850-60.

[7] Kai K, D'Costa S, Yoon BI, Brody AR, Sills RC, Kim Y. 2010. Characterization of side population cells in human malignant mesothelioma cell lines. *Lung Cancer* 70(2):146-151.

[4] Kanungo J, Paule MG. 2011. Disruption of blastomeric F-actin: a potential early biomarker of developmental toxicity in zebrafish. *Mol Cell Biochem* 353(1-2):283-290.

[4] Karmakar A, Xu Y, Mahmood MW, Zhang YB, Saeed LM, Mustafa T, Ali S, Biris AR, Biris AS. 2011. Radio-frequency induced *in vitro* thermal ablation of cancer cells by EGF functionalized carbon-coated magnetic nanoparticles. *J Materials Chem* 21(34):12761-12769.

[7] Ke H, Zhang JY, Akiyama SK, French JE. 2011. BCL2 interaction with actin *in vitro* may inhibit cell motility by enhancing actin polymerization. *Cell Adhesion Migration* 5(1):6-10.

[4] Kimoto T, Suzuki K, Kobayashi XM, Dobrovolsky VN, Heflich RH, Miura D, Kasahara Y. 2011. Manifestation of Pig-a mutant bone marrow erythroids and peripheral blood erythrocytes in mice treated with N-ethyl-N-nitrosourea: Direct sequencing of Pig-a cDNA from bone marrow cells negative for GPI-anchored protein expression. *Mut Res-Gen Toxicol Environ Mut* 723(1):36-42.

[4] Kisby GE, Fry RC, Lasarev MR, Bammler TK, Beyer RP, Churchwell M, Doerge DR, Meira LB, Palmer VS, Ramos-Crawford AL, Ren XF, Sullivan RC, Kavanagh TJ, Samson LD, Zarbl H, Spencer PS. 2011. The cycad genotoxin MAM modulates brain cellular pathways involved in neurodegenerative disease and cancer in a DNA damage-linked manner. *PLOS One* 6(6): e20911.

[2] Kisin ER, Murray AR, Sargent L, Lowry D, Chirila M, Siegrist KJ, Schwegler-Berry D, Leonard S, Castranova V, Fadeel B, Kagan VE, Shvedova AA. 2011. Genotoxicity of carbon nanofibers: Are they potentially more or less dangerous than carbon nanotubes or asbestos? *Toxicol Appl Pharmacol* 252(1):1-10.

[4] Koturbash I, Beland FA, Pogribny IP. 2011. Role of epigenetic events in chemical carcinogenesis – a justification for incorporating epigenetic evaluations in cancer risk assessment. *Toxicol Mech Meth* 21(4):289-297.

[4] Koturbash I, Scherhag A, Sorrentino J, Sexton K, Bodnar W, Swenberg JA, Beland FA, de Villena FPM, Rusyn I, Pogribny IP. 2011. Epigenetic mechanisms of mouse interstrain variability in genotoxicity of the environmental toxicant 1,3-butadiene. *Toxicol Sci* 122(2):448-456.

[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 the NTP/NHGRI/EPA/FDA Interagency Memorandum of Understanding
[6] Funded by the NIEHS/EPA Interagency Agreement
[7] Funded by NIEHS voluntary allocations to the NTP

[4] Koturbash I, Scherhag A, Sorrentino J, Sexton K, Bodnar W, Tryndyak V, Latendresse JR, Swenberg JA, Beland FA, Pogribny IP, Rusyn I. 2011. Epigenetic alterations in Liver of C57BL/6J mice after short-term inhalational exposure to 1,3-butadiene. *Environ Health Perspect* 119(5):635-640.[7] Kraft AD, Harry GJ. 2011. Features of microglia and neuroinflammation relevant to environmental exposure and neurotoxicity. *Int J Environ Res Public Health* 8(7):2980-3018.

[7] Kulpa-Eddy J, Srinivas G, Halder M, Brown K, Draayer H, Galvin J, Claassen I, Gifford G, Woodland R, Doelling V, Jones B, Stokes WS. 2011. Alternative methods and strategies to reduce, refine, and replace animal use for veterinary vaccine post-licensing safety testing: state of the science and future directions. In: International Workshop on Alternative Methods to Reduce, Refine, and Replace the Use of Animals in Vaccine Potency and Safety Testing: State of the Science and Future Directions (Kulpa-Eddy J, McFarland R, Stokes WS, eds). *Procedia Vaccinol* 5:106-119.

[7] Kulpa-Eddy J, Srinivas G, Halder M, Hill R, Brown K, Roth J, Draayer H, Galvin J, Claassen I, Gifford G, Woodland R, Doelling V, Jones B, Stokes WS. 2011. Non-animal replacement methods for veterinary vaccine potency testing: state of the science and future directions. In: International Workshop on Alternative Methods to Reduce, Refine, and Replace the Use of Animals in Vaccine Potency and Safety Testing: State of the Science and Future Directions (Kulpa-Eddy J, McFarland R, Stokes WS, eds). *Procedia Vaccinol* 5:60-83.

[7] Lahousse SA, Hoenerhoff M, Collins J, Ton TV, Masinde T, Olson D, Rebolloso Y, Koujitani T, Tomer KB, Hong HH, Bucher J, Sills RC. 2011. Gene expression and mutation assessment provide clues of genetic and epigenetic mechanisms in liver tumors of oxazepam-exposed mice. *Vet Pathol* 48(4):875-84.

[1] Laney AS, McCauley LA, Schubauer-Berigan MK. 2011. Workshop summary: epidemiologic design strategies for studies of nanomaterial workers. *J Occ Environ Med 53 Suppl* (6S):S87-S90.

[7] Lau C, Abbott BD, Corton JC, Cunningham ML. 2010. PPARs and xenobiotic-induced adverse effects: relevance to human health. *PPAR Research* 954639.

[2] Law BF, Pearce T, Siegel PD. 2011. Safety and chemical exposure evaluation at a small biodiesel production facility. *J Occ Environ Hyg* 8(7):D68-D72.

[2] Lebouf RF, Stefaniak AB, Chen BT, Frazer DG, Virji MA. 2011. Measurement of airborne nanoparticle surface area using a filter-based gas adsorption method for inhalation toxicology experiments. *Nanotoxicol* 5(4):687-699.

[2] Lee EG, Slaven J, Bowen RB, Harper M. 2011. Evaluation of the COSHH essentials model with a mixture of organic chemicals at a medium-sized paint producer. *Ann Occ Hyg* 55(1):16-29.

[2] Lee EG, Pang TWS, Nelson J, Andrew M, Harper M. 2011. Comparison of mounting methods for the evaluation of fibers by phase contrast microscopy. *Ann Occ Hyg* 55(6):644-657.

[2] Lee LA, Lee EG, Lee T, Kim SW, Slaven JE, Harper M. 2011. Size-selective sampling of particulates using a physiologic sampling pump. *J Environ Mon* 13(3):527-535.

[2] Lee T, Harper M, Slaven JE, Lee K, Rando RJ, Maples EH. 2011. Wood dust sampling: Field evaluation of personal samplers when large particles are present. *Ann Occ Hyg* 55(2):180-191.

[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 the NTP/NHGRI/EPA/FDA Interagency Memorandum of Understanding
[6] Funded by the NIEHS/EPA Interagency Agreement
[7] Funded by NIEHS voluntary allocations to the NTP

[2] Leonard SS, Chen BT, Stone SG, Schwegler-Berry D, Kenyon AJ, Frazer D, Antonini JM. 2010. Comparison of stainless and mild steel welding fumes in generation of reactive oxygen species. *Particle Fibre Toxicol* 7:32.

[7] Levis S, Strickman-Stein N, Ganjei-Azar P, Xu P, Doerge DR, Krischer J. 2011. Soy isoflavones in the prevention of menopausal bone loss and menopausal symptoms a randomized, double-blind trial. *Arch Int Med* 171(15):1363-1369.

[7] Leung MCK, Goldstone JV, Boyd WA, Freedman JH, Meyer JN. 2010. *Caenorhabditis elegans* generates biologically relevant levels of genotoxic metabolites from aflatoxin B-1 but not benzo(a)pyrene *in vivo*. *Toxicol Sci* 118(2):444-453.

[4] Li ZG, Branham WS, Dial SL, Wang YX, Guo L, Shi LM, Chen T. 2010. Genomic analysis of microRNA time-course expression in liver of mice treated with genotoxic carcinogen N-ethyl-N-nitrosourea. *BioMed Cent Genom* 11:609.

[1] Lindsley WG, Blachere FM, Thewlis RE, Vishnu A, Davis KA, Cao G, Palmer JE, Clark KE, Fisher MA, Khakoo R, Beezhold DH. 2010. Measurements of airborne influenza virus in aerosol particles from human coughs. *PLOS One* 5(11):e15100.

[4] Liu F, Paule MG, Ali S, Wang C. 2011. Ketamine-induced neurotoxicity and changes in gene expression in the developing rat brain. *Curr Neuropharmacol* 9(1):260-265.

[4] Liu F, Zou X, Sadovova N, Zhang X, Shi L, Guo L, Qian F, Wen Z, Patterson TA, Hanig JP, Paule MG, Slikker W, Wang C. 2011. Changes in gene expression after phencyclidine administration in developing rats: A potential animal model for schizophrenia. *Int J Devel Neurosci* 29(3):351-358.

[4] Liu YX, Lo YC, Qian L, Crews FT, Wilson B, Chen HL, Wu HM, Chen SH, Wei K, Lu RB, Ali S, Hong JS. 2011. Verapamil protects dopaminergic neuron damage through a novel anti-inflammatory mechanism by inhibition of microglial activation. *Neuropharmacol* 60(2-3):373-380.

[4] Lucas PW, Schmit JM, Peterson QP, West DC, Hsu DC, Novotny CJ, Dirikolu L, Churchwell MI, Doerge DR, Garrett LD, Hergenrother PJ, Fan TM. 2011. Pharmacokinetics and derivation of an anticancer dosing regimen for PAC-1, a preferential small molecule activator of procaspase-3, in healthy dogs. *Invest New Drugs* 29(5):901-911.

[2] Ma JY, Zhao HW, Mercer RR, Barger M, Rao M, Meighan T, Schwegler-Berry D, Castranova V, Ma JK. 2011. Cerium oxide nanoparticle-induced pulmonary inflammation and alveolar macrophage functional change in rats. *Nanotoxicol* 5(3):312-325.

[5] Mahadevan B, Snyder RD, Waters MD, Benz RD, Kemper RA, Tice RR, Richard AM. 2011. Genetic toxicology in the 21st century: Reflections and future directions. *Environ Mol Mut* 52(5):339-354.

[4] Mahmood M, Casciano DA, Mocan T, Iancu C, Xu Y, Mocan L, Iancu DT, Dervishi E, Li ZR, Abdalmuhsen M, Biris AR, Ali N, Howard P, Biris AS. 2010. Cytotoxicity and biological effects of functional nanomaterials delivered to various cell lines. *J Appl Toxicol* 30(1):74-83.

[7] Maronpot RR, Yoshizawa K, Nyska A, Harada T, Flake G, Mueller G, Singh B, Ward JM. 2010. Hepatic enzyme induction: Histopathology. *Toxicol Path* 38(5):776-795.

[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 the NTP/NHGRI/EPA/FDA Interagency Memorandum of Understanding
[6] Funded by the NIEHS/EPA Interagency Agreement
[7] Funded by NIEHS voluntary allocations to the NTP

[2,4] Mattison DR, Plant TM, Lin HM, Chen HC, Chen JJ, Twaddle NC, Doerge D, Slikker W Jr, Patton RE, Hotchkiss CE, Callicott RJ, Schrader SM, Turner TW, Kesner JS, Vitiello B, Petibone DM, Morris SM. 2011. Pubertal delay in male nonhuman primates (Macaca mulatta) treated with methylphenidate. *PNAS* 108(39):16301-16306.

[2] McCarthy BJ, Rankin KM, Aldape K, Bondy ML, Brännström T, Broholm H, Feychting M, Il'Yasova D, Inskip PD, Johansen C, Melin BS, Ruder AM, Butler MA, Scheurer ME, Schüz J, Schwartzbaum JA, Wrensch MR, Davis FG. 2011. Risk factors for oligodendroglial tumors: A pooled international study. *Neuro-oncol* 13(2):242-250.

[4] Mei N, Guo L, Fu PP, Fuscoe JC, Luan Y, Chen T. 2010. Metabolism, genotoxicity, and carcinogenicity of comfrey. *J Toxicol Environ Health B Crit Rev* 13(7-8):509-526.

[2] Mercer RR, Hubbs AF, Scabilloni JF, Wang LY, Battelli LA, Schwegler-Berry D, Castranova V, Porter DW. 2010. Distribution and persistence of pleural penetrations by multi-walled carbon nanotubes. *Particle Fibre Toxicol* 7:28.

[2] Mercer RR, Hubbs AF, Scabilloni JF, Wang LY, Battelli LA, Friend S, Castranova V, Porter DW. 2011. Pulmonary fibrotic response to aspiration of multi-walled carbon nanotubes. *Particle Fibre Toxicol* 8(21):1-11.

[7] Merrick BA, Dhungana S, Williams JG, Aloor JJ, Peddada S, Tomer KB, Fessler MB. 2011. Proteomic profiling of S-acylated macrophage proteins identifies a role for palmitoylation in mitochondrial targeting of phospholipid scramblase 3. *Mol Cell Proteomics* 10(10):M110.006007.

[4] Miura D, Shaddock JG, Mittelstaedt RA, Dobrovolsky VN, Kimoto T, Kasahara Y, Heflich RH. 2011. Analysis of mutations in the Pig-a gene of spleen T-cells from N-Ethyl-N-nitrosourea-treated Fisher 344 rats. *Environ Mol Mut* 52(5):419-423.

[7] Morgan DL, Nyska A, Harbo SJ, Grumbein SL, Dill JA, Roycroft JH, Kissling GE, Cesta MF. 2011. Multisite carcinogenicity and respiratory toxicity of inhaled 1-bromopropane in rats and mice. *Toxicol Pathol* 39(6):938-48.

[7] Morrison TE, Oko L, Montgomery SA, Whitmore AC, Lotstein AR, Gunn BM, Elmore SA, Heise MT. 2011. A mouse model of chikungunya virus-induced musculoskeletal inflammatory disease: Evidence of arthritis, tenosynovitis, myositis, and persistence. *Amer J Path* 178(1):32-40.

[1] Murashov V, Schulte P, Geraci C, Howard J. 2011. Regulatory approaches to worker protection in nanotechnology industry in the USA and European Union. *Ind Health* 49(3):280-296.

[1] Nayak AP, Blachere FM, Hettick JM, Lukomski S, Schmechel D, Beezhold DH. 2011. Characterization of recombinant terrelysin, a hemolysin of Aspergillus terreus. *Mycopathologia* 171(1):23-34.

[1] Nayak AP, Green BJ, Janotka E, Blachere FM, Vesper SJ, Beezhold DH, Schmechel D. 2011. Production and characterization of IgM monoclonal antibodies against hyphal antigens of *Stachybotrys* species. Hybridoma 30(1):29-36.

[1] Nayak AP, Green BJ, Janotka E, Hettick JM, Friend S, Vesper SJ, Schmechel D, Beezhold DH. 2011. Monoclonal antibodies to hyphal exoantigens derived from the opportunistic pathogen *Aspergillus terreus*. *Clin Vacc Immunol* 18(9):1568-1576.

[7] Newbold RR. 2010. Impact of environmental endocrine disrupting chemicals on the development of obesity. Hormones 9(3): 206-217.

[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 the NTP/NHGRI/EPA/FDA Interagency Memorandum of Understanding
[6] Funded by the NIEHS/EPA Interagency Agreement
[7] Funded by NIEHS voluntary allocations to the NTP

[2] Nitsche JM, Frasch H. 2011. Dynamics of diffusion with reversible binding in microscopically heterogeneous membranes: General theory and applications to dermal penetration. *Chem Eng Sci* 66(10):2019-2041.

[2] O'Callaghan JP, Miller DB. 2010. Spinal glia and chronic pain. *Metab-Clin Exp* 59(Suppl 1):S21-S26.

[2] Olsen LD, Snawder JE, Kriech AJ, Osborn LV. 2011. Development of a 5-layer passive organic dermal (POD) sampler. *Polycyclic Arom Comp* 31(3):154-172.

[4] Onaivi ES, Benno R, Halpern T, Mehanovic M, Schanz N, Sanders C, Yan X, Ishiguro H, Liu QR, Berzal AL, Viveros MP, Ali SF. 2011. Consequences of cannabinoid and monoaminergic system disruption in a mouse model of autism spectrum disorders. *Curr Neuropharmacol* 9(1):209-214.

[2] Pacurari M, Qian Y, Porter DW, Wolfarth M, Wan Y, Luo D, Ding M, Castranova V. Guo NL. 2011. Multi-walled carbon nanotube-induced gene expression in the mouse lung: Association with lung pathology. *Toxicol Appl Pharmacol* 255(1):18-31.

[2] Pacurari M, Schwegler-Berry D, Friend S, Leonard SS, Mercer RR, Vallyathan V, Castranova V. 2011. Raw single-walled carbon nanotube-induced cytotoxic effects in human bronchial epithelial cells: comparison to asbestos. *Toxicol Environ Chem* 93(5):1045-1072.

[1] Page EH, Dowell CH, Mueller CA, Biagini RE, Heederik D. 2010. Exposure to flour dust and sensitization among bakery employees. *Amer J Ind Med* 53(12):1225-1232.

[7] Palmer SM, Flake GP, Kelly FL, Zhang HL, Nugent JL, Kirby PJ, Foley JF, Gwinn WM, Morgan DL. 2011. Severe airway epithelial injury, aberrant repair and bronchiolitis obliterans develops after diacetyl Instillation in rats. *PLOS One* 6(3):e17644.

[3] Pandiri AR, Sills RC, Hoenerhoff MJ, Peddada SD, Ton TT, Hong HL, Flake GP, Malarkey DE, Olson GR, Pogribny IP, Walker NJ, Boudreau MD. 2011. *Aloe vera* Non-Decolorized Whole Leaf Extract-Induced Large Intestinal Tumors in F344 Rats Share Similar Molecular Pathways with Human Sporadic Colorectal Tumors. *Toxicol Pathol* 2011 39:1065.

[1] Parks CG, Biagini RE, Cooper GS, Gilkeson GS, Dooley MA. 2010. Total serum IgE levels in systemic lupus erythematosus and associations with childhood onset allergies. *Lupus* 19(14):1614-1622.

[4] Patterson TA, Li M, Hotchkiss CE, Mauz A, Eddie M, Greischel A, Stierstorfer B, Deschl U, Paule MG. 2010. Toxicity assessment of pramipexole in juvenile rhesus monkeys. *Toxicol* 276(3):164-171.

[4] Paule MG, Li M, Allen RR, Liu F, Zou X, Hotchkiss C, Hanig JP, Patterson TA, Slikker W, Jr., Wang C. 2011. Ketamine anesthesia during the first week of life can cause long-lasting cognitive deficits in rhesus monkeys. *Neurotoxicol Teratol* 33(2):220-230.

[4] Paule M. 2011. Preclinical neurotoxicity assessments of pediatric anesthetics: Translational approaches using a nonhuman primate model. *Neurotoxicol Teratol* 33(4):506-507.

[4] Pereira FC, Gough B, Macedo TR, Ribeiro CF, Ali SF, Binienda ZK. 2011. Buprenorphine modulates methamphetamine-induced dopamine dynamics in the rat caudate nucleus. *Neurotox Res* 19(1):94-101.

[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 the NTP/NHGRI/EPA/FDA Interagency Memorandum of Understanding
[6] Funded by the NIEHS/EPA Interagency Agreement
[7] Funded by NIEHS voluntary allocations to the NTP

[4] Pogribny IP, Muskhelishvili L, Tryndyak VP, Beland FA. 2011. The role of epigenetic events in genotoxic hepatocarcinogenesis induced by 2-acetylaminofluorene. *Mut Res-Gen Toxicol Environ Mut* 722(2):106-113.

[2] Qian Y, Ducatman A, Ward R, Leonard S, Bukowski V, Guo NL, Shi XL, Vallyathan V, Castranova V. 2010. Perfluorooctane sulfonate (PFOS) induces reactive oxygen species (ROS) production in human microvascular endothelial cells: Role in endothelial permeability. *J Toxicol Environ Health A* 73(12):819-836.

[7] Qu W, Cheng L, Dill AL, Saavedra JE, Hong SY, Keefer LK, Waalkes MP. 2011. Nitric oxide donor, V-PROLI/NO, provides protection against arsenical induced toxicity in rat liver cells: Requirement for Cyp1a1. *Chemico-Biol Int* 193(1):88-96.

[7] Rao DB, Little PB, Malarkey DE, Herbert RA, Sills RC. 2011. Histopathological evaluation of the nervous system in national toxicology program rodent studies: a modified approach. *Toxicol Path* 39(3):463-470.

[7] Rao JS, Kim HW, Kellom M, Greenstein D, Chen M, Kraft AD, Harry GJ, Rapoport SJ, Basselin M. 2011. Increased neuroinflammatory and arachidonic acid cascade markers, and reduced synaptic proteins, in brain of HIV-1 transgenic rats. *J Neuroinflammation* 8:101.

[4] Ray PC, Yu HT, Fu PP. 2011. Nanogold-based sensing of environmental toxins: Excitement and challenges. *J Environ Sci Health C Environ Carc Ecotoxicol Rev* 29(1):52-89.

[7] Reagan WJ, Irizarry-Rovira A, Poitout-Belissent F, Bolliger AP, Ramaiah SK, Travlos G, Walker D, Bounous D, Walter G. 2011. Best practices for evaluation of bone marrow in nonclinical toxicity studies. *Vet Clin Path* 40(2):119-134.

[2] Roberts JR, Chapman RS, Tirumala VR, Karim A, Chen BT, Schwegler-Berry D, Stefaniak AB, Leonard SS, Antonini JM. 2011. Toxicological evaluation of lung responses after intratracheal exposure to non-dispersed titanium dioxide nanorods. *J Toxicol Environ Health A* 74(12):790-810.

[2] Rocheleau CM, Bertke SJ, Deddens JA, Ruder AM, Lawson CC, Waters MA, Hopf NB, Riggs MA, Whelan EA. 2011. Maternal exposure to polychlorinated biphenyls and the secondary sex ratio: An occupational cohort study. *Environ Health* 10:20.

[4] Rothfuss A, Honma M, Czich A, Aardema MJ, Burlinson B, Galloway S, Hamada S, Kirkland D, Heflich RH, Howe J, Nakajima M, O'Donovan M, Plappert-Helbig U, Priestley C, Recio L, Schuler M, Uno Y, Martus HJ. 2011. Improvement of *in vivo* genotoxicity assessment: Combination of acute tests and integration into standard toxicity testing. *Mut Res-Gentic Toxicol Environ Mut* 723(2):108-120.

[2] Ruder AM, Yiin JH. 2011. Mortality of U.S. pentachlorophenol production workers through 2005. *Chemosphere* 83(6):851-861.

[2] Rushton EK, Jiang J, Leonard SS, Eberly S, Castranova V, Biswas P, Elder A, Han XL, Gelein R, Finkelstein J, Oberdorster,G. 2010. Concept of assessing nanoparticle hazards considering nanopartile dosemetric and chemical/biological response metrics. *J Toxicol Environ Health A* 73(5-6):445-461.

[2] Sargent LM, Reynolds SH, Castranova V. 2010. Potential pulmonary effects of engineered carbon nanotubes: *In vitro* genotoxic effects. *Nanotoxicol* 4(4):396-408.

[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 the NTP/NHGRI/EPA/FDA Interagency Memorandum of Understanding
[6] Funded by the NIEHS/EPA Interagency Agreement
[7] Funded by NIEHS voluntary allocations to the NTP

[2] Saxena RK, McClure ME, Hays MD, Green FHY, McPhee LJ, Vallyathan V, Gilmour MI. 2011. Quantitative assessment of elemental carbon in the lungs of never smokers, cigarette smokers, and coal miners. *J Toxicol Environ Health A* 74(11):706-715.

[1] Schubauer-Berigan MK, Dahm MM, Yencken MS. 2011. Engineered carbonaceous nanomaterials manufacturers in the United States: Workforce size, characteristics, and feasibility of epidemiologic studies. *J Occ Env Med 53 Suppl* (6S):S62-S67.

[2] Scuri M, Chen BT, Castranova V, Reynolds JS, Johnson VJ, Samsell L, Walton C, Piedimonte G. 2010. Effects of titanium dioxide nanoparticle exposure on neuroimmune responses in rat airways. *J Toxicol Environ Health A* 73(20):1353-1369.

[7] Seibold MA, Wise AL, Speer MC, Steele MP, Brown KK, Loyd JE, Fingerlin TE, Zhang WM, Gudmundsson G, Groshong SD, Evans CM, Garantziotis S, Adler KB, Dickey BF, du Bois RM, Yang IV, Herron A, Kervitsky D, Talbert JL, Markin C, Park J, Crews AL, Slifer SH, Auerbach S, Roy MG, Lin J, Hennessy CE, Schwarz MI, Schwartz DA. 2011. A common MUC5B promoter polymorphism and pulmonary fibrosis. *New Engl J Med* 364(16):1503-1512.

[2] Sellamuthu R, Umbright C, Roberts JR, Chapman R, Young SH, Richardson D, Leonard H, McKinney W, Chen B, Frazer D, Li SQ, Kashon M, Joseph P. 2011. Blood gene expression profiling detects silica exposure and toxicity. *Toxicol Sci* 122(2):253-264.

[4] Shpyleva SI, Tryndyak VP, Kovalchuk O, Starlard-Davenport A, Chekhun VF, Beland FA, Pogribny IP. 2011. Role of ferritin alterations in human breast cancer cells. Breast Cancer Res Treat 126(1):63-71.

[7] Silbergeld EK, Contreras EQ, Hartung T, Hirsch C, Hogberg H, Jachak AC, Jordan W, Landsiedel R, Morris J, Patri A, Pounds JG, de Vizcaya Ruiz A, Shvedova A, Tanguay R, Tatarazako N, van Vliet E, Walker NJ, Wiesner M, Wilcox N, Zurlo J. 2011. t[4] workshop report. Nanotoxicology: "the end of the beginning" – signs on the roadmap to a strategy for assuring the safe application and use of nanomaterials. ALTEX 28(3):236-41.

[7] Sills RC, Garman RH. 2011. Gene expression, biomarkers, and glial cells in nervous system diseases. *Toxicol Path* 39(1):97-98.

[4] Slikker W, Zhang X, Newport GD, Paule MG, Liu F, Berridge MS, Kabalka G, Wang C. 2011. Minimally invasive quantitative assessment of inhalation anesthetic-induced brain cell death using microPET imaging. *Toxicol Lett* 205(S237-S238).

[2] Smith J, Sammons D, Robertson S, Biagini R, Snawder J. 2010. Measurement of multiple drugs in urine, water, and on surfaces using fluorescence covalent microbead immunosorbent assay. *Toxicol Mech Meth* 20(9):587-593.

[7] Smith MJ, Germolec DR, Luebke RW, Sheth CM, Auttachoat W, Guo TL, White KL. 2010. Immunotoxicity of dibromoacetic acid administered via drinking water to female B6C3F1 mice. *J Immunotoxicol* 7(4):333-343.

[2] Snawder JE, Striley CAF, Esswein EJ, Hessel J, Sammons DL, Robertson SA, Johnson BC, MacKenzie BA, Smith JP, Walker CV. 2011. Use of direct reading surface sampling methods for site characterization and remediation of methamphetamine contaminated properties. *J ASTM Int* 8(6):1-11.

[2] Snyder BN, Cho Y, Qian Y, Coad JE, Flynn DC, Cunnick JM. 2011. AFAP1L1 is a novel adaptor protein of the AFAP family that interacts with cortactin and localizes to invadosomes. *Eur J Cell Biol* 90(5):376-389.

[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 the NTP/NHGRI/EPA/FDA Interagency Memorandum of Understanding
[6] Funded by the NIEHS/EPA Interagency Agreement
[7] Funded by NIEHS voluntary allocations to the NTP

[2] Springs M, Wells JR, Morrison GC. 2011. Reaction rates of ozone and terpenes adsorbed to model indoor surfaces. *Indoor Air* 21(4):319-327.

[7] Stanko JP, Enoch RR, Rayner JL, Davis CC, Wolf DC, Malarkey DE, Fenton SE. 2010. Effects of prenatal exposure to a low dose atrazine metabolite mixture on pubertal timing and prostate development of male Long-Evans rats. *Rep Toxicol* 30(4):540-549.

[4] Starlard-Davenport A, Tryndyak V, Kosyk O, Ross SR, Rusyn I, Beland FA, Pogribny IP. 2010. Dietary methyl deficiency, microRNA expression and susceptibility to liver carcinogenesis. *J Nutrigenetics Nutrigenomics* 3(46):259-266.

[7] Starr JM, Scollon EJ, Hughes MF, Graham SE, Ross DG, Crofton KM, Wolansky M, DeVito M, Tornero-Velez R. 2011. Using a chemical mixture of pyrethroid pesticides to determine rodent tissue clearance rates. *Epidemiol* 22(1):S249-S250.

[2] Steiner AZ, Herring AH, Kesner JS, Meadows JW, Stanczyk FZ, Hoberman S, Baird DD. 2011. Antimullerian hormone as a predictor of natural fecundability in women aged 30-42 years. *Obst Gyn* 117(4):798-804.

[4] Stingley, RL, Zou, W, Heinze, TM, Chen, HZ, Cerniglia, CE. 2010. Metabolism of azo dyes by human skin microbiota. *J Med Microbiol* 59(1):108-114.

[7] Stokes WS. 2011. Best practices for the use of animals in toxicological research and testing. *Ann N Y Acad Sci* 1245(1):17-20.

[7] Stokes WS, Brown K, Kulpa-Eddy J, Srinivas G, Halder M, Draayer H, Galvin J, Claassen I, Gifford G, Woodland R, Doelling V, Jones B. 2011. Improving animal welfare and reducing animal use for veterinary vaccine potency testing: state-of-the-science and future directions. In: International Workshop on Alternative Methods to Reduce, Refine, and Replace the Use of Animals in Vaccine Potency and Safety Testing: State of the Science and Future Directions (Kulpa-Eddy J, McFarland R, Stokes WS, eds). *Procedia Vaccinol* 5:84-105.

[7] Stokes WS, Kulpa-Eddy J, McFarland R. 2011. The International Workshop on Alternative Methods to Reduce, Refine, and Replace the Use of Animals in Vaccine Potency and Safety Testing: introduction and summary. In: International Workshop on Alternative Methods to Reduce, Refine, and Replace the Use of Animals in Vaccine Potency and Safety Testing: State of the Science and Future Directions (Kulpa-Eddy J, McFarland R, Stokes WS, eds). *Procedia Vaccinol* 5: 1-15.

[7] Sun Y, Kojima C, Chignell C, Mason R, Waalkes MP. 2011. Arsenic transformation predisposes human skin keratinocytes to UV-induced DNA damage yet enhances their survival apparently by diminishing oxidant response. *Toxicol Appl Pharmacol* 255(3):242-250.

[4] Sun, JC, Schnackenberg, LK, Hansen, DK, Beger, RD. 2010. Study of valproic acid-induced endogenous and exogenous metabolite alterations using LC-MS-based metabolomics. *Bioanalysis* 2(2):207-216.

[4] Sun JC, Schnackenberg LK, Pence L, Bhattacharyya S, Doerge DR, Bowyer JF, Beger RD. 2010. Metabolomic analysis of urine from rats chronically dosed with acrylamide using NMR and LC/MS. *Metabolomics* 6(4):550-563.

[4] Teeguarden JG, Calafat AM, Ye XY, Doerge DR, Churchwell MI, Gunawan R, Graham MK. 2011. Twenty-four hour human urine and serum profiles of bisphenol A during high-dietary exposure. *Toxicol Sci* 123(1):48-57.

[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 the NTP/NHGRI/EPA/FDA Interagency Memorandum of Understanding*
[6] *Funded by the NIEHS/EPA Interagency Agreement*
[7] *Funded by NIEHS voluntary allocations to the NTP*

[2] Teeguarden JG, Webb-Robertson BJ, Waters KM, Murray AR, Kisin ER, Varnum SM, Jacobs JM, Pounds JG, Zanger RC, Shvedova AA. 2011. Comparative proteomics and pulmonary toxicity of instilled single-walled carbon nanotubes, crocidolite asbestos, and ultrafine carbon black in mice. *Toxicol Sci* 120(1):123-135.

[1] Templeton SP, Buskirk AD, Law B, Green BJ, Beezhold DH. 2011. Role of germination in murine airway CD8+ T-cell responses to *Aspergillus conidia*. *PLOS One* 6(4):e18777.

[7] Teng CT, Li Y, Stockton P, Foley J. 2011. Fasting induces the expression of PGC-1α and ERR isoforms in the outer stripe of the outer medulla (OSOM) of the mouse kidney. *PLoS One* 6(11):e26961.

[7] Teng CT, Teng P. 2011. Estrogen-related receptors and breast cancer: a review in Breast Cancer – Carcinogenesis, Cell Growth and Signalling Pathways, Eds. Gunduz M, and Esra Gunduz E, Intech:313-330.

[7] Thackaberry EA, Kopytek S, Sherratt P, Trouba K, McIntyre B. 2010. Comprehensive investigation of hydroxypropyl methylcellulose, propylene glycol, polysorbate 80, and hydroxypropyl-beta-cyclodextrin for use in general toxicology studies. *Toxicol Sci* 117(2):485-492.

[7] Thomas AC, Nouls JC, Driehuys B, Voltz JW, Fubara B, Foley J, Bradbury JA, Zeldin DC. 2011. Ventilation defects observed with hyperpolarized 3He magnetic resonance imaging in a mouse model of acute lung injury. *Amer J Resp Cell Mol Biol* 44(5):648-654.

[7] Thoolen B, Maronpot RR, Harada T, Nyska A, Rousseaux C, Nolte T, Malarkey DE, Kaufmann W, Kuttler K, Deschl U, Nakae D, Gregson R, Vinlove MP, Brix AE, Singh B, Belpoggi F, Ward JM. 2010. Proliferative and nonproliferative lesions of the rat and mouse hepatobiliary system. *Toxicol Path* 38(suppl 7):5S-81S.

[7] Tokar EJ, Benbrahim-Tallaa L, Ward JM, Lunn R, Sams RL, Waalkes MP. 2010. Cancer in experimental animals exposed to arsenic and arsenic compounds. *Crit Rev Toxicol* 40(10):912-927.

[7] Tokar EJ, Diwan BA, Ward JM, Delker DA, Waalkes MP. 2011. Carcinogenic effects of "whole-life" exposure to inorganic arsenic in CD1 mice. *Toxicol Sci* 119(1):73-83.

[7] Tokar EJ, Qu W, Waalkes MP. 2011. Arsenic, stem cells, and the developmental basis of adult cancer. *Toxicol Sci* 120(Suppl 1):S192-203.

[7] Travlos GS, Hard GC, Betz LJ, Kissling GE. 2011. Chronic progressive nephropathy in male F344 rats in 90-day toxicity studies: Its occurrence and association with renal tubule tumors in subsequent 2-year bioassays. *Toxicol Path* 39(2):381-389.

[4] Trickler WJ, Lantz SM, Murdock RC, Schrand AM, Robinson BL, Newport GD, Schlager JJ, Oldenburg SJ, Paule MG, Slikker W, Hussain SM, Ali SF. 2010. Silver nanoparticle induced blood-brain barrier inflammation and increased permeability in primary rat brain microvessel endothelial cells. *Toxicol Sci* 118(1):160-170.

[4] Tryndyak VP, Han T, Muskhelishvili L, Fuscoe JC, Ross SA, Beland FA, Pogribny IP. 2011. Coupling global methylation and gene expression profiles reveal key pathophysiological events in liver injury induced by a methyl-deficient diet. *Mol Nut Food Res* 55(3):411-418.

[7] Tubbs JT, Kissling GE, Travlos GS, Goulding DR, Clark JA, King-Herbert AP, Blankenship-Paris TL. 2011. Effects of buprenorphine, meloxicam, and flunixin meglumine as postoperative analgesia in mice. *J Amer Assoc Lab Animal Sci* 50(2):185-191.

[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 the NTP/NHGRI/EPA/FDA Interagency Memorandum of Understanding*
[6] *Funded by the NIEHS/EPA Interagency Agreement*
[7] *Funded by NIEHS voluntary allocations to the NTP*

[2] Tucker JD, Sorensen KJ, Ruder AM, McKernan LT, Forrester CL, Butler MA. 2011. Cytogenetic analysis of an exposed-referent study: Perchloroethylene-exposed dry cleaners compared to unexposed laundry workers. *Environ Health* 10:16.

[3] Twaddle NC, Churchwell MI, Vanlandingham M, Doerge DR. 2010. Quantification of deuterated bisphenol A in serum, tissues, and excreta from adult Sprague-Dawley rats using liquid chromatography with tandem mass spectrometry. *Rapid Comm Mass Spect* 24(20):3011-3020.

[4] Valentine CR, Delongchamp RR, Pearce MG, Rainey HF, Dobrovolsky VN, Malling HV, Heflich RH. 2010. *In vivo* mutation analysis using the Phi X174 transgenic mouse and comparisons with other transgenes and endogenous genes. *Mut Res Rev Mut Res* 705(3):205-216.

[4] Von Tungeln LS, Zhou T, Woodling KA, Doerge DR, Greenlees KJ, Beland FA. 2011. Benzocaine-induced methemoglobinemia in an acute-exposure rat model. *Food Chem Toxicol* 49(10):2530-2535.

[2] Waggoner JK, Kullman GJ, Henneberger PK, Umbach DM, Blair A, Alavanja MCR, Kamel F, Lynch CF, Knott C, London SJ, Hines CJ, Thomas KW, Sandler DP, Lubin JH, Freeman LE, Hoppin JA. 2011. Mortality in the Agricultural Health Study, 1993-2007. *Amer J Epidemiol* 173(1):71-83.

[7] Waidyanatha S, Johnson JD, Hong SP, Godfrey-Robinson VD, Graves SW, Cristy T, Dunnick JK, Smith CS. 2011. Toxicokinetics of bis(2-chloroethoxy) methane following intravenous administration and dermal application in male and female F344/N rats and B6C3F1 mice. *Toxicol Lett* 205(2):215-226.

[2] Wang LY, Castranova V, Mishra A, Chen B, Mercer RR, Schwegler-Berry D, Rojanasakul Y. 2010. Dispersion of single-walled carbon nanotubes by a natural lung surfactant for pulmonary *in vitro* and *in vivo* toxicity studies. *Particle Fibre Toxicol* 7:31.

[2] Wang LY, Luanpitpong S, Castranova V, Tse W, Lu YJ, Pongrakhananon V, Rojanasakul Y. 2011. Carbon nanotubes induce malignant transformation and tumorigenesis of human lung epithelial cells. *Nano Lett* 11(7):2796-2803.

[7] Wang PM, Kachel DL, Cesta MF, Martin WJ 2nd. 2011. Direct leukocyte migration across pulmonary arterioles and venules into the perivascular interstitium of murine lungs during bleomycin injury and repair. *Amer J Path* 178(6):2560-2572.

[2] Wang XA, Xia TA, Ntim SA, Ji ZX, George S, Meng HA, Zhang HY, Castranova V, Mitra S, Nel AE. 2010. Quantitative techniques for assessing and controlling the dispersion and biological effects of multiwalled carbon nanotubes in mammalian tissue culture cells. *Am Chem Soc Nano* 4(12):7241-7252.

[2] Ward EM, Schulte PA, Straif K, Hopf NB, Caldwell JC, Carreon T, DeMarini DM, Fowler BA, Goldstein BD, Hemminki K, Hines CJ, Pursiainen KH, Kuempel E, Lewtas J, Lunn RM, Lynge E, McElvenny DM, Muhle H, Nakajima T, Robertson LW, Rothman N, Ruder AM, Schubauer-Berigan MK, Siemiatycki J, Silverman D, Smith MT, Sorahan T, Steenland K, Stevens RG, Vineis P, Zahm SH, Zeise L, Cogliano VJ. 2010. Research recommendations for selected IARC-classified agents. *Environ Health Perspect* 118(10):1355-1362.

[1] Waring MS, Wells JR, Siegel JA. 2011. Secondary organic aerosol formation from ozone reactions with single terpenoids and terpenoid mixtures. *Atmosph Environ* 45(25):4235-4242.

[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 the NTP/NHGRI/EPA/FDA Interagency Memorandum of Understanding*
[6] *Funded by the NIEHS/EPA Interagency Agreement*
[7] *Funded by NIEHS voluntary allocations to the NTP*

[7] Wei BR, Martin PL, Hoover SB, Spehalski E, Kumar M, Hoenerhoff MJ, Rozenberg J, Vinson C, Simpson RM. 2011. Capacity for resolution of Ras-MAPK-initiated early pathogenic myocardial hypertrophy modeled in mice. *Comp Med* 61(2):109-18.

[7] White SS, Fenton SE, Hines EP. 2011. Endocrine disrupting properties of perfluorooctanoic acid. *J Steroid Biochem Mol Biol* 127(1-2)16-26.

[7] White SS, Stanko JP, Kato K, Calafat AM, Hines EP, Fenton SE. 2011. Gestational and chronic low-dose PFOA exposures and mammary gland growth and differentiation in three generations of CD-1 mice. *Environ Health Perspect* 119(8):1070-1076.

[7] Witt KL, Moorman PG, Kovalchuk O, Holland N, Block G, Andreassen PR. 2010. Genetics and women's health issues – The commitment of EMS to women scientists and gender-associated disease topics. *Environ Mol Mut* 51(8-9):774-780.

[3] Wu QE, Beland FA, Chang CW, Fang JL. 2011. XPC is essential for nucleotide excision repair of zidovudine-induced DNA damage in human hepatoma cells. *Toxicol Appl Pharmacol* 251(2):155-162.

[5] Xia MH, Shahane SA, Huang RL, Titus SA, Shum E, Zhao Y, Southall N, Zheng W, Witt KL, Tice RR, Austin CP. 2011. Identification of quaternary ammonium compounds as potent inhibitors of hERG potassium channels. *Toxicol Appl Pharmacol* 252(3):250-258.

[2] Xia TA, Zhao Y, Sager T, George S, Pokhrel S, Li N, Schoenfeld D, Meng HA, Lin SJ, Wang X, Wang MY, Ji Z, Zink JI, Mädler L, Castranova V, Nel AE. 2011. Decreased dissolution of ZnO by iron doping yields nanoparticles with reduced toxicity in the rodent lung and zebrafish embryos. *Amer Chem Soc Nano* 5(2):1223-1235.

[2] Xiao L, O'Callaghan JP, O'Donnell JM. 2011. Effects of repeated treatment with phosphodiesterase-4 inhibitors on cAMP signaling, hippocampal cell proliferation and behavior in the Forced-Swim test. *J Pharmacol Exp Ther* 338(2):641-647.

[5] Yamamoto KN, Hirota K, Kono K, Takeda S, Sakamuru S, Xia M, Huang R, Austin CP, Witt KL, Tice RR. 2011. Characterization of environmental chemicals with potential for DNA damage using isogenic DNA repair-deficient chicken DT40 cell lines. *Environ Mol Mutagen* 52(7): 547-561.

[1] Yeang HY, Hamilton RG, Bernstein DI, Arif SAM, Chow KS, Loke YH, Raulf-Heimsoth M, Wagner S, Breiteneder H, Biagini RE. 2010. Allergen concentration in natural rubber latex. *Clin Exp Allergy* 40(5): 831-831.

[7] Yoshizawa K, Walker NJ, Nyska A, Kissling GE, Jokinen MP, Brix AE, Sells DM, Wyde ME. 2010. Thyroid follicular lesions induced by oral treatment for 2 years with 2,3,7,8-tetrachlorodibenzo-p-dioxin and dioxin-like compounds in female Harlan Sprague-Dawley rats. *Toxicol Pathol* 38(7):1037-50.

[2] Young SH, Cox-Ganser JM, Shogren ES, Wolfarth MG, Li S, Antonini JM, Castranova V, Park JH. 2011. Pulmonary inflammation induced by office dust and the relation to 1→3-β-glucan using different extraction techniques. *Toxicol Environ Chem* 93(4):806-823.

[1] Yucesoy B, Johnson VJ. 2011. Genetic variability in susceptibility to occupational respiratory sensitization. *J Allergy* (Cairo) Epub.

[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 the NTP/NHGRI/EPA/FDA Interagency Memorandum of Understanding
[6] Funded by the NIEHS/EPA Interagency Agreement
[7] Funded by NIEHS voluntary allocations to the NTP

[2] Zeidler-Erdely PC, Battelli LA, Salmen-Muniz R, Li Z, Erdely A, Kashon ML, Simeonova PP, Antonini JM. 2011. Lung tumor production and tissue metal distribution after exposure to manual metal ARC-stainless steel welding fume in A/J and C57BL/6J mice. *J Toxicol Environ Health A* 74(11):728-736.

[2] Zeidler-Erdely PC, Battelli LA, Stone S, Chen BT, Frazer DG, Young SH, Erdely A, Kashon ML, Andrews R, Antonini JM. 2011. Short-term inhalation of stainless steel welding fume causes sustained lung toxicity but no tumorigenesis in lung tumor susceptible A/J mice. *Inhal Toxicol* 23(2):112-120.

[4] Zhang X, Paule MG, Newport GD, Sadovova N, Berridge MS, Apana SM, Kabalka G, Miao W, Slikker W Jr, Wang C. 2011. MicroPET imaging of ketamine-induced neuronal apoptosis with radiolabeled DFNSH. *J Neural Trans* 118(2):203-211.

[7] Zhao R, Hou Y, Xue P, Woods CG, Fu J, Feng B, Guan D, Sun G, Chan JY, Waalkes MP, Andersen ME, Pi J. 2011. Long isoforms of NRF1 contribute to arsenic-induced antioxidant response in human keratinocytes. *Environ Health Perspect* 119(1):56-62.

[4] Zhao Y, Xia Q, Yin JJ, Lin G, Fu PP. 2011. Photoirradiation of dehydropyrrolizidine alkaloids-formation of reactive oxygen species and induction of lipid peroxidation. *Toxicol Lett* 205(3):302-309.

[4] Zhao Y, Xia Q, Yin JJ, Yu H, Fu PP. 2011. Photoirradiation of polycyclic aromatic hydrocarbon diones by UVA light leading to lipid peroxidation. *Chemosphere* 85(1):83-91.

[4] Zhou Y, Li N, Choi FFK, Qiao CF, Song JZ, Li SL, Liu X, Cai ZW, Fu PP, Lin G, Xu HX. 2010. A new approach for simultaneous screening and quantification of toxic pyrrolizidine alkaloids in some potential pyrrolizidine alkaloid-containing plants by using ultra performance liquid chromatography-tandem quadrupole mass spectrometry. *Anal Chimica Acta* 681(1-2):33-40.

[4] Zou X, Liu F, Zhang X, Patterson TA, Callicott R, Liu S, Hanig JP, Paule MG, Slikker W Jr, Wang C. 2011. Inhalation anesthetic-induced neuronal damage in the developing rhesus monkey. *Neurotoxicol Teratol* 33(5):592-597.

[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 the NTP/NHGRI/EPA/FDA Interagency Memorandum of Understanding
[6] Funded by the NIEHS/EPA Interagency Agreement
[7] Funded by NIEHS voluntary allocations to the NTP

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

National Toxicology Program
PO Box 12233
111 TW Alexander Drive
Research Triangle Park, NC 27709
www.ntp.niehs.nih.gov

NIH Publication No. 12-5971