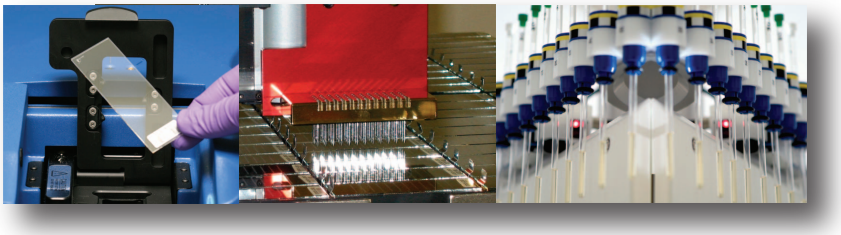
The National Center for Toxicological Research

An Internationally Recognized Resource for Innovative and Integrative Research



Established by executive order in 1971, the National Center for Toxicological Research (NCTR) is internationally recognized for research that addresses the mechanisms of toxicity of chemicals and pharmaceutical drugs, defines the risks associated with chemical and microbial food contamination, and identifies biomarkers for terrorism due to biological and/or chemical exposure.

NCTR has the staff, the facilities, and the research tools to conduct innovative, integrative research that is used to guide and support regulatory decisions.

Chemicals and pharmaceutical drugs evaluated for adverse health outcomes:

Cancer, birth defects, neurological disease, and liver toxicity

Foods safe from microbial and chemical contamination

Homeland secure from biological and chemical terrorism





Core Capabilities:

Secure Research Campus:

Located adjacent to the Pine Bluff Arsenal in Jefferson, Arkansas, the Jefferson Laboratories of the FDA resides on 500 acres. Jefferson Labs is home to and managed by the staff of the NCTR and also houses the Office of Regulatory Affairs' Arkansas Regional Laboratory (ARL). The facility consists of 30 buildings with approximately one million square feet of floor space and $20 million in capital equipment. Only 700,000 square feet of the facility is currently occupied. The remaining square footage is available to establish new research programs and capabilities.

AAALAC Accredited Animal Research Facility:

NCTR is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC). NCTR's policies and procedures on animal husbandry, veterinary care, and the physical plant promote animal well-being and enhance the scientific research. NCTR maintains its own breeding colony, has specific pathogen-free (SPF) barrier facilities, and a unique dietary preparation facility. There are both general purpose and high containment laboratories. While the majority of animal research involves rodents, other species (including non-human primates) are available or can be obtained and accommodated to meet the goals of specific research projects. The NCTR non human primate research center is a unique resource that is available for collaborative projects.

GLP-Compliant Research:

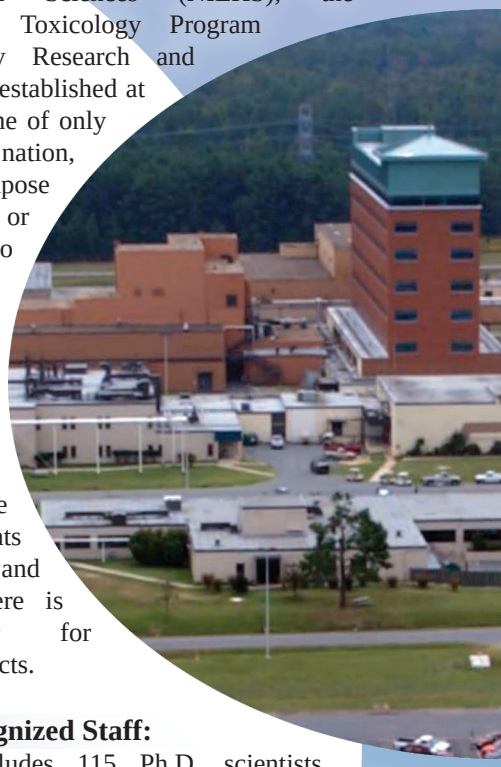
NCTR conducts large scale, Good Laboratory Practice (GLP)-compliant animal research studies. The Quality Assurance staff at NCTR provides knowledgeable oversight of experimental studies and assures that the data generated in these studies can be utilized for regulatory purposes. The chemistry and microbiology analytical staffs have extensive expertise and experience in assuring agent purity, determining accurate dose, and monitoring animal health.

Biological Safety Laboratories:

In response to the national need for additional capability to conduct high biological hazard research, NCTR has recently completed a state-of-the-art BSL-3 containment facility. The BSL-3 facility has 10 individual BSL-3 suites (~120 ft^2 each) equipped with Biosafety cabinets, workbench, and sink. The suites are supported by a shared preparation laboratory of 300 ft^2. Currently, in collaboration with the Environmental Protection Agency, NCTR is utilizing this facility to investigate an infectivity model for *Crytosporidium*. The NCTR BSL-3 facility is available for additional collaborative public health-related research projects.

NTP Center for Phototoxicology:

Via an Interagency Agreement with the National Institutes for Environmental Health Sciences (NIEHS), the FDA/NIEHS National Toxicology Program (NTP) Phototoxicology Research and Testing Laboratory was established at NCTR. This facility, one of only two such facilities in the nation, can be used to expose animals, cell cultures, or chemical mixtures to simulated solar light. The light source can be adjusted to simulate specific exposure scenarios or specific geographic locations. Currently the facility is used to study the potential toxic components in cosmetic ingredients and tattoo pigments. There is sufficient capability for additional research projects.



Internationally Recognized Staff:

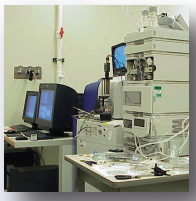
The NCTR staff includes 115 Ph.D. scientists representing a wide array of scientific expertise. The program is supported by approximately 470 support scientists, on-site contractors, and administrative staff. Many of the senior staff members have extensive experience conducting multi-disciplinary public health research. Under-graduate and graduate students, post-doctoral fellows, and visiting scientists come to NCTR to learn new technologies and scientific disciplines and to contribute their skills and perspectives to the NCTR research program.

Multi-disciplinary Toxicology Research Team:

NCTR is a center for toxicology research excellence. Throughout its history, NCTR scientists have provided the international health community with research that addresses important public health questions. The NCTR multi-disciplinary scientific team conducts research for a number of adverse health outcomes. The capability to conduct GLP and non-GLP studies for cancer, neurological diseases, birth defects, thyroid toxicity, and liver toxicity is widely recognized and utilized. NCTR is noted for the development of new technologies and new assays to evaluate adverse toxicological effects. Methods developed by NCTR scientists are incorporated into regulatory agency policies and guidance documents for industry.







NCTR capabilities include the ability to develop new research standards for and to conduct:

- Mechanistically-based rodent cancer bioassays
- Multigenerational developmental studies
- *In vitro* and *in vivo* studies to assess the ability of chemicals to induce mutations
- Developmental toxicology studies
- Studies to identify genetic variants that make individuals more susceptible to disease or more susceptible to the adverse effects of chemical exposure
- Neuropathological, neurophysiological, and neurobehavioral assessments
- Physiological responses
- Organ specific toxicities, such as liver and thyroid

Based upon the specific health issue, NCTR can assemble a team of scientists with the appropriate cross-discipline toxicological expertise to design, conduct, and communicate research for use in making regulatory decisions.

Microbiology and Chemistry Research and Support Team:

The NCTR microbiology research team utilizes its extensive scientific expertise and state-of-the-art equipment to address a variety of public health issues and to provide core microbiological support to assure the health of the NCTR animal colonies. Research is focused on developing the methods and the capabilities to:

- Detect foodborne pathogens (both naturally occurring and resulting from terrorist acts)
- Evaluate antimicrobial resistance
- Understand the relationship between gastrointestinal microbiology and host interactions
- Use microbes for bioremediation
- Perform microbiological surveillance
- Develop microorganisms as models to predict the metabolic pathways by which drugs are metabolized in mammals

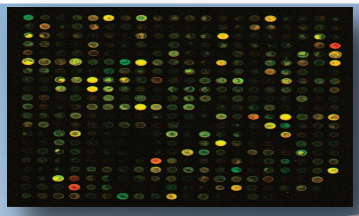
A critical component of the NCTR research capability is the outstanding chemistry expertise assembled at NCTR. This expertise is applied to both routine chemical analysis for compound composition and stability and to the development of new technologies that can be applied to the detection of pathogen and chemical contaminants both naturally occurring and applied as a terrorist attack. The chemistry staff, using analytical mass spectrometry, can perform the quality assurance analysis that allows for the conduct of GLP-compliant research. The counter bioterrorism research group has developed and is now applying rapid, reliable, and cost effective mass spectrometric methods to identify pathogenic agents. These methods use pattern recognition-based biomarker methods to detect pathogens and make it possible to distinguish between real and hoax counterterrorist incidents. In collaboration with the University of Arkansas at Little Rock, the nanotechnology and sensory technology group has developed two nanotechnology-based cancer therapies, several large scale nanoparticle production patents, and a novel nanoparticle-based filter technology to protect the public from chemical and biological contaminants. This group has also developed a sensor technology for food freshness and quality that is now under development for potential commercial application. This sensor technology, which is now being applied to the detection of NOx and nitroaromatics and is of interest to the Federal Aviation Administration, has great potential and can be developed for the detection of other chemicals.

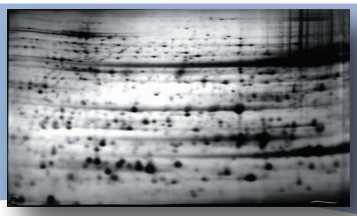
Risk Assessment and Statistics:

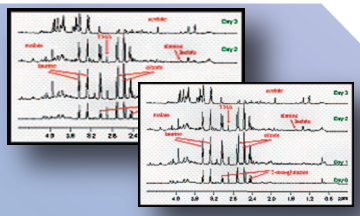
NCTR has assembled a team of internationally recognized scientists (including statisticians, mathematicians, and risk assessors) who not only utilize existing statistical and risk assessment methodologies, but also develop new approaches that can be applied to improve the interpretation and utilization of data for regulatory decision-making.

Toxicoinformatics and Computational Models:

NCTR is internationally recognized for its informatic and computational modeling capabilities. Computational modeling, using structure activity relationships (SAR), can be applied to large numbers of chemical classes to predict various toxicity or other biological activity outcomes. A variety of artificial intelligence-based neural net approaches to data analysis are under development. The infrastructure is in place to handle the large quantities of data generated from the new genomic, metabolomic, and proteomic (”omics”) technologies. NCTR developed ArrayTrack, a publicly available database of NCTR “omics” data that can not only process but can also integrate “omics” data. It has libraries that can access public toxicology data and tools for analyzing and visualizing the data. One of the visualization tools permits cross species chromosomal mapping to assist with data interpretation and the generation of hypotheses concerning the pathways that are modified following chemical exposure. They also allow for an evaluation of the applicability of rodent model data to humans.







Genomics:

NCTR has two Centers of Excellence that address issues related to the genetic makeup of individuals (the genome). The Center for Structural Genomics (CSG) provides the tools for and addresses questions concerning individual genetic differences and the impact that these genetic differences have on the development of disease. The CSG uses molecular techniques to identify single nucleotide polymorphisms (SNPs) in humans. Currently the CSG is developing a genome haplotype map for prostate, breast, and colorectal cancer susceptibility. Using this approach, the CSG researchers can provide information that can be used to assess an individual's risk for developing cancer based on the person's inherited genetic characteristics.

The Center for Functional Genomics (CFG) provides the tools for and conducts research to understand the genetic functional consequences following exposure to chemicals or pharmaceutical drugs. The CFG includes a microarray facility that can print customized arrays for mouse, rat, or human studies. While the majority of the arrays use oligos, the CFG can customize arrays that are optimized to address a wide variety of research questions. The CFG staff of highly experienced individuals interacts effectively with other research scientists to appropriately design, conduct, and interpret the data from microarray experiments.

In addition, NCTR scientists are developing microarray technology to identify the presence of microorganisms. This application is not only being developed for use in screening food supplies for naturally occurring pathogenic microorganisms, but also for identifying highly infectious pathogenic microorganisms intentionally released as part of a terrorist event.

Metabolomics:

The NCTR metabolomic group develops biomarkers of toxicity and disease. The core metabolomic facility is equipped with a Brucker 600 MHz nuclear magnetic resonance (NMR) that has a cryoprobe to analyze endogenous metabolites in biological samples. Capabilities of performing mass spectrometry (MS)-based metabolomic analysis will soon be expanded with the addition of a Waters LTQ Premiere mass spectrometer. The group has initially focused on the development of biomarkers of acute toxicity that can be applied to a variety of research questions. Currently the group is evaluating the effects of renal, liver, and cardiotoxins using serum, urine, and various tissues. This technology is readily applicable to cross species comparisons and for preclinical and clinical studies. NCTR is using Scaled-to-Maximum, Aligned, and Reduced Trajectories (SMART) analysis to map trajectories of change in physiological space to expand its ability to conduct cross species analysis.

Proteomics:

The proteomics group includes seven highly experienced staff members dedicated to mass spectrometry-based methodologies for qualitatively and quantitatively analyzing proteins from a variety of biological matrices. With an emphasis on nano LC MS/MS (liquid chromatography/mass spectometry) with ion trap mass spectrometers, this group is currently involved in multiple protein profiling projects including rat liver mitochondria, mouse liver, virulence factors in *Staphylococcus aureus*, and the characterization of the 19S mouse proteosome. The proteomics group is developing improved methods for serum biomarker discovery by isolating the low molecular weight peptide components interacting with abundant high molecular weight proteins. The group has multiple external collaborations with both academic institutions and pharmaceutical companies.

NCTR At A Glance

Employs 115 Ph.D. scientists (including post doctoral scientists), supported by 470 government and contract personnel representing a broad array of toxicological expertise.

Physical facilities, located in central Arkansas, include 30 buildings spanning one million square feet of floor space, and housing approximately $20 million in capital equipment. There are 132 general or special purpose research labs, 82 AAALAC-accredited breeding and conventional animal rooms, primate research facilities, 23 specialized labs for pathological processing and evaluation, biocontainment level 3 laboratories, a scientific and technical library, on-site hazardous waste disposal, and diet preparation facilities. An on-site housing unit for visiting scientists consists of eight two-person units and a commons building.

Modern scientific equipment includes molecular biology tools, laser capture microdissection microscopes, flow cytometers, mass spectrometers, nuclear magnetic resonance spectrometers, microarray printers, and hardware/software infrastructure to foster science and scientific computing.

March 10, 2006

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