

For the past 37 years, NTP has been a leader in toxicology testing, research, and analysis and provided important scientific information upon which public health decisions are based.

NTP has earned distinction as an honest broker through its continuing commitment to open debate, impartiality, and rigorous review.

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## The National Toxicology Program

# milestones

1978–2015  
**Thirty-Seven Years  
of Toxicology  
for Public Health**

Since 1978, NTP has played a critical role in generating and interpreting toxicological information about potentially hazardous substances in our environment and communicating that knowledge to government agencies, medical and scientific communities, and the public. In the 21<sup>st</sup> century, NTP strives to remain at the cutting edge of scientific research and the development and application of new technologies to provide a strong science base for decisions that protect human health and the environment.

# Research Information Communication

NTP's expertise in toxicology combined with the experience and needs of other agencies provides a consolidated approach to identifying and controlling hazardous substances in our environment and safeguarding public health. NTP has evaluated more than 2800 environmental substances for a variety of health-related effects, among them general toxicity, carcinogenicity, reproductive and developmental toxicity, genetic toxicity, immunotoxicity, and neurotoxicity, in appropriate experimental systems. Its disseminations, including technical reports, toxicity reports, reports on genetically modified models, the Report on Carcinogens, monographs on non-cancer health hazards, and other special reports, are used widely as authoritative resources.

NTP and its federal partners support the development and validation of alternative toxicological tests that meet regulatory needs and reduce, refine, or replace the use of animals. NTP leads the interagency Tox21 effort to characterize key steps in toxicity pathways through new and innovative methods and prioritize substances for in-depth toxicological evaluation through high throughput screening techniques.

Sponsorship of more than 75 conferences, over 130 public advisory committee meetings, and more than 30 special panels reflects NTP's commitment to openness, transparency, and careful examination of scientific issues important to public health.

# NTP exists to develop the information and the tools that both agencies of government and industry need so that we can all live together safely in the same world

—DAVID P. RALL, MD, PhD  
DIRECTOR, 1978–1990

## milestones

▶ Department of Health, Education, and Welfare established NTP  
▶ David P. Rall, MD, PhD, named 1<sup>st</sup> director  
▶ NCI/NTP published 100<sup>th</sup> technical report

▶ HHS transferred NCI Carcinogenesis Testing Program to NIEHS

▶ Technical Reports series on carcinogenesis bioassay broadened to include toxicology evaluations  
▶ Cellular and genetic toxicity integrated into cancer bioassays

▶ NIEHS/NTP established an interagency agreement with CDC/NIOSH for immunotoxicity of workplace xenobiotics

▶ NIEHS/NTP established interagency agreement with FDA/NCTR for conducting comprehensive toxicological evaluations for substances of concern to FDA

▶ Scientific consensus toward mechanistic-based approaches for understanding toxicity reached  
▶ International workshop on validation and regulatory acceptance of alternative toxicological methods convened with ad hoc ICCVAM

▶ ICCVAM established to support the development, validation, acceptance, and harmonization of alternative toxicological test methods  
▶ NIEHS/NTP established interagency agreement with CDC/NIOSH to characterize and evaluate adverse effects of complex occupational exposures

▶ Regulatory acceptance of the Murine Local Lymph Node Assay and Corrositex<sup>®</sup> for dermal safety testing achieved through ICCVAM

▶ 10<sup>th</sup> RoC published  
▶ NICEATM initiated first international validation study with the European Centre for the Validation of Alternative Methods

▶ Use of toxic equivalency factor approach for cancer risk assessment of dioxin mixtures supported by NTP studies  
▶ Roadmap completed and a course planned for the 21<sup>st</sup> century to include a greater use of high and medium throughput, mechanism-based assays

▶ NIEHS/NTP funded dense single nucleotide polymorphisms mapping of 15 mouse strains to identify genetic variation as a tool for exploring genetic susceptibility to environmental diseases  
▶ Samuel H. Wilson, MD, designated as acting director  
▶ NRC report *Toxicity Testing in the 21<sup>st</sup> Century* echoed themes from NTP Roadmap (2004) in calling for new approaches to toxicity screening  
▶ Prenatal exposure as default paradigm in toxicity testing adopted

▶ New criteria for evaluation of outcomes from studies on reproduction, development, or immune system announced  
▶ NIEHS/NTP established ICATM—formal agreement to cooperate on alternative test methods with Europe, Japan, and Canada

▶ Scientific literature assessments expanded to include all non-cancer toxicities  
▶ Korea joined ICATM  
▶ Modified one generation reproduction study design adopted  
▶ 12<sup>th</sup> RoC published

▶ Nonneoplastic lesion atlas as guide for standardizing terminology in toxicologic pathology launched  
▶ Systematic review methodology adopted for literature-based scientific assessments  
▶ Research to evaluate WV Elk River spilled chemicals combining high throughput, computational, and traditional toxicology approaches initiated  
▶ 13<sup>th</sup> RoC published

- Key**
- CDC—Centers for Disease Control and Prevention
  - CERHR—Center for the Evaluation of Risks to Human Reproduction
  - EPA—Environmental Protection Agency
  - FDA—Food and Drug Administration
  - HHS—Department of Health and Human Services
  - ICATM—International Cooperation on Alternative Test Methods
  - ICCVAM—Interagency Coordinating Committee on the Validation of Alternative Methods
  - NCEH—National Center for Environmental Health
  - NCI—National Cancer Institute
  - NCTR—National Center for Toxicological Research
  - NICEATM—NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
  - NIEHS—National Institute of Environmental Health Sciences
  - NIH—National Institutes of Health
  - NIOSH—National Institute for Occupational Safety and Health
  - NRC—National Research Council
  - NTP—National Toxicology Program
  - OECD—Organisation for Economic Co-operation and Development
  - RoC—Report on Carcinogens
  - WV—West Virginia

1978 1980 1981 1982 1985 1986 1990 1991 1992 1993 1995 1996 1997 1998 1999 2000 2002 2003 2004 2005 2007 2008 2009 2010 2011 2012 2014 2015

▶ 1<sup>st</sup> RoC published; 26 listings  
▶ NCI/NTP published 200<sup>th</sup> technical report  
▶ Developmental toxicity testing initiated

▶ Immunotoxicology incorporated into testing strategy and comprehensive testing battery defined to evaluate immune system alterations  
▶ Reproductive Assessment by Continuous Breeding studies initiated

▶ Standards for quality assurance for pathology established  
▶ 5 categories to define levels of evidence of carcinogenic activity set  
▶ 1<sup>st</sup> systematic evaluation of the predictability of various genetic toxicity screens for cancer published  
▶ 300<sup>th</sup> technical report published

▶ Kenneth Olden, PhD, named director  
▶ Toxicity Report series initiated

▶ 400<sup>th</sup> technical report published

▶ HHS approved revised listing criteria for RoC allowing consideration of all relevant information  
▶ Formal process for removing a listing from the RoC established  
▶ NIEHS/NTP initiated agreement with CDC/NCEH to provide funding for expanded biomonitoring of environmental toxicants in the National Health and Nutrition Examination Survey

▶ NICEATM established to convene scientific panels to evaluate alternative toxicological methods  
▶ CERHR established to conduct scientific assessments of the reproductive and developmental toxicity literature on selected environmental agents  
▶ 8<sup>th</sup> RoC published; 1<sup>st</sup> report to apply revised criteria

▶ 9<sup>th</sup> RoC published; 1<sup>st</sup> report to apply new criteria to remove listings: saccharin and ethyl acrylate and to upgrade listings based on consideration of mechanistic data: dioxin and ethylene oxide  
▶ ICCVAM became permanent under NICEATM with passage of ICCVAM Authorization Act of 2000  
▶ Center for Phototoxicology established  
▶ Collaborations with the European Ramazzini Foundation of Oncology and Environmental Sciences formalized through NIEHS/NTP  
▶ 500<sup>th</sup> technical report published

▶ NTP-CERHR monograph series initiated  
▶ Technical Report series for genetically modified models created  
▶ Regulatory acceptance of revised Up-and-Down Procedure achieved through ICCVAM  
▶ NICEATM and ICCVAM proposed and defined performance standards concept to allow for regulatory acceptance of proprietary test methods

▶ 11<sup>th</sup> RoC published; 1<sup>st</sup> report to list biological agents  
▶ Celebrated a quarter century of toxicology for public health and unveiled a new toxicology for the 21<sup>st</sup> century  
▶ Program to identify and evaluate high throughput screening assays for toxicity testing initiated  
▶ David A. Schwartz, MD, PhD, named director

▶ Collins et al. *Perspectives* article in *Science* responded to 2007 NRC report *Toxicity Testing in the 21<sup>st</sup> Century* by laying out a comprehensive federal agency response  
▶ NIEHS/NTP established formal agreement with EPA and NIH Chemical Genomics Center for high throughput toxicity testing; Tox21  
▶ NTP-CERHR Monograph on Bisphenol A released  
▶ Linda S. Birnbaum, PhD, named director

▶ Chemical Effects in Biological Systems—new database for housing, integrating, and managing data—published  
▶ FDA joined Tox21

▶ Regulatory acceptance of Bg1 luciferase estrogen receptor transactivation test method by EPA and 1<sup>st</sup> OECD performance-based test guideline for estrogen receptor agonists (PBTG 455) achieved through ICCVAM

▶ Diversity outbred mouse as a tool for identifying inter-individual variation in toxicity response demonstrated  
▶ Collaboration with EPA enabled waivers of animal-based uterotrophic testing for EPA Endocrine Disruptor Screening Program, the first use of Tox21 approaches by a regulatory agency to replace animal testing  
▶ Funding to map gene expression during differentiation in mouse and human stem cells and to standardize zebrafish development protocols awarded