



NTP
National Toxicology Program

The National Toxicology Program Update

Board of Scientific Counselors

December 6, 2007

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Associate Director, NTP

National Institute of Environmental Health Sciences





Recent events

- Realignment of Division of Intramural Research to create the NTP at NIEHS, 28 October 2007
- NTP composed of a program office and 5 branches
 - Deputy Program Director for Policy- Dr. Mary Wolfe
 - Deputy Director for Science- Dr. Nigel Walker
 - Office of Nominations and Selection- Dr. Scott Masten
 - Office of Liaison, Policy & Review- Dr. Mary Wolfe
 - Report on Carcinogens- Dr. Bill Jameson
 - NTP Interagency Center for the Evaluation of Alternative Toxicological Methods- Dr. Bill Stokes
 - Center for the Evaluation of Risks to Human Reproduction- Dr. Mike Shelby

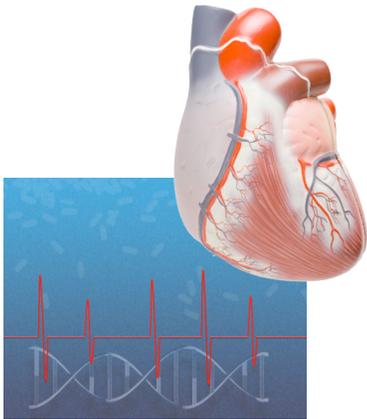


Recent events

- Realignment of Division of Intramural Research to create the NTP at NIEHS, 28 October 2007
- NTP's 5 branches
 - Toxicology Branch- Acting Chief, Dr. Paul Foster
 - Cellular and Molecular Pathology Branch- Chief, Dr. Robert Sills
 - Program Operations Branch- Acting Chief, Dr. Cynthia Smith
 - Host Susceptibility Branch- Acting Chief, Dr. Jef French
 - Bio-molecular Screening Branch- Acting Chief, Dr. Ray Tice



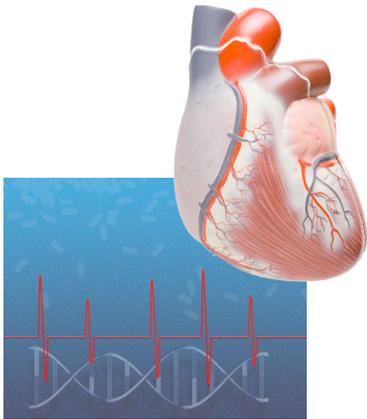
Toxicology Branch



- (1) Designs, reviews, and reports general toxicity and carcinogenicity studies and studies of specialized areas of toxicology such as immunotoxicity, reproductive and developmental toxicity, and genotoxicity for substances studied by the NTP
- (2) Integrates information derived from toxicokinetic and toxicogenomic studies and physiologically-based pharmacokinetic models in interpretation and reporting of these studies



Toxicology Branch- Activities



- (1) Dr. Ron Melnick receives the David P. Rall Award for Advocacy in Public Health from the American Public Health Association, November 2007
- (2) Dr. Frank Johnson, co-author- Frazer *et al.* A sequence-based variation map of 8.27 million SNPs in inbred mouse strains (2007) *Nature* 448:1050-1053
- (3) Interagency Agreements reassigned:
 - (1)NCTR- Dr. Nigel Walker
 - (2)NIOSH- Dr. Dori Germolec
- (4) Radiofrequency radiation studies begin



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Program Operations Branch

- (1) Provides oversight for NTP support functions including chemistry, ADME studies, quality assurance, maintenance and development of data capture and retrieval systems, central data repository and the NTP website
- (2) Provides expertise in development and administration of contracts for procurement of goods or services in support of NTP and NIEHS scientific activities





Cellular and Molecular Pathology Branch

- (1) Manages, evaluates, reviews and reports all pathology data generated through conduct of NTP toxicity and carcinogenicity studies
- (2) Establishes standards, terminology and diagnostic criteria for rodent pathology
- (3) Provides laboratory animal medicine support for the NTP and NIEHS
- (4) Maintains the NTP Archives; manages pathology, toxicology, and other contracts to support NTP and intramural investigators
- (5) Utilizes staff veterinary scientists to provide collaborative pathology diagnostic support for Intramural investigators and mentoring/training in toxicologic pathology and laboratory animal medicine





Cellular and Molecular Pathology Branch- Activities

- (1) Emphasis on developing enhanced expertise in interpreting and understanding mechanisms in toxicologic pathology
- (2) Immunopathology workshop scheduled for December 10, 2007
- (3) Reproductive and developmental pathology workshop planned for 2008
- (4) Atlas on background non-neoplastic lesions in rodents planned
- (5) Elmore *et al.* (2006) The transduction of rat submandibular glands by an adenoviral vector carrying the human growth hormone gene is associated with limited and reversible changes at the infusion site. *Toxicol. Pathol.* 34:385-392. Best paper in 2006 award.

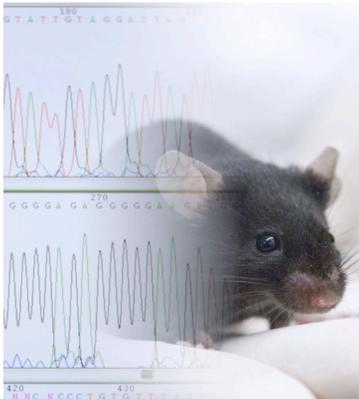




Host Susceptibility Branch- Activities

- (1) Request for Information: Genetic Variation and the Basis for Individual Susceptibility to Environmental Toxicant Associated Disease- 29 responses, most from NIH grantees- strong support
- (2) Met with Program Staff responsible for the NCI and NIH RAID Programs (Rapid Access to Intervention Development)
- (3) Establish BSC Workgroup
- (4) Communicate program plans and goals

- SOT workshop on toxicogenetics, Charlotte, March 2007
- Complex Traits Consortium, Braunschweigen, Germany, May 2007
- Toxicology Forum, Aspen, July 2007
- Complex Traits Analysis, Bar Harbor, October 2007
- SOT workshop on host susceptibility, Seattle, March 2008

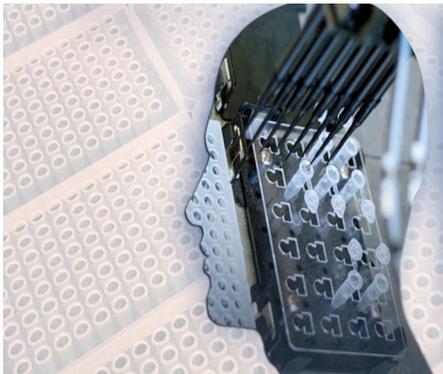




Bio-molecular Screening Branch

- (1) Develops NTP research and testing activities in high* and medium-throughput screening assays for rapid detection of biological activities of significance to toxicology and carcinogenesis
- (2) Carries out the NTP automated screening assays with *C. elegans*
- (3) Develops analysis tools and approaches to allow an integrated assessment of HTS endpoints and associations with findings from traditional toxicology and cancer models

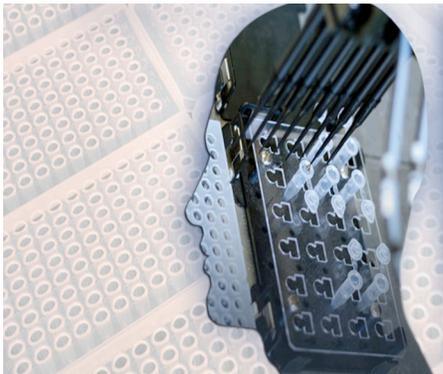
*Collaborations with EPA ToxCast program and NIH Chemical Genomics Center, Molecular Libraries Initiative





Bio-molecular Screening Branch- Activities

- (1) First chemical set screened in 41 of 61 assays currently running at NCGC
- (2) Second set of 1408 chemicals is being selected
- (3) Assay selection continues
 - Discussions with commercial suppliers- Invitrogen, DiscoverRx
 - Targets on Toxicity Pathways* are being identified
- (4) IAG with NCGC established and funded
- (5) MOU with EPA and NCGC is nearing completion
- (6) Establish BSC Workgroup



**Toxicity Testing in the 21st Century: A Vision and a Strategy, National Research Council, National Academies Press, August, 2007*





NICEATM
National Toxicology Program Interagency Center
for the Evaluation of Alternative Methods



ICCVAM
Interagency Coordinating Committee
on the Validation of Alternative Methods

Ten-Year Anniversary Symposium

**Celebrating the Advancement
of Public Health and Animal Welfare
With Sound Science:
Envisioning New Directions in Toxicology**

*Distinguished speakers addressing ICCVAM's role in
advancing toxicology testing in the 21st Century
and
the NICEATM-ICCVAM Five-Year Plan*

Tuesday, February 5, 2008 1:00 - 5:00 P.M.
U.S. Consumer Product Safety Commission Headquarters
Bethesda Towers Bldg., 4330 East West Highway
Bethesda, MD

*The Symposium is open to the public at no cost. For more information and
to register, please contact NICEATM:
<http://iccvam.niehs.nih.gov>
919-541-2384
niceatm@niehs.nih.gov*

ICCVAM Agencies: Consumer Product Safety Commission, Department of Agriculture, Department of Defense, Department of Energy, Food and Drug Administration, National Cancer Institute, Department of Transportation, National Institute for Occupational Safety and Health, National Institute of Environmental Health Sciences, NIH Office of the Director, National Library of Medicine, Department of the Interior, Occupational Safety and Health Administration, Environmental Protection Agency





Interagency Coordinating Committee on the Validation of Alternative Methods

February 5, 2008

Consumer Product Safety Commission

Bethesda, Maryland

- The NICEATM-ICCVAM Five-Year Plan
- Dr. Bern Schwetz: The Evolution and Future of Toxicology Testing
- Dr. Dan Krewski: Toxicology Testing in the 21st Century
- Future Directions in Test Method Development: NIEHS/NTP, FDA, EPA
- Panel: The Way Forward for ICCVAM and its Stakeholders



Workshop on Acute Chemical Safety Testing: Advancing *In Vitro* Approaches and Humane Endpoints for Systemic Toxicity Evaluations

NICEATM - National Toxicology Program
Interagency Center for the Evaluation of
Alternative Toxicological Methods

ICCVAM - Interagency Coordinating
Committee on the Validation of Alternative
Methods

ECVAM - European Centre for the Validation of
Alternative Methods

JaCVAM - Japanese Center for the
Validation of Alternative Methods



This workshop will identify new approaches to understanding key pathways involved in acute systemic toxicity in order to develop new in vitro methods and earlier humane endpoints that will further reduce, refine, and eventually replace animal use for chemical safety testing.

February 6-7, 2008 | NIH - Natcher Conference Center | Bethesda, MD

For more information, please contact NICEATM:
Phone: 919-541-2384
Email: niceatm@niehs.nih.gov



ICCVAM Agencies: Consumer Product Safety Commission, Department of Agriculture, Department of Defense, Department of Energy, Food and Drug Administration, National Cancer Institute, Department of Transportation, National Institute for Occupational Safety and Health, National Institute of Environmental Health Sciences, NIH Office of the Director, National Library of Medicine, Department of the Interior, Occupational Safety and Health Administration, Environmental Protection Agency



- **February 6-7, 2008**

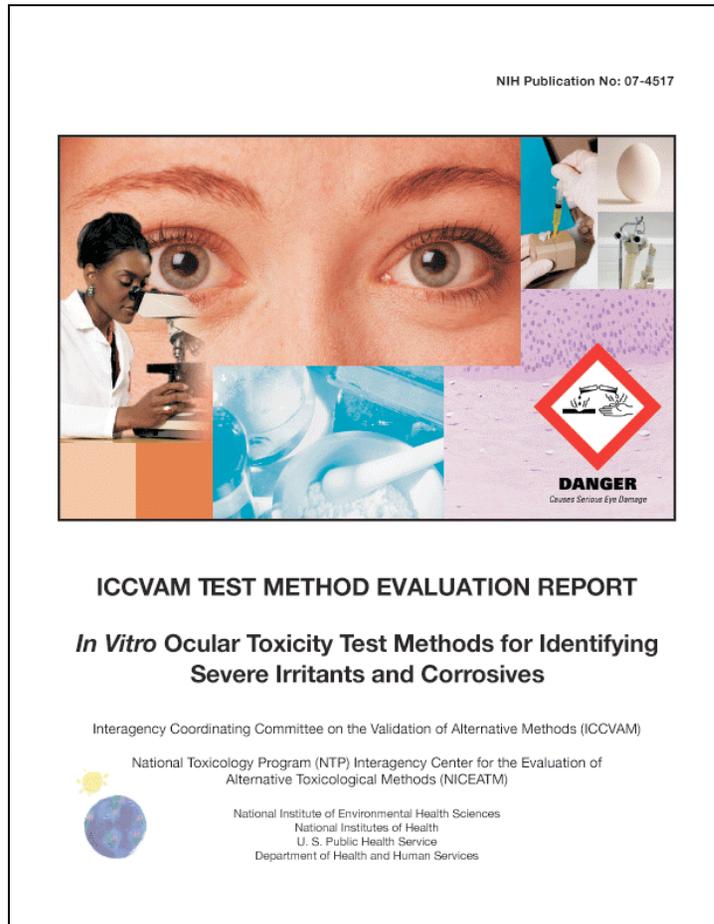
- NIH, Bethesda, Maryland
- Co-organized with ECVAM and JaCVAM

- **Workshop Goal**

- *Review current knowledge and identify approaches to better understand key pathways in acute systemic toxicity in order to advance the development of predictive mechanism-based in vitro test systems and earlier humane endpoints*

- **Workshop Sessions**

- Assessing Acute Systemic Toxicity
- Key Pathways and Biomarkers in Acute Systemic Toxicity
- Identifying Earlier Humane Endpoints
- Using *In Vitro* Methods to Predict Acute Systemic Toxicity: current status and future directions



- **Test Method Evaluation Report forwarded to Agencies: October 2007**
- **ICCVAM Recommendations:**
 - *Always consider before using rabbits for ocular testing; use when determined appropriate*
 - Testing protocols
 - Reference chemicals for further validation
 - Future efforts to improve accuracy
- **Impact: Ocular testing is one of the 4 most commonly performed product safety tests; Now available:**
 - ***Partial replacement alternative:*** no animals required for positive results
 - ***Refinement alternative:*** Positive result avoids testing that is likely to cause significant pain and distress



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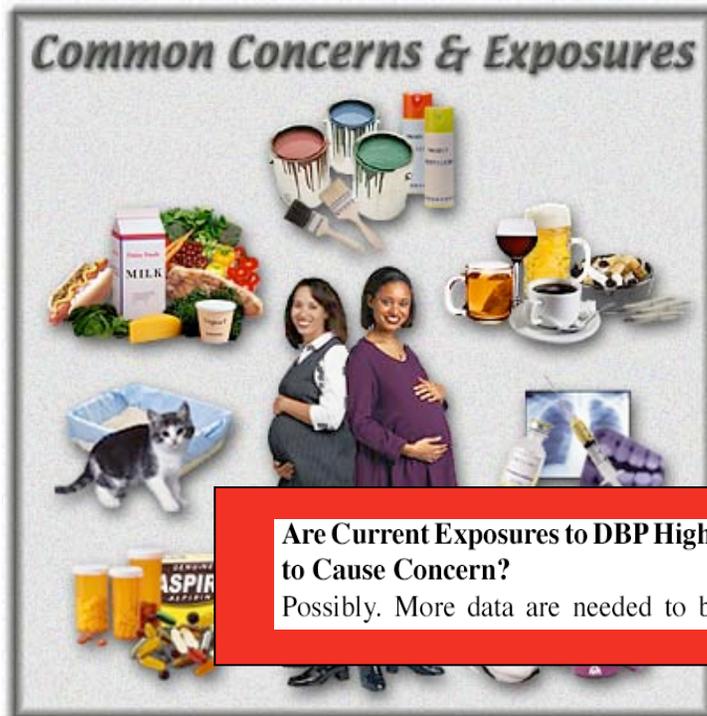
Center for the Evaluation of Risks to Human Reproduction

Provides expert assessments of adverse effects on reproduction and development caused by agents in the environment



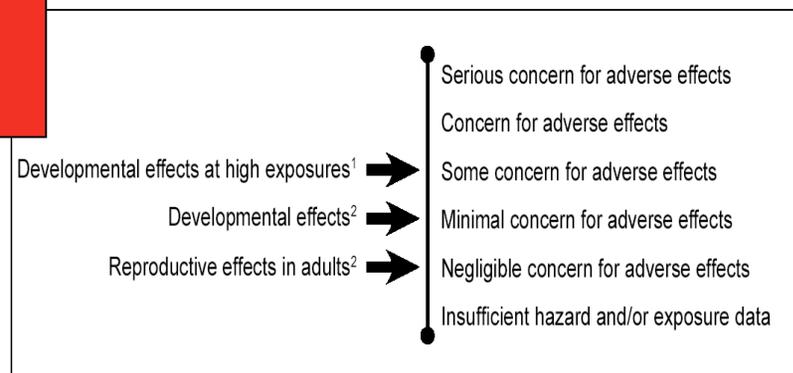


NTP-CERHR Monographs



- Monographs on ~20 Chemicals
- Recent: Prozac, Acrylamide, Ritalin, Soy formula
- Upcoming: Genistein, Bisphenol A

Figure 3. NTP conclusions regarding the possibilities that human development or reproduction might be adversely affected by exposure to DBP





NTP CERHR Bisphenol A Expert Panel Review

Expert panel report drafts

- December 2006 draft with expert panel input released for public comment
- March 2007 draft updated literature and included panel additions in response to public comments
- Allegations of potential conflict of interest with support contract

- 1st expert panel meeting on Bisphenol A- March 5-7, 2007
 - April 20, 2007 Interim draft expert panel report released for public comment
- 2nd expert panel meeting- Aug 6-8, 2007
 - November 26, 2007 Final expert panel report released for public comment
- NTP BPA Brief peer review, BSC meeting May 6-7, 2008



Steps to address issues related to conflict of interest

- Review all NTP contracts for potential for conflict of interest
- Develop COI language to incorporate in all NTP contracts
- Conduct an audit of draft Bisphenol A expert panel reports
 - Audit the literature search/selection
 - Audit the fidelity of changes to the December and March versions of the expert panel report



Overall Audit Conclusions

- The audit provided assurance that the draft Bisphenol A expert panel reports included consideration of all relevant references and reliably included changes requested by the expert panel members.
- NTP concluded that the draft expert panel reports were useful for the continued CERHR evaluation of Bisphenol A



Next steps

- Public comments on the final expert panel report, due date January 25, 2008
- NTP Brief and NTP-CERHR Monograph will be prepared by CERHR staff, reviewed by Core Committee, and released for public comment
- Peer review of draft NTP Brief will be carried out at a meeting of the NTP Board of Scientific Counselors, supplemented with *ad hoc* experts
- NTP-CERHR Monograph will be finalized and released



Program expectations

- Continue to provide basic toxicology information for public health protection
- Increase emphasis on understanding and explaining exposure-response relationships and genetic determinants of response
- Integrate results from new “data rich” techniques; genomics, proteomics, HTS screens with existing testing information
- Develop new methodologies for toxicological assessments
- Provide guidance for the proper utilization of new types of information in hazard identification, characterization and regulation

- Be the leading toxicology program in the world



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Audit

- Period covered
 - February 2006 to March 2007
- Materials covered
 - Literature summarized by contractor in initial August 2006 draft and literature provided to expert panel for review- August 2006 to March 2007
 - E-mail records of changes requested by expert panel to August 2006 and December 2006 drafts
- Contributors
 - Literature review- NIEHS staff
 - Changes to draft expert panel reports- Dynamac Inc.



Literature audit

- Findings
 - Approximately 50 papers identified that were presumably available in February 2006 that were not in the bibliography of the August 2006 draft
 - Nine of these papers were added to the December 2006 or March 2007 drafts
 - Approximately 50 papers were identified that were not included in the 742 references under consideration by the expert panel for the December 2006 and March 2007 drafts.
 - Review of these citations resulted in 5 additional papers sent to panel for consideration

- Conclusion
 - Appropriate reference materials were made available to the expert panel for their consideration during development of the December 2006 and March 2007 draft expert panel reports.



Audit of requested changes

- Strategy
 - Dynamac staff audited e-mail records of requests to the contractor for changes to the December 2006 and March 2007 draft expert panel reports.
- Findings
 - Six changes requested in over 300 e-mails containing from 1 to more than 50 separate requests were not included in the specified drafts.
 - These changes were made to subsequent drafts.
 - Additional changes were identified that were not specified in e-mail requests from the expert panel.
 - These changes were attributed to the addition of new literature, and changes as a result of the contractor's editing and fact checking processes.
- Conclusions
 - The contractor reliably made changes to the draft reports requested by expert panel members.