UPDATE National Toxicology Program
Headquartered at the National Institute of Environmental Health Sciences NIH-DHHS
October 2004

A National Toxicology Program for the 21st Century

The last two decades have produced dramatic technological advances in molecular biology and computer science. During this period, scientists have increasingly identified critical cellular and molecular events (mechanisms) that lead to adverse responses to toxicants. The NTP recognizes that over the next decade the expanding knowledge of the physiological, biochemical, and molecular basis of disease will lead to improvements in our ability to predict the toxicological impact of environmental agents. As a focal point within the federal government for providing information about potentially hazardous agents, the NTP seeks to take advantage of these advances and identify and incorporate more mechanistic approaches into its toxicology assessments. The NTP Vision for the 21st Century is to support the evolution of toxicology from a predominantly observational science at the level of disease-specific models to a predominantly predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations. The intent of the NTP vision is to expand the scientific basis for making public health decisions on the potential toxicity of environmental agents.

In August 2004, the NTP began a yearlong process to evaluate its key activities and determine how best to incorporate new scientific technologies into its research and testing strategies and broaden scientific knowledge on the linkage between mechanism and disease. The goal of this activity was to develop a "roadmap" or framework for implementation of the NTP vision that would strategically position the program at the forefront for providing scientific data and guiding the interpretation of those data to maximize their impact on public health. The URL for the NTP Roadmap web site is http://ntp-server.niehs.nih.gov/main_pages/NTPVisionPg.html

Steps in the Process

In inviting input on the NTP vision, the program asked four general questions:

(1) What scientific information should the NTP be producing and what technical capabilities should the NTP have by 2008? By 2013?
(2) How do you envision that the refinement/replacement of classical toxicological studies with mechanism-based assays will impact the evaluation of public health hazards?
(3) How can the NTP best structure itself to provide this information and ensure its optimal utilization in the protection of public health?
(4) What resources will be needed to realize the vision and how long will it take?

The process for crafting the NTP roadmap included several steps: (1) forming three working groups-the NIEHS working group, the NTP Executive Committee working group, and the NTP Board of Scientific Counselors working group--to independently examine the vision and offer input on elements for the roadmap, (2) holding a public meeting at Lister Hill Auditorium, National Library of Medicine, National Institutes of Health in Bethesda, Maryland on January 29, 2004, to receive input from the public and other interested groups, (3) providing opportunity for discussion at the Scientific Advisory Committee on Alternative Toxicological Methods public meeting on March 10-11, 2004 and the NTP Board of Scientific Counselors public meeting on June 29, 2004, and (4) holding a retreat on August 10-12, 2004, where attendees reviewed, edited and provided input on the draft NTP roadmap. In addition, the NTP discussed the vision and roadmap with its federal agency partners on several other occasions.

NTP Web Site Has New Look

Over the past few months, the NTP has been working to give its web site a new look. In early October 2004, the NTP launched its revised web site. The information on the site is the same, but with a new format. The NTP redesigned the site to make information more accessible. The URL for the web site also changed to http://ntp.niehs.nih.gov although the old URL will still work. The NTP invites comments on the revised web site – the ease of navigating and finding information. Comments can be sent to Dr. Skip Eastin (eastin@niehs.nih.gov).

Scientific Advisory Committee on Alternative Toxicological Methods (SACATM)

The next meeting of the SACATM will be held on October 20, 2004, at the U.S. Environmental Protection Agency (EPA), 109 TW Alexander Drive, Research Triangle Park, NC (Building C, Room C111, Auditorium sections A and B). The meeting begins at 8:30 a.m. until adjournment and is open to the public with attendance limited only by available space. A map of the EPA campus, including visitor parking, is available at http://www.epa.gov/rtp/transportation/parking/map.htm. **Please note that a photo ID is required to access the EPA campus**. Individuals who plan to attend are asked to register with Dr. Kristina Thayer (contact information below).

Agenda and details of the meeting were announced in the *Federal Register* on September 8, 2004 [(69FR54298) and posted on the NTP web site (http//:ntp@niehs.nih.gov *select* "What's New?").

The 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 1-31d). The SACATM provides advice to the fifteen Federal agencies represented on the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), the Director of the NIEHS, and the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) regarding statutorily mandated duties of the ICCVAM and activities of the NICEATM. The Advisory Committee for Alternative Toxicological Methods (ACATM) previously provided advice. This advice addresses priorities and directives related to the development, validation, scientific review and regulatory acceptance of new or revised toxicological test methods, especially those that reduce, refine or replace the use of animals in testing. The SACATM also provides input on ways to foster partnerships and communication with interested parties. The NIEHS Director appoints voting members to the SACATM and membership is defined in the ICCVAM Authorization Act of 2000 to include representatives from academia, state government, industry, and animal protection organizations. The SACATM typically meets twice a year.

Contact Information: Dr. Kristina Thayer, Executive Secretary, NTP Liaison and Scientific Review Office, NIH/NIEHS, P.O. Box 12233, MD A3-07, Research Triangle Park, North Carolina 27709; T: (919) 541-5021; FAX: (919) 541-0295; thayer@niehs.nih.gov

NTP Board of Scientific Counselors

The next meeting of the Board of Scientific Counselors (Board) will be held on October 26, 2004, at the National Institute of Environmental Health Sciences in the Rodbell Auditorium, Rall Building. The meeting begins at 8:30 a.m. until adjournment and is open to the public with attendance limited only by space available. **Please note that a photo ID is required to access the NIEHS campus**. Individuals who plan to attend are asked to register with Dr. Barbara Shane (contact information below).

Primary agenda topics include: (1) NTP initiatives to enhance toxicology, (2) substances nominated to the NTP for study and recommendations of the NTP Interagency Committee for Chemical Evaluation and Coordination (ICCEC), (3) new approaches for statistical analyses for chronic tests, (4) a proposed process for evaluating chemicals with limited data sets by the Center for the Evaluation of Risks to Human Reproduction, and (5) a research program on *Caenorhabditis elegans*. The NTP Board will also review three concept proposals for the conduct of research through the use of a contract mechanism. These concepts include: (1) the evaluation of chemicals for their potential to modulate immune responses, (2) chemical characterization of substances for testing in high-throughput screening and chronic assays, and (3) application of automated techniques to toxicity testing. Time is allotted during the meeting for the public to present comments to the NTP Board and NTP staff on any agenda topic.

The agenda and background materials on agenda topics, as available, will be posted on the NTP web site (http://ntp.niehs.nih.gov, *see* What's New) or available upon request to the NTP Executive Secretary. The NTP is making plans to videocast the meeting through the Internet at http://www.niehs.nih.gov/external/video.htm.

The NTP Board is a technical advisory body comprised of scientists from the public and private sectors who provide primary scientific oversight to the overall program and its centers.

Contact Information: Dr. Barbara Shane, Executive Secretary, NTP Liaison and Scientific Review Office, NIH/NIEHS, P.O. Box 12233, MD A3-07, Research Triangle Park, North Carolina 27709; T: (919) 541-4253; FAX: (919) 541-0295; shane@niehs.nih.gov

NTP Testing Program

NTP Solicits Input on New Testing Nominations

The NTP continuously solicits and accepts nominations for toxicological studies to be undertaken by the program. The nominations are subject to several levels of review before final selections for testing are made and toxicological studies are designed and implemented. As part of this review process, the NTP Interagency Committee for Chemical Evaluation and Coordination (ICCEC) met on June 24, 2004, to review 10 new nominations and make study recommendations. The NTP requests public comment on the nominations and study recommendations and asks for the submission of additional relevant information for these substances. A *Federal Register* notice published on August 20, 2004 (69FR51691) formally solicited public comment (available on the NTP web site at http://ntp.niehs.nih.gov). The NTP web site also provides Internet links to electronic versions of supporting documents for each nomination and further information on the NTP and the NTP Chemical Nomination and Selection Process. Persons submitting comments and information are asked to include their name, affiliation, mailing address, phone, fax, e-mail address and sponsoring organization (if any) with the submission. Written submissions should be sent to Dr. Scott Masten (contact information below) and will be posted electronically on the NTP web site as they are received.

Nominations for new toxicology studies are welcome at any time and should be addressed to Dr. Scott Masten. Further information on how to submit testing nominations is available at http://ntp.niehs.nih.gov/NomPage/noms.html

Contact Information: Dr. Scott A. Masten, Office of Chemical Nomination and Selection, NIH/NIEHS, P.O. Box 12233, MD A3-07, Research Triangle Park, North Carolina 27709; T: (919) 541-5710; FAX: (919) 541-3647; masten@niehs.nih.gov

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Substances recommended for testing by the ICCEC

- Bitter orange extract [No CAS No.]: recommended studies – developmental toxicity, physiological responses (e.g., cardiovascular and cerebrovascular) via telemetry, subchronic toxicity, toxicokinetics (of constituents); studies should be conducted with bitter orange extract alone and in combination with caffeine in rats and possibly miniature pigs.
- n-Butyl glycidyl ether [2426-08-6]: recommended studies – toxicological characterization including reproductive toxicity, carcinogenicity, and analysis of urinary metabolites.
- Di-(2-ethylhexyl)phthalate [117-81-7]: recommended studies – tiered research program encompassing: (1) quantitative studies of toxicokinetics and biotransformation following intravenous exposure in neonatal male nonhuman primates and (2) of toxicokinetics, reproductive and immune endpoints following acute and subchronic intravenous exposure to neonatal male rats and nonhuman primates.
- Ionic liquids (1-Butyl-3-methylimidazolium chloride [79917-90-1]; 1-Butyl-1-methylpyrrolidinium chloride [479500-35-1]; *N*-Butylpyridinium chloride [1124-64-7]): recommended studies – toxicological characterization.
- Perfluorinated compounds class study [Multiple CAS Nos.]: recommended studies – tiered research program to include pharmacokinetics, mechanistic, reproductive toxicity, and carcinogenicity studies (for specific compounds, see supporting document available at http://ntp.niehs.nih.gov/NomPage/2004Noms.html).
- *Stachybotrys chartarum* [67892-26-6]: recommended studies – toxicological characterization including immunotoxicity.
- Tungsten trioxide [1314-35-8] and fibrous tungsten suboxides: recommended studies – toxicological characterization, genotoxicity, characterization of fiber stability and biopersistence, *in vitro* toxicity to lung cells, comparative intratracheal toxicity studies with a known hazardous fiber; further studies including carcinogenicity will be considered following completion of initial studies.

Substances for Which Studies were Deferred Pending Review of Additional Information:

- Butylparaben [94-26-8]: recommendation – review data on estrogen receptor binding, pharmacokinetics, dose-response of male reproductive effects, and human exposure.
- Decane [124-18-5]: recommendation – review industry's voluntary activities for development of additional data
- Undecane [1120-21-4]: recommendation – review industry's voluntary activities for development of additional data

Upcoming Events*

October 20, 2004	Scientific Advisory Committee on Alternative Toxicological Methods Meeting, EPA, Building C-111, Research Triangle Park, NC 27709
October 26, 2004	NTP Board of Scientific Counselors Meeting, Rodbell Auditorium, Rall Building, NIEHS, 111 T.W. Alexander Dr., Research Triangle Park, NC 27709
December 9-10, 2004	NTP Board of Scientific Counselors Technical Reports Review Subcommittee Meeting, Rodbell Auditorium, Rall Building, NIEHS, 111 T.W. Alexander Dr., Research Triangle Park, NC 27709
January 10-12, 2005	CERHR Expert Panel meeting on Amphetamines and Methylphenidate, Holiday Inn Select, Old Town Alexandria, Alexandria, VA

Report on Carcinogens

Report on Carcinogens, 11th Edition

The scientific review of nominations to the 11th RoC is complete and publication is anticipated in 2004. The recommendations from the three scientific peer review committees for listing the new nominations in the 11th RoC, all public comments on these nominations, the background documents in PDF format, and the criteria and process used for review of these nominations can be accessed through the NTP home page (http://ntp.niehs.nih.gov *select* "Report on Carcinogens") or by contacting Dr. Jameson.

Contact Information: Dr. C.W. Jameson, Report on Carcinogens, NIH/NIEHS, 79 TW Alexander Drive, Room 3118, P.O. Box 12233, MD EC-14, Research Triangle Park, NC 27709; T: 919-541-4096, FAX: 919-541-0144, jameson@niehs.nih.gov

NTP Interagency Center for the Evaluation of Alternative Toxicology Methods (NICEATM)

Meeting to Evaluate *In Vitro* Test Methods for Ocular Irritants

NICEATM in collaboration with the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) is convening an independent scientific expert panel to evaluate the validation status of *in vitro* test methods for determining the potential ocular irritancy of chemicals and other substances. The meeting will be held on the National Institutes of Health campus in Bethesda, Maryland at the Natcher Conference Center on January 11-12, 2005. The official announcement of this meeting, details for registering to attend, and availability of the Background Review Documents will be provided in an upcoming *Federal Register* notice in early November 2004.

This expert panel will evaluate the usefulness of *in vitro* test methods for predicting severe and/or irreversible ocular irritation/corrosion effects. Future panels will evaluate test methods for their usefulness in evaluating reversible ocular irritation effects. Methods proposed for assessing both types of effects will be evaluated at this meeting for their usefulness in predicting irreversible effects. Test methods that will be evaluated in this initial review include:

- Bovine Corneal Opacity and Permeability (BCOP) test
- Isolated Rabbit Eye (IRE) test or the Rabbit Enucleated Eye Test (REET)
- Isolated Chicken Eye (ICE) test or the Chicken Enucleated Eye Test (CEET)
- Hen's Egg Test – Chorion Allantoic Membrane (HET-CAM)

The expert panel will develop conclusions and recommendations on the validation status and demonstrated usefulness and limitations of the methods. ICCVAM will use the expert panel report and public comments to develop ICCVAM recommendations for the four test methods. Additional information about ICCVAM and NICEATM and the current review of ocular toxicity test methods is available at the following web site: *http://iccvam.niehs.nih.gov*.

Availability of Standardized Test Method Protocols for Estimating Starting Doses for *In Vivo* Acute Oral Toxicity Tests

NICEATM announces the availability of standardized test method protocols for two *in vitro* cytotoxicity test methods to estimate starting doses for *in vivo* acute oral systemic toxicity tests. These test methods were previously recommended by the ICCVAM as an approach to reduce the number of animals required for acute oral toxicity testing. Updated standardized protocols for two neutral red uptake assays using either BALB/c 3T3 cells or normal human keratinocytes are now available on the NICEATM/ICCVAM web site at *http://iccvam.niehs.nih.gov/methods/invitro.htm*. These test method protocols have been improved to maximize intra- and inter-laboratory reproducibility and are currently being used for the final phase of a joint NICEATM-European Center for the Validation of Alternative Methods (ECVAM) validation study. NICEATM recommends that these updated test method protocols be used in place of standard operating procedures previously recommended by ICCVAM (ICCVAM. 2001. Report of the International Workshop on *In Vitro* Methods for Assessing Acute Systemic Toxicity. NIH Publication No. 01-4499, NIEHS, Research Triangle Park, NC http://iccvam.niehs.nih.gov/docs/docs.htm#invitro)

Request for *In Vivo* and *In Vitro* Acute Toxicity Data

NICEATM is requesting data on chemicals and products tested for acute, oral, systemic toxicity in animals to estimate LD50 and tested *in vitro* using standardized cytotoxicity testing methods. The *in vitro* cytotoxicity data of interest are from methods demonstrated to be useful for estimating starting doses for acute oral toxicity tests as described in the "Guidance Document on Using *In Vitro* Data to Estimate *In Vivo* Starting Doses for Acute Toxicity" (ICCVAM, 2001, NIH Publication 01-4500, available at http://iccvam.niehs.nih.gov/). These data will be used to further evaluate the usefulness and limitations of cytotoxicity data for estimating *in vivo* acute oral toxicity. The data will also be used to establish a database to support the investigation of other test methods necessary to improve the accuracy of *in vitro* assessments of acute systemic toxicity. Toxicity data should be sent by mail, fax or e-mail to NICEATM [Dr. William S. Stokes, Director (see contact information below)].

While data will be accepted at any time, data submitted during the next 8 months will be used in conjunction with the results of a validation study to assess the usefulness of the *in vitro* methods. Chemical and protocol information/test data submitted in response to this request may be incorporated in future NICEATM and ICCVAM reports and publications as appropriate.

NICEATM prefers data to be submitted as copies of pages from study notebooks and/or study reports, if available. Each submission for a chemical should include the following information, as appropriate:

- Common and trade name
- Chemical Abstracts Service Registry Number
- Chemical and/or product class
- Commercial source
- *In vitro* basal cytotoxicity test protocol used
- *In vitro* cytotoxicity test results
- *In vivo* acute oral toxicity test protocol used
- Individual animal responses at each observation time and dose (if available)
- The extent to which the study complied with national or international Good Laboratory Practice guidelines
- Date and testing organization

Those persons submitting data on chemicals tested for *in vitro* basal cytotoxicity are referred to the standard test-reporting template recommended for the High Production Volume (HPV) program at http://www.epa.gov/chemrtk/toxprtow.htm (PDF) or http://iccvam.niehs.nih.gov/methods/invitro.htm). *In vivo* data for the same chemicals should be reported as recommended in the test reporting section of the current Environmental Protection Agency's guideline for acute oral toxicity [Health Effects Test Guidelines, (2002) OPPTS 870.1100, Acute Oral Toxicity, EPA 712-C-02-19] available at *http://www.epa.gov/opptsfrs/OPPTS_Harmonized/870_Health_Effects_Test_Guidelines/Series/870-1100.pdf*

Questions about NICEATM and ICCVAM activities can be directed to Dr. William S. Stokes (see contact information below.)

Contact information: Dr. William S. Stokes, Director, NICEATM, NIEHS/NIH, 79 TW Alexander Drive, Room 3129, P.O. Box 12233, MD EC-17, Research Triangle Park, NC 27709; T: 919-541-2384; F: 919-541-0947; e-mail: iccvam@niehs.nih.gov

Center for the Evaluation of Risks to Human Reproduction (CERHR)

Expert Panel to Review Amphetamines and Methylphenidate

CERHR will hold an expert panel meeting on January 10-12, 2005, at the Holiday Inn Select, Old Town Alexandra, Alexandria, VA. At this meeting, the expert panel will review and revise the draft expert panel report and reach conclusions regarding whether exposure to amphetamines and/or methylphenidate is a hazard to human development or reproduction. The expert panel will also identify data gaps and research needs. This meeting is open to the public. The NTP invites the submission of written comments and/or the presentation of oral comments at the meeting. Additional information will be published in the Federal Register, posted on the NTP web site (http://ntp.niehs.nih.gov), or from the CERHR (contact information below), as available.

Amphetamines and methamphetamine are central nervous system stimulants. Amphetamine is indicated for the treatment of narcolepsy and attention deficit hyperactivity disorder (ADHD), and methamphetamine is indicated for the treatment of ADHD and for short-term treatment of obesity. Methylphenidate (CAS Registry Number 298-59-9) is a central nervous system stimulant approved by the Food and Drug Administration for the treatment of ADHD and narcolepsy in persons six years and older. The CERHR selected amphetamines and methylphenidate for expert panel evaluation because of widespread usage in children, availability of developmental studies in children and experimental animals, and public concern about the effects of these stimulants on child development.

Sections 1-4 of the draft expert panel report will be available on November 15, 2004 in PDF format from the CERHR web site (http://cerhr.niehs.nih.gov) or from the CERHR in hardcopy or as a PDF on a compact disk.

Contact information: Dr. Michael Shelby, Director CERHR NIEHS/NIH, 79 T.W. Alexander Drive, Building 4401, Room 103, P.O. Box 12233, MD EC-32, Research Triangle Park, NC 27709, T: 919-541-3455; F: 919-316-4511; shelby@niehs.nih.gov

How to Subscribe to the NTP List-serv

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Contact information: NTP Liaison and Scientific Review Office, NIEHS, P.O. Box 12233, MD A3-01, Research Triangle Park, NC 27709; T: (919) 541-0530; F: (919) 541-0295; liaison@starbase.niehs.nih.gov

The ehpOnline maintains issues of the Report on Carcinogens, the library of NTP Technical Reports and the NTP Toxicity Reports and adds new reports as available. The electronic PDF files of completed reports are available free-of-charge and printed reports can be purchased through ehpOnline. To gain access to these reports, go to http://ehp.niehs.nih.gov or call (866) 541-3841.