UPDATE National Toxicology Program
Headquartered at the National Institute of Environmental Health Sciences NIH-DHHS
July 2005

Rodent Cancer Bioassay: Strains & Stocks - Should We Switch?

On June 16-17, 2005, the NTP held a workshop titled *Animal Models for the NTP Rodent Cancer Bioassay: Strains & Stocks - Should We Switch?* The goal of this workshop was to seek scientific input as to whether the NTP should continue to use both the F344 rat and B6C3F1 mouse models in the cancer bioassay, use other strains, and/or use multiple strains.

In brief, the workshop participants recommended that the NTP switch to another rat strain or F344 stock because problems with the current NTP strain F344/N are significant; however, they did not feel at this time that the NTP needs to change from using the mouse model B6C3F1/N in the cancer bioassay. Two of three breakout groups suggested that NTP consider utilizing a multiple strain approach for cancer hazard evaluation. The breakout group reports and additional information on the workshop, including participants, presentations, public comments and background materials, are posted on the NTP website (http://ntp.niehs.nih.gov select *Meetings and Workshops*).

This workshop was conducted as part of an effort to implement the NTP Roadmap (http://ntp.niehs.nih.gov select *NTP Vision & Roadmap*). Future workshops related to the NTP Roadmap will address other study design issues such as diet, length of study, and age at exposure. The overall purpose of the workshop series is to improve the ability of NTP bioassays to identify substances that may pose a carcinogenic or other health hazard for humans.

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NTP Board of Scientific Counselors Meeting Rescheduled

The meeting of the NTP Board of Scientific Counselors ("the NTP Board") initially scheduled for June 23, 2005, at the NIEHS has been rescheduled for August 18, 2005. The meeting will be held in the Rodbell Auditorium in the Rall Building, is open to the public, and begins at 8:30 AM. The NIEHS is located at 111 TW Alexander Drive, Research Triangle Park, NC.

Tentative agenda topics include NTP initiatives to carry out the NTP Roadmap (see *NTP Update*, January 2005) and actions from the NTP Board's Technical Reports Review Subcommittee at its December meeting. The NTP Board will also hear about and provide comment on the Interagency Committee for Chemical Evaluation and Coordination's recommendations for agents nominated to the NTP for study. The NTP will present information about implementation of the Office of Management and Budget's guidelines for peer review to NTP reports. Additional items may be added as the agenda is finalized.

The NTP initially announced and provided details about the meeting in the Federal Register (Vol.70, No.93, pp. 25830-25831). Both written and oral comments are welcome on any agenda topic. Individuals who submitted comments in response to the Federal Register announcement do not need to resubmit them; because the meeting is rescheduled, the deadline for submission of written comments is extended to August 8, 2005.

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Perspectives

NIEHS DIRECTOR'S PERSPECTIVE

The NIEHS and the National Toxicology Program: An Integrated Scientific Vision

The National Toxicology Program (NTP) is an interagency program[1] whose mission is to coordinate, conduct, and communicate toxicological research findings across the U.S. government. The NTP is administratively housed at the NIEHS, and David Schwartz serves as the director of both the NTP and the NIEHS. The NTP and the NIEHS share an integrated vision that serves to enhance the productivity of each program by promoting extensive collaboration across the broad spectrum of environmental health sciences. One of the emerging challenges for the NTP and the NIEHS is to use the best science to create, validate, and implement in environmental health research novel, robust, and efficient biological assays that will more effectively predict the risk of human disease and protect the health of our public.

The NTP and the NIEHS share an integrated vision that serves to enhance the productivity of each program by promoting extensive collaboration across the broad spectrum of environmental health sciences.

Recently the NTP developed a vision statement, "Toxicology in the 21st Century: The Role of the National Toxicology Program," and a roadmap for implementing this vision (available at http://ntp-server.niehs. nih.gov/). The NTP vision is to develop and use the best science possible to achieve a greater understanding of the mechanisms of toxicity, and to apply this understanding to the study of a broad array of environmental agents through the most effective and efficient use of resources. This vision is consistent with the need of the NIEHS to identify and understand the human biologic and pathophysiologic response to toxicants. As we begin to develop a strategic plan for the NIEHS, an understanding of the NTP vision and roadmap can help to inform and guide this process.

The NTP roadmap has identified four key scientific areas as priorities. First, the NTP needs to modernize the mammalian assays used to screen for toxicity. NIEHS research will lead the development of such assays. Critical to this process is increasing our understanding of the similarities and differences between laboratory species and humans. It is clear that both the quality and the interpretability of toxicity data will improve through the strategic use of new approaches to comparative biology.

Second, the NTP needs to develop and implement high- and medium-throughput screens to identify and understand potential targets for environmentally mediated disease. Such screens, ranging in complexity from simple subcellular fractions to complicated mixtures of primary cultures, can address a variety of biochemical, mechanistic, and functional end points. The availability of these screens will allow the NTP to establish priorities for full-scale, resource-intensive mammalian assays, and will provide direct links into the hypothesis-driven research supported by the NIEHS. As part of this process, the NTP and the NIEHS are collaborating with investigators in the NIH Roadmap Molecular Libraries and Imaging Initiative who are screening more than 100,000 compounds against multiple cellular targets to identify possible therapeutic agents and basic biologic responses. The *in vivo* toxicity data in the NTP archives will be incorporated into this high-throughput screen, and will serve as a cornerstone for the NIEHS and others to develop linkages between basic biologic responses and pathophysiologic outcomes.

Third, recent developments in biomedical research and molecular genetics have created a tremendous need to develop better ways to store, retrieve, analyze, and interpret vast amounts of data. The need for databases and repositories is critical for evaluating the toxicity of potentially hazardous agents. The NTP and the NIEHS will play important and complementary roles in developing these resources, and will partner with others to develop similar tools for the wider range of toxicologic, biologic, genetic, genomic, and biochemical information.

Finally, training the next generation of scientists is critical to the environmental health sciences. In collaboration with the NTP member agencies and our colleagues at the National Institutes of Health, we will support the development of training programs focused on creating integrated teams of scientists to understand and attack environmental health problems of concern to the public.

The fields of toxicology and environmental health sciences are intimately linked, and the future for both is challenging. We are excited by the possibilities posed by the new directions of the NTP and the NIEHS, and look forward to the continued evolution of this vital and productive relationship.

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[1]The other major contributors to the NTP are the National Center for Toxicological Research of the Food and Drug Administration and the National Institute of Occupational Safety and Health of the Centers for Disease Control and Prevention.

Arnold Greenwell/EHP

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

Expert Panel Meeting on Styrene
CERHR held an expert panel meeting on styrene on June 1–3, 2005, at the Holiday Inn Select Old Town Alexandria, Alexandria, VA. The expert panel, composed of 10 independent scientists, reviewed and evaluated the available scientific evidence on styrene in three primary areas: human exposure, reproductive toxicity, and developmental toxicity. They considered the quality, quantity, and strength of the evidence in their deliberations about the potential for this chemical to cause adverse effects on human reproduction and prenatal or postnatal development.

Based on experimental animal data, *the expert panel concluded there is negligible concern for developmental toxicity in humans*. Animal data also indicate that styrene is not a reproductive toxicant; therefore, *the expert panel concluded there is negligible concern for reproductive toxicity in humans*. The conclusions noted above are those of the Styrene Expert Panel and should not be construed to represent the views of the NTP.

The final expert panel report will be available for public comment in electronic PDF format on the CERHR web site and in hardcopy or on CD-ROM from CERHR after July 18. Public comments received on this report will be posted on the CERHR web site.

Expert Panel Meeting on DEHP
An expert panel evaluation of di(2-ethylhexyl)phthalate (DEHP) is planned for October 2005 at the Holiday Inn Select Old Town Alexandria in Alexandria, Virginia. The draft expert panel report on DEHP will be available electronically (PDF) on the CERHR web site or in hardcopy or on CD-ROM from CERHR in August. The NTP will publish details about the meeting in the Federal Register and NTP Update and post them on the CERHR web site in the near future. Time will be set-aside at the expert panel meeting for presentation of oral public comments.

Symposium at Teratology Society Meeting
With support from the NIH Office of Rare Diseases, the CERHR co-sponsored a symposium at the Annual Teratology Society Meeting on June 25-30, 2005, in St. Pete Beach, Florida. The symposium, *Gene/ Environment Interactions in Rare Diseases that include Common Birth Defects*, took place on Tuesday June 28. Details can be found at the following web site: http://www.teratology.org/.

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How to Subscribe to the NTP List-serv

To subscribe to the list-serv and receive the *NTP Update* as well as other NTP news and announcements electronically, register online at http://ntp.niehs.nih.gov or send e-mail to ntpmail-request@list.niehs.nih.gov with the word "subscribe" as the body of the message or contact the NTP Liaison and Scientific Review Office. Additional information about the NTP along with announcements of meetings, publications, study results and its centers is available on the Internet at http://ntp.niehs.nih.gov.

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The NTP website offers electronic files of the Report on Carcinogens and the library of NTP Technical Reports and NTP Toxicity Reports. The PDF files of these reports are available free-of-charge through the NTP website at http://ntp.niehs.nih.gov (see *Resources*) or in printed text from Central Data Management [cdm@niehs.nih.gov or (919) 541-3419].

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

Ocular Toxicity Scientific Symposia
The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) in collaboration with the European Center for the Validation of Alternative Methods (ECVAM) sponsored two ocular toxicity symposia entitled, *Mechanisms of Chemically-Induced Ocular Injury and Recovery* (May 11-12, 2005) and *Minimizing Pain and Distress in Ocular Toxicity Testing* (May 13, 2005) at the Natcher Conference Center, NIH in Bethesda, Maryland.

During the symposium, *Mechanisms of Chemically-Induced Ocular Injury and Recovery*, participants (1) discussed the state-of-the-science and the current understanding of the pathophysiology and mechanisms of chemically induced ocular injury and recovery (reversibility versus irreversibility) and (2) identified knowledge gaps to understanding these mechanisms. The participants proposed research initiatives that would advance development of test systems necessary to meet regulatory requirements and provide for protection of human health while reducing, refining (less pain and distress), and/or replacing the use of animals.

Participants recommended additional biomarkers that should be considered for inclusion in *in vitro* test systems for ocular irritation testing. These include indicators of cytotoxicity and cytokine measurements as potential markers of inflammatory processes, depth of injury, and histopathology. They also identified areas for future research. Finally, the participants identified endpoints that should be considered in the current *in vivo* rabbit eye test and in human chemical injuries to support the development and validation of predictive *in vitro* test methods and improve hazard characterization and reliability. Some of the useful additions to the *in vivo* rabbit eye test would include slit lamp biomicroscopy with fluorescein staining, pachymetry, photo documentation of the injury, and histopathology. Suggested additions for routine assessment of human injury include a description of the offending agent, standardized/comprehensive eye examination, pachymetry, photo documentation, and clinical outcome.

During the second symposium, *Minimizing Pain and Distress in Ocular Toxicity Testing,* participants reviewed the current understanding of the sources and mechanisms of pain and distress in ocular toxicity testing. They identified current, best practices for preventing, recognizing, and alleviating ocular pain and distress that include combinations of either general or topical anesthesia. Finally, participants identified additional research, development, and validation studies necessary to support scientifically valid ocular testing procedures that avoid pain and distress**.**

NICEATM will publish a summary of both symposia in the near future. Additional information about these symposia can be found on the ICCVAM/NICEATM web site: http://iccvam.niehs.nih.gov/.

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Upcoming Events

August 18, 2005	NTP Board of Scientific Counselors Meeting, NIEHS, Research Triangle Park, NC
Sept. 27-28, 2005	NTP Board of Scientific Counselors Technical Reports Review Subcommittee Meeting, NIEHS, Research Triangle Park, NC
October 2005	Expert Panel Evaluation of DEHP, Holiday Inn Select Old Town Alexandria, Alexandria, VA

NTP Technical Reports Review Subcommittee Meeting

The NTP Technical Reports Review Subcommittee will meet on September 27-28, 2005, at the NIEHS, 111 TW Alexander Drive, Research Triangle Park, NC to peer review the findings and conclusions from draft NTP Technical Reports.

The draft reports tentatively scheduled for review are:

Bromodichloromethane	Alpha- and beta-hydroxy acids in combination with solar light
Dibromoacetic acid	Methyl isobutyl ketone
Dicloroacetic acid	4-Methylimidazole
Diisopropylcarbodiimide	Sodium Bromate
Divinylbenzene	

Details about this meeting will be announced in the Federal Register and posted on the NTP web site (http://ntp.niehs.nih.gov select *Advisory Committees and Board*) or can be obtained by contacting the Executive Secretary, Dr. Barbara Shane. This meeting is open to the public and public comment, both written and oral, is welcome on any report.

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NTP Testing Program

Request for Study Nominations

With a broad mandate to provide toxicological characterizations for chemicals and other agents of public health concern, the NTP accepts nominations for new toxicological studies at any time. Anyone including labor unions, academic scientists, federal and state agencies, industry, and the general public are welcome to make nominations for specific substances or for general issues related to the potential human health hazards of occupational or environmental exposures. As available, a rationale for study should accompany the nomination along with background information describing sources of exposure and possible adverse health effects or concerns associated with exposure, the chemical name, and the Chemical Abstract Service (CAS) registry number. Details about the nomination process are available on the NTP web site (http://ntp.niehs.nih.gov, select *Nominations to the Testing Program* under the heading *Testing Information*)

or contact the NTP Office of Chemical Nomination and Selection (contact information below).

Current areas of focus in the NTP's testing program include potential hazards associated with nanoscale materials, herbal dietary supplements, radio-frequency radiation emissions from cellular telephones, photoactive chemicals, brominated flame retardants, certain complex occupational exposures, dioxin-like compounds, contaminants of finished drinking water, endocrine-disrupting substances, and methods for assessing potential cardiac toxicity.

All nominations undergo several levels of review before selected by the NTP for study. These steps of review help to ensure that the NTP's testing program addresses toxicological concerns pertinent to all areas of public health and helps maintain balance among the types of substances and issues evaluated. Studies are initiated on selected nominations as time and resources permit.

Study Nominations Currently in Review

A Federal Register notice published on May 5, 2005, (70FR23877) solicits comment on the 15 new nominations listed below (available on the NTP web site at http://ntp.niehs.nih.gov *select* Nominations to the Testing Program). The NTP Board of Scientific Counselors will review these nominations at its August 18, 2005 meeting. The NTP web site also provides Internet links to electronic versions of supporting documents for each nomination and additional information on the NTP Study Nomination Review and Selection Process. The NTP invites interested persons or groups to submit written comments to Dr. Scott Masten (contact information below). 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 will be posted electronically on the NTP web site as they are received and distributed to the NTP Board and NTP staff.

- **Acetyl-L-carnitine hydrochloride [5080-50-2] and alpha-Lipoic acid [62-46-4]**: recommended studies – Subchronic toxicity studies (individual and combination studies)
- **Antimony trioxide [1309-64-4]**: recommended studies – Chronic toxicity, carcinogenicity, and cardiotoxicity studies
- **Antimony trisulfide [1345-04-6]**: No additional studies at this time due to presumed lower workplace exposures relative to other antimony compounds
- **4-Bromofluorobenzene [460-00-4]**: Defer pending review of anticipated industry submissions on exposure and toxicity information to the U.S. Environmental Protection Agency and possible sponsorship in the High Production Volume Challenge Program
- **Butylparaben [94-26-8]**: recommended studies – Toxicological characterization including reproductive toxicity studies
- **2,6-Diaminopyridine [141-86-6]:** Defer pending review of additional information on uses and potential exposure from hair dyes
- **1,3-Dichloropropanol [96-23-1]:** recommended studies – Toxicological characterization, including metabolism and disposition, reproductive toxicity, and carcinogenicity studies; coordinate studies with voluntary data development activities of the U.S. Environmental Protection Agency
- **2,5-Dimercapto-1,3,4-thiadiazole [1072-71-5]**: recommended studies – Genotoxicity, metabolism and disposition, and subchronic toxicity studies
- **3-Dimethylaminopropylamine [109-55-7]**: recommended studies – *In vitro* genotoxicity studies (in combination with a nitrosating agent); dermal absorption and metabolism studies with a focus on nitrosamine formation
- **Garcinia cambogia extract [90045-23-1**]: Defer pending further review of recently published studies
- **Gum guggul extract [No CAS No**.]: recommended studies – Toxicological characterization
- **Imidazolidinyl urea [39236-46-9**]: recommended studies – Genotoxicity and dermal absorption studies; evaluation of potential degradation products (e.g., diazolidinyl urea and formaldehyde)
- **Permanent makeup inks [No CAS No.]**: recommended studies – For representative Premier Products True Color pigments: *in vitro* and *in vivo* allergenicity, photoallergenicity, and phototoxicity studies; chemical characterization studies
- **Usnic acid [125-46-2] and Usnea herb [No CAS No.]:** recommended studies – Toxicological characterization including genotoxicity, pharmacokinetic, developmental and reproductive toxicity, and *in vitro* mitochondrial toxicity studies
- **Vincamine [1617-90-9]:** recommended studies – Integrate studies into current NTP research program on QT interval prolongation

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